Dissertation

Effectiveness and drug survival of biologic treatment in psoriasis patients

submitted by

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For the Academic Degree of

Doctor of Medical Science

(Dr. scient. med.)

at the

Medical University of Graz

Department of Dermatology and Venereology

under the Supervision of

Prof. Dr. Peter Wolf

Graz, December 8, 2023

Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the „Guidelines of the Medical University of Graz on Good Scientific Practice“.

Graz, December 8, 2023.

Disclosures

The current dissertation has been published as the following articles:

1. Graier T, Salmhofer W, Jonak C, et al. Biologic drug survival rates in the era of anti-interleukin-17 antibodies: a time-period-adjusted registry analysis. Br J Dermatol. 2021 Jun;184(6):1094-105.
2. Graier T, Weger W, Sator PG, et al. Effectiveness and clinical predictors of drug survival in psoriasis patients receiving apremilast: A registry analysis. JAAD Int. 2020 Dec;2:62-75.
3. Graier T, Weger W, Jonak C, et al. Real-world effectiveness of anti-interleukin-23 antibodies in chronic plaque-type psoriasis of patients from the Austrian Psoriasis Registry (PsoRA). Sci Rep. 2022 Sep;12(1):15078.
4. Graier T, Salmhofer W, Jonak C, et al. Evolution of characteristics and biologic treatment effectiveness in patients of the Austrian psoriasis registry from 2004-2022. J Dtsch Dermatol Ges. 2023 Dec 1;21(12):1513–23.

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Acknowledgements

This dissertation was performed at the Medical University of Graz, Doctoral School of Sustainable Health Research.

My deepest gratitude belongs to my supervisor, Prof. Peter Wolf, who gave me the opportunity to conduct these studies under his guidance. For the last years, I felt constantly supported and free to bring in new ideas, while at the same time, Prof. Wolf would show me sincere appreciation of my work and provide me with advice and guidance when I needed it. Moreover, I dearly appreciated his open door or open Skype channels for discussing results and manuscripts often late at night, even in a time, when he had to guide the clinic through the COVID-19 pandemic as head of the department. I admire him for his innovative ideas, time management, and relentless curiosity, but mostly for his capability to inspire young students and pique their curiosity. Prof. Wolf sustainably shaped my future and I look happily forward to our future projects.

I also want to thank Doz. Wolfgang Weger, who accompanied my first clinical steps in the most sincere way, immediately relieved me from all doubts and fears that young physicians may have at the beginning. I am incredibly grateful for his continuous support of our projects, as they could not be conducted without him. I admire him for his affectionate care towards patients and constantly try to adopt his valuable patient handling.

I am deeply grateful to Prof. Constanze Jonak, for being willing to supervise this thesis and for her constant support throughout the last years, clearly enriching our projects and manuscripts.

I want to thank Prof. Wolfgang Salmhofer for his continuous patronage of our projects and support of new research ideas. I am grateful for his sheer endless knowledge regarding all dermatologic disciplines, providing me with constant advice in my daily routine.

Special thanks belong to Dr. Franz Quehenberger, representing the statistical backbone of our projects. I dearly appreciate all the work he put into analysing our projects, always willing to face and overcome the challenges the data would provide.

My thanks also go to my colleagues at the dermatology department for the great work environment and the clinical and scientific collaboration and support.

I would also like to thank my parents, my father, who encouraged my scientific curiosity and constantly provided valuable (academic) advice, and my mother, who silently held everything together and supported me whenever I needed it.

Finally, my deepest gratitude belongs to my partner Kizi for all the love and support throughout the years. You reminded me of the importance of family and enriched all of my days.

Funding: The doctoral candidate worked in the framework of the Psoriasis Registry Austria, which has been supported by unrestricted research grants or educational grants from the following pharmaceutical companies: AbbVie, Astropharma, Amgen, Almirall, Boehringer-Ingelheim, BMS, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz, UCB Pharma and Pfizer.

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Abbreviations

ASOB	as observed
IL	interleukin
IQR	interquartile range
HR	hazard ratio
LFA	lymphocyte function-associated antigen
LOCF	last observation carried forward
PASI	Psoriasis Area and Severity Index
PDE-4	phosphodiesterase-4
PsoRA	Psoriasis Registry Austria
PUVA	psoralen plus ultraviolet A
SD	standard deviation
TNF	tumor necrosis factor
UVB	ultraviolet B

Zusammenfassung

Die Einführung von Biologika zur Behandlung der moderat-bis-schweren Plaque-Psoriasis hat die Behandlung dieser Erkrankung revolutioniert, da Biologika vielen PatientInnen eine anhaltende, nahezu vollständige oder komplette Abheilung der Hautveränderungen ermöglichen. Nichtsdestotrotz haben kürzlich veröffentlichte Daten gezeigt, dass die Ergebnisse klinischer Studien nicht direkt auf PatientInnen des klinischen Alltags übertragen werden können. Zudem ist nur wenig über jene Faktoren bekannt, welche die Behandlungseffektivität bzw. die Therapietreue beeinflussen können. Die Nutzung von Registern, welche PatientInnen im klinischen Alltag erfassen, wurde zu einem nützlichen Instrument um Behandlungseffektivität, Therapietreue und Medikamentensicherheit zu analysieren.

Ziel der Dissertation war es, Daten des österreichischen Psoriasisregister (PsoRA) zu analysieren, um die folgenden Fragestellungen zu behandeln:

i. Der erste Artikel handelt von Therapietreue in PatientInnen, welche Adalimumab, Etanercept, Ixekizumab, Secukinumab oder Ustekinumab erhalten haben. Der Artikel beschreibt ein behandlungsunabhängiges erhöhtes Risiko für Therapieabbrüche bei Frauen sowie PatientInnen, welche zuvor bereits eine Biologikatherapie erhalten hatten. Zudem zeigt dieser Artikel, dass die Therapietreue auch hinsichtlich verfügbarer Therapiealternativen analysiert werden sollte, da die Einführung hochwirksamer neuer Therapien die Therapietreue bestehender Biologika reduziert.
ii. Der zweite Artikel behandelt die Therapietreue bei PatientInnen mit Apremilast und beschreibt eine Biologika-Vortherapie sowie ein Alter < 40 bei Therapiestart als Risikofaktoren für einen vorzeitigen Abbruch der Therapie. Der Befall der Kopfhaut, der Handflächen/Fußsohlen, intertriginöser Areale oder Nägel, oder eine begleitende Psoriasisarthritis stellten dabei kein erhöhtes Risiko für einen vorzeitigen Therapieabbruch dar.
iii. Der dritte Artikel handelt von der Behandlungseffektivität der kürzlich zugelassenen IL-23p19 Inhibitoren Guselkumab, Risankizumab und Tildrakizumab. Diese Studie zeigte, dass alle drei Biologika ähnliche Effektivität besitzen, welche bei PatientInnen mit einer Biologika-Vortherapie reduziert ist.

iv. Der vierte Artikel beschreibt die medikations- und therapiewechselungsunabhängige Effektivität von Biologika im ersten Behandlungsjahr. Der Artikel berichtet über signifikante Verbesserungen der Therapieeffektivität in den letzten 20 Jahren. Zudem zeigte sich auch, dass sich PsoriasispatientInnen von vor 20 Jahren signifikant von heutigen PsoriasispatientInnen unterscheiden.

Zusammenfassend lässt sich festhalten, dass Biologika zu einer signifikanten Verbesserung der Behandlungseffektivität bei PsoriasispatientInnen im klinischen Alltag führten. Faktoren wie weibliches Geschlecht, das Vorhandensein einer Biologika-Vortherapie, oder die Verfügbarkeit effektiver Therapiealternativen können die Therapietreue von Biologika beeinflussen. Nichtsdestotrotz, einer/eine von drei bis fünf PatientInnen zeigt nach wie vor kein zufriedenstellendes Ergebnis auf Biologika-Therapien. Psoriasisregister, welche PatientInnen im klinischen Alltag erfassen, können helfen Risikofaktoren zu identifizieren, die das Ergebnis von Biologikatherapien beeinflussen.

Abstract

The introduction of biologics for the treatment of moderate-to-severe plaque psoriasis has revolutionized anti-psoriatic treatment, providing sustainable complete or nearly complete skin clearance to a large proportion of patients. However, recent data have shown that results from clinical trials cannot automatically be applied to real-world patients. Moreover, little is known about factors influencing treatment effectiveness or drug survival in those patients. Therefore, real-world psoriasis registries have emerged into a valuable instrument analysing treatment effectiveness, drug survival and safety in psoriasis patients.

The aim of this dissertation thesis was to scrutinize data from the Psoriasis Registry Austria (PsoRA) and addresses the following topics:

i. The first article analysing drug survival in patients with adalimumab, etanercept, ixekizumab, secukinumab, and ustekinumab, described a treatment-independent increased risk for treatment discontinuation in female patients, as well as patients that had been treated with biologics in the past. Moreover, this article described that drug survival has to be analysed with regard to alternative treatment options, as the introduction of highly effective treatments reduces the drug survival of existing biologics.

ii. The second article described drug survival of apremilast and reported previous biologic exposure as well as age < 40 at treatment start, as risk factors for treatment discontinuation, whereas the involvement of scalp, palms and/or soles, inverse areas or nails, and concomitant arthritis did not alter drug survival of apremilast.

iii. The third article focused on the treatment effectiveness of the recently introduced IL-23p19 inhibitors guselkumab, risankizumab and tildrakizumab. This study revealed that all three drugs share similar effectiveness, which is reduced in biologic non-naïve patients.

iv. The fourth article analysed the first-year biologic treatment effectiveness, irrespective of the prescribed treatment or treatment switches. The article reported significant improvement in biologic effectiveness over the last twenty years. Moreover, apart from improvements in effectiveness, the psoriasis patient from twenty years ago significantly differs from patients nowadays.

Taken together, biologics have led to a significant improvement in treatment effectiveness in real-world psoriasis patients. Factors like sex, previous biologic exposure, or the availability of effective treatment alternatives can influence drug survival. However, despite all progress made, one out of three to five patients do still not respond to biologic treatment sufficiently. Real-world psoriasis registries can help to identify factors influencing the outcome of biologic treatment.

Introduction

Plaque psoriasis is a common autoinflammatory skin disease affecting approximately 2% of the world`s population (1). A considerable proportion of these patients (20-30%) suffers from moderate to severe disease; thus, these patients require systemic anti-psoriatic treatment (2,3). Psoriasis is a complex disease that is associated with multiple comorbid diseases, high psychological distress in patients and partners/relatives of psoriasis patients, and occupational impairments, ultimately also resulting in substantial indirect economic costs (4–9). For decades treatment of moderate-to-severe psoriasis consisted of photo(chemo)therapy (ultraviolet [UV] B and psoralen plus UV-A [PUVA]) and conventional systemic treatment with methotrexate, cyclosporine, retinoids (acitretin, isotretinoin) and fumaric acid (10,11). However, most of these treatments are not capable of long-term disease control due to high rates of primary or secondary treatment failure, adverse events and cumulative toxic effects (2,12–20). The turn of the millennium ushered a new therapeutic era, as the first monoclonal antibodies and fusion proteins (targeting TNF-α) – also referred to as *biologics* – have revolutionized anti-psoriatic treatment (2,21,22). These biologics target specific cytokines that are crucial for the pathogenesis of psoriasis (23). Continuous research in this area has led to the discovery of more target cytokines (i.e. IL-17 and IL-23) contributing to the disease and has resulted in the development of highly effective and self-injectable drugs (24–29). Moreover, the armamentarium of orally administrable drugs has also expanded in 2015 with the phosphodiesterase-4 (PDE-4) inhibitor apremilast. Apremilast has shown to be an effective anti-psoriatic drug leading to the improvement and remission of skin lesions and symptoms of psoriatic arthritis in clinical trials compared to the placebo group (30,31). However, the efficacy, safety, and treatment adherence of clinical trials cannot automatically be translated into the outcome of routine care, because real-world patients may differ from patients in clinical trials (32,33). In fact, recent studies estimated that 46.6–78.4% of patients would not have been eligible for clinical trials due to strict inclusion and exclusion criteria, and a worse effectiveness and a higher risk for serious adverse events for such patients were reported (32,33). Therefore, the monitoring of treatment effectiveness, adverse events, and treatment adherence/persistence in real-world patients receiving those drugs has become necessary, as these parameters determine the clinical outcome in this population (34–36). All these parameters can be studied using real-world data registries, which have emerged as crucial instruments for this purpose (37,38).

Nevertheless, despite all progress, psoriasis is a chronic disease and biologic treatment was considered to be a symptomatic treatment with reoccurrence and worsening of skin lesions and joint pain after treatment discontinuation in most patients (11,39,40). However, recent real-world data show a potential disease-modifying effect on the development and progression of psoriatic arthritis, as well as prohibiting effect on the development of severe psoriatic disease, if biologic therapies are administered in early disease (41,42). Therefore, dermatologists are awaiting results from the GUIDE study and the STEP-IN study, two clinical trials designed to study the impact of guselkumab and secukinumab as potential disease-modifying drugs (43,44). Therefore, biologics could possibly gain even more importance as treatment may not only improve skin lesions and patients` health-related quality of life, but could significantly reduce the indirect costs of psoriatic disease in the future (4). This is in part already reflected in the holistic approach of personalized treatment selection, which takes into account the disease severity, involvement of sensitive body sites, health-related quality of life, patient comorbidities, the patient's life plans, and both the physician's and patient's treatment preferences (45–47).

Disease severity can be measured using the Psoriasis Area and Severity Index (PASI), which is a score calculated by physicians (48,49). For the calculation of PASI, physicians use three parameters (erythema, scaling and induration) to assess the severity of skin lesions (graded from 0 [normal] to 4 [maximal clinical extent]) in four different body sites (head, upper extremities, lower extremities, and trunk) (48,49). The body-site-specific surface area is rated on a scale from 0 (no skin lesions) to 7 (body-site covered with skin lesions to 90-100%). PASI is calculated using severity of skin lesions and body-site specific surface area, ultimately resulting in a PASI between 0 and 72 (48,49). Patients with a PASI > 10 are considered to suffer from moderate-to-severe-psoriasis (47). Therefore, these patients are eligible for systemic treatment (47). However, as outlined above, patients with a severe impairment of health-related quality of life, involvement of sensitive body sites, or comorbid diseases may be eligible for systemic treatment with PASI ≤ 10 (45–47). Treatment effectiveness is frequently reported in terms of PASI response or PASI reduction category, which describe the resolution of skin lesions to a certain extent (i.e. PASI < 50 [less than 50% resolution of skin lesions], PASI 50 [resolution of at least 50% of skin lesions], PASI 75 [resolution of at least 75% of skin lesions], PASI 90 [resolution of at least 90% of skin lesions] and PASI 100 (complete remission) (47,50–52).

The main goal of this dissertation thesis was to elucidate treatment effectiveness, drug survival and treatment safety of recently introduced biologic drugs, due to the increasing importance of these drugs in psoriatic disease and the lack of real-world data about them. Furthermore, this dissertation aimed to analyse treatment effectiveness, drug survival and treatment safety of the recently introduced oral anti-psoriatic drug apremilast. Apremilast is the first drug in its class with an entirely new mode of action, however, little real-world data for it was available at that timepoint.

This cumulative doctoral thesis comprises four first-author articles published since 2020 analyzing clinical effectiveness, safety, and drug adherence of psoriasis patients receiving biologic or conventional systemic treatment with apremilast.

Results

The following section briefly summarizes the results of the four original articles:

- Graier T, Salmhofer W, Jonak C, et al. Biologic drug survival rates in the era of anti-interleukin-17 antibodies: a time-period-adjusted registry analysis. Br J Dermatol. 2021 Jun;184(6):1094-1105. (Original article) (37)
- Graier T, Weger W, Sator PG, et al. Effectiveness and clinical predictors of drug survival in psoriasis patients receiving apremilast: A registry analysis. JAAD Int. 2020 Dec;2:62-75. (Original article) (53)
- Graier T, Weger W, Jonak C, et al. Real-world effectiveness of anti-interleukin-23 antibodies in chronic plaque-type psoriasis of patients from the Austrian Psoriasis Registry (PsoRA). Sci Rep. 2022 Sep;12(1):15078. (Original article) (50)
- Graier T, Salmhofer W, Jonak C, et al. Evolution of characteristics and biologic treatment effectiveness in patients of the Austrian psoriasis registry from 2004-2022. J Dtsch Dermatol Ges. 2023 Dec;21(12):1513–23. (Original article) (54)

The article titled “Biologic drug survival rates in the era of anti-interleukin-17 antibodies: a time-period-adjusted registry analysis” scrutinized data from 1572 patients (36.5% women), who received a total of 1848 biologic treatment cycles consisting of 294 cycles adalimumab, 96 etanercept, 406 ixekizumab, 390 secukinumab and 662 cycles with ustekinumab (37). Concomitant psoriatic arthritis was present in 547 patients (34.7%) (37). The mean PASI at treatment start was highest in patients receiving ixekizumab and secukinumab with a PASI of 9.65 and 9.60, followed by ustekinumab, adalimumab and etanercept with a PASI of 8.20, 7.23 and 6.07, respectively (37). Twelve months after treatment start the observed PASI values were lowest for patients receiving ixekizumab (0.90) and secukinumab (0.99), followed by ustekinumab (1.08), etanercept (1.98) and adalimumab (2.13) (37). Similar rankings were observed in LOCF analysis, except for ustekinumab, which achieved lowest PASI score and adalimumab achieving the second lowest PASI prior to etanercept (37). The 12-months drug survival rates were highest for ustekinumab (89.0%) and ixekizumab (86.0%), followed by secukinumab (78.1%), adalimumab (76.5%) and etanercept (66.0%) (37). A treatment-independent increased risk for treatment discontinuation was found for female gender (relative HR 1.50, $p = 0.019$) and patients with previous biologic treatment (relative HR 2.10, $p < 0.001$), but not for patients

with concomitant psoriatic arthritis (relative HR 1.12, p = 0.21) (37). The introduction of ixekizumab increased the risk for treatment discontinuation in the remaining biologic drugs (relative HR 1.6, p = 0.001), irrespective of the prescribed treatment (p = 0.858) (37). Five hundred forty-four treatment (29.4%) treatment cycles were discontinued (37). The main reasons for discontinuation were primary therapeutic failure (30.3%), secondary treatment failure (26.1%), and side effects (17.3%), with differences in the reason for treatment discontinuation in the drug-specific analysis (37).

For the article titled "Effectiveness and clinical predictors of drug survival in psoriasis patients receiving apremilast: A registry analysis" data from 367 patients (37.6% women) receiving apremilast were eligible for analysis (53,55). Concomitant psoriatic arthritis was observed in 21.8% of male patients and 28.3% of female patients (p = 0.21) (53). The most frequently psoriasis type treated with apremilast was plaque type (87.7%), followed by involvement of nails (24.8%), scalp (20.2%), palms and/or soles (11.2%), or inverse/genital involvement (10.1%) (53). In total, 83.9% of the patients had already received previous treatment with phototherapy, conventional systemic or systemic biologic treatment (53). Mean PASI (SD) at treatment start was 6.48 (6.37) and declined to 3.76 (5.58) and 2.84 (6.13) 3 and 12 months after treatment start in the per protocol analysis, respectively (53). In the LOCF analysis, mean PASI (SD) decreased to 5.03 (5.96) 3 months after treatment start, and to 4.79 (6.21) 12 months after treatment start (53). The analysis regarding the achievement of treatment goals revealed that 36.8% and 56.4% of patients achieved a PASI 75 response at 3 and 12 months after treatment start, whereas this was only the case for 23.5% and 31.9% of patients in the LOCF analysis (53). The median survival time of apremilast was 15.7 months, and after 12 months drug survival rate was 57.3% (53). The risk for treatment discontinuation was not influenced by female gender (RR 0.885, p = 0.4077), concomitant psoriatic arthritis (RR 0.893, p = 0.5126) or obesity (0.576, p = 0.1075) (53,55). Additionally, drug survival of apremilast was not significantly altered in patients with involvement of palms and soles (RR 0.986, p = 0.9526), scalp (RR 1.228, p = 0.2396), nails (RR 1.143, p = 0.4288) or inverse involvement (RR 0.989, p = 0.9662) (53). However, drug survival decreased significantly in patients younger than 40 years (RR 1.493, p = 0.008) (53). Furthermore, due to two coding errors, 48 patients were falsely considered to be biologic-naïve (53,55). This led to a wrong evaluation of the drug survival of apremilast in this subgroup analysis (53,55). We initially reported no increased risk for treatment discontinuation in apremilast patients (RR 1.269, p = 0.108) (53). In fact, previous biologic

treatment increases the risk for treatment discontinuation in apremilast patients (RR 1.662, p = 0.002) (53,55). These errors, as well as a correction of the relative risk of previous biologic treatment, drug survival rates of biologic naïve and non-naïve patients, and a clarification regarding previously prescribed treatments were reported to the journal and published as a correction letter (55). The main reasons for treatment discontinuation were primary treatment failure (32.3%), side effects (31.3%) and secondary loss of efficacy (20.5%) (53). The most frequently reported side effects leading to treatment discontinuation were gastrointestinal symptoms (16.3%), symptoms of depression (5.6%) and headache (4.1%). After discontinuation of apremilast 61.6% of patients received subsequent treatment with biologics (53).

The article "Real-world effectiveness of anti-interleukin-23 antibodies in chronic plaque-type psoriasis of patients from the Austrian Psoriasis Registry (PsoRA) contains data from 197 patients (34.0% females) receiving IL-23p19 inhibitors (50). The most frequently prescribed drug was guselkumab (127 treatment cycles) followed by risankizumab (55 treatment cycles) and tildrakizumab (15 treatment cycles) (50). Concomitant psoriatic arthritis was reported in 51 patients (25.9%) (50). There were no significant differences regarding patient characteristics, class of previous biologic treatment, or number of previous biologic therapies (50). The observed mean PASI (SD) in guselkumab patients decreased from 8.42 (7.13) to 1.82 (3.34) and to 1.22 (2.84) at 3 and 12 months after treatment start, respectively (50). In risankizumab patients the observed mean PASI (SD) decreased from 10.07 (7.28) to 1.34 (2.28) at 3 months and to 0.93 (1.80) at 12 months after treatment start (50). In tildrakizumab patients the observed mean PASI (SD) decreased from 11.0 (9.74) to 4.13 (6.95) at 3 months and increased to 5.40 (6.79) at 12 months after treatment start (50). In general, similar but slightly higher PASI values were reported in the LOCF analysis (50). Moreover, Kruskal-Wallis test revealed significant differences regarding PASI for the LOCF analysis at 6 (p = 0.034) and 12 months (p = 0.024) after treatment start (50). However, significant differences were only found between risankizumab and tildrakizumab (p = 0.041) after post hoc analysis (50).

The fourth article, "Evolution of characteristics and biologic treatment effectiveness in patients of the Austrian psoriasis registry from 2004-2022" scrutinized data from 2729 patients (54). The study revealed significant changes in patient and disease characteristics since the introduction of biologics in Austria, as well as differences regarding treatment

effectiveness (54). A significant increase in the proportion of female patients nowadays (third-generation era) was observed compared to the former eras (36.5% vs. 29.9% and 32.6%, $p < 0.001$) (54). Concomitant psoriatic arthritis was reported less frequently in the third-generation era (30.0%) compared to the first-generation (36.6%) and second-generation era (33.0%) ($p < 0.001$) (54). The mean PASI (SD) significantly decreased from 17.9 (8.4) in the first-generation era to 9.0 (7.4) in the third-generation era ($p < 0.001$), while the proportion of patients with a PASI ≤ 3 at treatment start significantly increased from 0.2% in the first-generation era to 18.6% in the third-generation era ($p < 0.001$) (54). Furthermore, mean (SD) psoriatic disease duration prior to biologic treatment start significantly shortened from 20.5 (11.0) in the first-generation era to 15.9 (12.9) in the third-generation era ($p < 0.001$) (54). Treatment discontinuation and switches to other treatments were more frequently reported in the first-generation era (23.7% and 15.9%) compared to the third-generation era (5.5% and 9.4%) ($p < 0.001$) (54). However, an observation period shorter than one year was more frequently observed in the third-generation era (32.6%) compared to the former eras (1.3% and 4.7%) (54). Significantly higher rates of PASI 100, PASI 90, PASI 75 and PASI 50 response were observed in the third-generation era compared to the former eras ($p < 0.001$) at 3, 6 and 12 months after treatment start (54). LOCF analysis revealed a similar trend, though to a lower percentage (54). These findings are well in line with improvement in PASI (54). The mean (SD) observed PASI decreased from 5.6 (5.8) in the first-generation era to 1.2 (2.7) in the third-generation era three months after treatment start ($p < 0.001$), and from 4.6 (6.1) to 1.1 (2.8) twelve months after treatment start ($p < 0.001$) (54).

Discussion

The introduction of biologics since the start of the millennium has revolutionized anti-psoriatic treatment with a large proportion of patients achieving excellent treatment response (i.e. PASI 90 and PASI 100 response) (24-27,29). However, data from clinical trials regarding efficacy and safety may differ from outcome in patients in daily routine (32,33). In fact, reports from French and British psoriasis registries revealed that 46.6-78.4% of patients in daily routine would not have been eligible for clinical trials mainly due to insufficient disease severity or comorbid disease or older age (32,33). Furthermore, a higher incidence of adverse events and worse clinical effectiveness were observed in these patients (32,33). Moreover, a shorter drug survival in non-eligible patients was reported, but did not reach statistical significance (33). These results highlight the importance of real-world data registries as tools to investigate effectiveness, safety and drug survival in psoriasis patients receiving modern treatments.

In the herein presented study analyzing patient characteristics and clinical effectiveness, irrespective of the prescribed treatment or treatment switches, significant changes were observed with the continuous introduction of more effective biologic drugs since 2004 (54). The significant increase in female patients, treated with biologics, reported in this study (from 29.9% in the first-generation era to 36.2% in the third-generation era), was also observed in health data from Spain (from 38.0% in the period from 2008-2010 to 46.0% in the period from 2015-2018) (54,56). A similar trend was also reported from Germany with a non-significant increase in the proportion of female patients under dermatological treatment (from 42.2% in 2004/2005 to 45.2% in 2016/2017) (57). The decrease in rates of concomitant psoriatic arthritis in our study (from 36.6% in the first-generation era to 30.0% in the third-generation era) was also observed in Spanish patients (from 19.0% in the period from 2008-2010 to 14.0% in the period from 2015-2018) (54,56). Moreover, our study revealed that the mean (SD) duration of psoriatic disease significantly decreased from 20.5 (11.0) years in the first-generation era to 15.9 (12.9) years in the third-generation era (54). This finding is well in line with data from Spain where a decrease in mean (IQR) disease duration was observed from 16.9 (9.3-27.0) in the period from 2008-2010 to 13.9 (6.5-26.2) in the period from 2015-2018 (56). Disease severity in terms of mean PASI (SD) significantly decreased from 17.9 (8.4) in the first-generation era to 9.0 (7.4) and is consistent with observations for dermatological treated patients from Germany reporting

a decrease from 11.4 (9.6) in 2004/2005 to 7.1 (7.8) in 2016/2017, as well as for patients treated with biologics from Spain reporting a decrease in mean PASI (IQR) from 14.0 (9.6-20.0) for the period from 2008-2010 to 10.0 (6.4-14.4) for the period from 2015-2018 (54,56,57). Of note, the significantly reduced rates of concomitant psoriatic arthritis reported in our study and the Spanish study could be a result of the reduced disease duration, that had been observed, in these cohorts (54,56). In fact, recent studies have shown that subclinical psoriatic arthritis is already present in early psoriatic disease and that treatment with biologics in early disease could delay or even prevent the transition to manifest arthritis (42,54,56,58). Moreover, the decrease in disease duration prior to biologic treatment start, which had been observed in our and the Spanish study, could also contribute to the reported lower disease severity (as measured in PASI), as disease severity can increase with cumulative disease duration (3,54,56). Moreover, biologics have also been reported to have beneficial effects on other comorbid diseases including depression and cardiovascular disease (59,60).

Of note, disease duration and the assumed disease-modifying effect in early disease have emerged as an intensively investigated topic in clinical trials, but remain to be a double-edged sword (43,44). On the one hand, early intervention with secukinumab in patients with new onset psoriasis led to superior skin and health-related quality of life improvement compared to narrowband-UVB treatment at week 52 in the study (61). Moreover, another trial analyzed treatment responses in patients receiving guselkumab with a disease duration of ≤ 2 and > 2 years and observed significantly higher response rates in patients with shorter disease duration at week 28 of the trial (62). However, on the other hand most psoriasis patients suffer from mild disease for years prior to developing moderate-to-severe disease and, thus, are not in need for highly effective systemic therapies directly after disease onset (3). Moreover, both trials are still ongoing and reports regarding long-term effects are not available yet (61,62). The decrease in disease severity is also influenced by a significantly higher rate of patients starting biologic treatment with a PASI ≤ 3, namely from 0.2% in the first-generation era to 18.6% in the third-generation era (54). Further characterisation of these patients revealed that significantly more patients were smokers (57.1% in the PASI ≤ 3 group compared to 42.6% in the PASI > 3 group, $p = 0.02493$), females (42.5% versus 33.7%, $p = 0.011$) and suffering from concomitant arthritis (42.5% versus 25.7%, $p < 0.001$) (54). Moreover, palmar and/or plantar involvement was more frequently observed in patients with a PASI ≤ 3 (39.1%) compared to patients with a PASI > 3 (16.0%), whereas scalp involvement was less frequently observed in patients with PASI ≤ 3 (33.8%) compared to

patients with a PASI > 3 (43.2%) (54). There were no significant differences regarding rates of inverse/genital or nail involvement (54). This finding likely reflects the efforts for a more personalized approach in psoriatic treatment and treatment selection, allowing patients with mild and moderate disease, but treatment refractory skin lesions, comorbid diseases, severely impaired quality of life, or involvement of intimidating body-sites to be eligible for highly-effective biologic treatment (47,63,64).

The analysis regarding the overall biologic treatment effectiveness (i.e. independent from specific drugs) revealed significant differences in the achievement of PASI reduction categories (54). Observed rates for PASI 100 response increased from 11.7% and from 22.7% in the first-generation era to 38.5% and 47.6% in the third-generation era at 3 and 12 months after treatment start, respectively (54). Consequently, the observed rates for PASI 90 response were 22.0% and 39.8% in the first-generation era compared to 61.0% and 67.6% in the third-generation era, 3 and 12 months after treatment start, respectively (54). This indicates that nearly every second patient treated with biologics nowadays was fully relieved from psoriatic skin lesions, and that two out of three patients have a resolution of more than ninety percent of their skin lesions (54). Similar findings were observed in the LOCF analysis, though, to a lower extent (54). These findings are difficult to compare to other studies, as the treatment-independent analysis of effectiveness is not done frequently. A smaller study from Denmark analyzing effectiveness in patients treated with the latest class of biologic drugs, namely the IL-23p19 inhibitors guselkumab, risankizumab and tildrakizumab, reported an overall PASI 100 response in 25.7% and 44.4%, and an overall PASI 90 response in 45.7% and 44.4%, at 12-17 weeks and 40-60 weeks after treatment start, respectively (65). A study with data regarding treatment with adalimumab, etanercept, infliximab, secukinumab and ustekinumab from Switzerland and Germany observed a PASI 75 response in 47.1%, 58,2% and 62,8% compared to 77.3%, 80.6%, and 79.8% in the third-generation era in our study at 3, 6 and 12 months after treatment start, respectively (54,66). The observed achievement rates for PASI $\leq$ 3 at 3, 6 and 12 months after treatment start were 77.2%, 92.9% and 92.8% in our study compared to 52.0%, 64.0% and 66.7% in the Swiss and German cohort (54,66). Moreover, PASI $\leq$ 2 response was reported in 64.3% and 61.3% at 12-17 and 40-60 weeks after treatment start in Danish patients treated with IL-23p19 inhibitors, respectively (65). These results highlight the importance of the full armamentarium of available biologics (especially IL-17 inhibitors) as effective treatments. Of note the Danish study did not include IL-17 inhibitors at all, and the combined cohort

from Switzerland and Germany only reported patients treated with secukinumab (not ixekizumab), reflecting only 17.3% of all patients treated with biologics (65,66)

The improvement in treatment effectiveness can be traced back to dynamic changes of the biologic prescription pattern since 2004 (54). In the first-generation era TNF-α inhibitors (69.9%) were the most frequently prescribed biologics in biologic-naïve patients, followed by LFA inhibitors (30.1%) (54). The predominance of TNF-α inhibitors also persisted in the second-generation era with 68.1% of prescribed biologics, followed by ustekinumab as the first drug of the second-generation era with 31.5%, while the LFA-inhibitors alefacept and efalizumab were retrieved from the market in 2011 and 2009, respectively (54,67,68). This changed in the third-generation era when TNF-α inhibitors became the third most frequently prescribed biologics (23.6%), after IL-17 inhibitors (32.5%) and ustekinumab (32.0%) (54). However, the latest class of biologics (IL-23p19 inhibitors) were administered in 11.8% of biologic-naïve patients (54). Studying treatment prescription in biologic non-naïve patients in our other studies revealed that the IL-17 inhibitors ixekizumab and secukinumab (54.3%) and the IL-23p19 inhibitors guselkumab, risankizumab and tildrakizumab (52.3%) were most frequently used in biologic non-naïve patients compared to the TNF-α inhibitors adalimumab and etanercept (32.1%) and ustekinumab (33.5%) (37,50). Higher prescription rates of the latest classes of biologic treatment in biologic non-naïve patients have also been reported from the British biologics registry (ixekizumab [81.8%], guselkumab [76.4%] and secukinumab [64.2%] compared to adalimumab [25.2%] and ustekinumab [53.5%]) and a Danish cohort studying IL-23p19 inhibitors (guselkumab [100.0%], risankizumab [91.9%] and tildrakizumab [92.9%]) (65,69). Furthermore, in the international psoriasis study of health outcomes (PSoHO) a similar trend was observed with IL-23p19 inhibitors (48.6%) having the highest rate of biologic non-naïve patients, followed by IL-17 inhibitors (37.7%), ustekinumab (27.6%) and adalimumab (8.8%) (70). Taking together, these findings indicate that the administration of new biologics in biologic-naïve patients progresses slowly, whereas recently introduced drugs are more frequently prescribed in biologic non-naïve patients compared to existing biologics (37,50,54).

The general improvement in clinical effectiveness can also be observed on a single drug level with regard to the latest biologics (37,50). Treatment effectiveness was analyzed in two different studies: the first focused on adalimumab, etanercept, ixekizumab, secukinumab and ustekinumab, while the other one reported effectiveness for guselkumab,

risankizumab and tildrakizumab (37,50). Disease severity (mean PASI [95% confidential interval]) was highest for patients treated with ixekizumab (9.65 [9.25-10.05]), followed by secukinumab (9.60 [9.01-10.19]), ustekinumab (8.20 [7.93-8.47]), adalimumab (7.23 [6.72-7.74]) and etanercept (6.07 [5.11-7.02]) in the first study, with significant differences between these drugs (p = 0.028) (37). In the second study the mean (SD) PASI was found highest for patients treated with tildrakizumab with a PASI of 11.0 (9.74) compared to patients treated with risankizumab with a PASI of 10.07 (7.28), and guselkumab with a PASI of 8.42 (7.13) (p = 0.227) (50). Three months after treatment start, the observed PASI was lowest in patients treated with ixekizumab (1.70), followed by ustekinumab (2.33), secukinumab (2.34), etanercept (2.63) and adalimumab (2.71) (37). Twelve months after treatment start, PASI remained lowest for patients treated with ixekizumab (0.90), followed by secukinumab (0.99), ustekinumab (1.08), etanercept (1.98) and adalimumab (2.13) (37). Similar findings were observed in the LOCF analysis, except for adalimumab being superior to etanercept at all measured timepoints, and ustekinumab being the most effective drug at the 12-months analysis and afterwards (37). However, it is noteworthy that off-label dosage (90mg ustekinumab instead of 45mg in patients ≤ 90 kilograms) or shorter administration intervals were most frequently observed in patients treated with ustekinumab (21.3%) compared to etanercept (16.6%), adalimumab (13.9%), secukinumab (4.8%) and ixekizumab (0.9%) (37). Furthermore, ustekinumab was the drug with the second highest rate of biologic-naïve patients (66.5%) compared to ixekizumab (49.8%) and secukinumab (41.5%) (37). The superiority of ixekizumab compared to secukinumab could also be traced back to the imbalance in biologic-naïve patients between them, however, obese patients were significantly more frequently treated with ixekizumab (18.5%) compared to secukinumab (12.1%) (37). A recently published study with data from an Italian psoriasis cohort reported a slightly higher PASI (mean [SD]) for patients treated with ixekizumab (2.88 [6.04]) and secukinumab (2.76 [3.72]) at 4 months after treatment start, and a slightly higher PASI at 12 months after treatment start (ixekizumab 0.98 [2.17], secukinumab 1.69 [3.36]) compared to our data (37,71). Of note, the worse treatment effectiveness in the Italian cohort could at least partly be explained by the much higher PASI at treatment start (ixekizumab 17.79 [7.0], secukinumab 15.82 [5.64]) (37,71). Data regarding effectiveness in patients treated with adalimumab, etanercept and ustekinumab revealed lower PASI 12 months after treatment start in our cohort compared to a British cohort, despite of a larger proportion of patients receiving higher off label dosage (37,72). However, biologic naivety for patients receiving those drugs was more common in the Austrian than the British cohort. (37,72). In patients

treated with IL-23p19 inhibitors the observed PASI was lowest for risankizumab (1.34), followed by guselkumab (1.82) and tildrakizumab (4.13) at 3 months after treatment start, despite similar patient characteristics between these drugs (50). The superiority of risankizumab persisted during the 12-months observation period reaching a mean PASI of 0.93, compared to 1.22 in guselkumab patients and 5.40 in tildrakizumab patients (50). A similar ranking, but with a higher PASI was observed in the LOCF analysis (50). Consequently, the rates for the achievement of a PASI 100 and PASI 90 response were superior for patients treated with risankizumab as compared to guselkumab and tildrakizumab (50). However, data for tildrakizumab in this study is limited due to the low patient number (50). Furthermore, subgroup analysis revealed significantly lower PASI in biologic-naïve patients at 3 ($p = 0.048$) and 6 months ($p < 0.001$) as compared to non-naïve patients, despite a significantly higher PASI prior to treatment start in biologic-naïve patients ($p = 0.033$) (50). Of note, after adjustment for previous biologic exposure, there were no significant differences in PASI between these biologics at 3, 6 or 12 months after treatment start, except for 12-months PASI in biologic non-naïve patients (limited by the low tildrakizumab patient number) (50). Furthermore, the class of the previously exposed biologic (i.e. TNF-α-, IL-17- or IL-12/23p40-inhibitor) in the group of biologic non-naïve patients appeared to have no impact on treatment effectiveness, despite significant differences in PASI prior to treatment start between the classes ($p = 0.001$) (50). A slightly higher PASI for guselkumab, risankizumab and tildrakizumab at 4 months after treatment start was recently reported from an Italian cohort, but a lower PASI was observed 12 months after treatment start compared to our data (50,71). A similar discrepancy could be observed by comparing PASI 100 and PASI 90 response rates between the Italian and the Austrian cohorts (50,71). However, rates for the achievement of a PASI ≤ 3 were comparable between the two cohorts (50,71). The difference in PASI between these studies could be the result of different patient characteristics including different rates of biologic-naïve patients, and unequal PASI at treatment start (50,71). Taking together, the data indicate a high effectiveness of IL-17 and IL-23p19 inhibitors in biologic-naïve and non-naïve patients (37,50).

Furthermore, we analysed the effectiveness in terms of PASI and PASI reduction categories for the small molecule apremilast, which was introduced in 2015 in Austria, and for which only limited real-world data were available at that timepoint (53). The observed mean (SD) PASI decreased from 6.48 (6.37) at treatment start to 2.84 (6.13) at 12 months after treatment start (53). A similar trend was found in the LOCF-analysis, though with a

higher PASI (53). Consequently, the observed PASI 100 response increased from 9.0% to 22.7%, and the PASI 90 response increased from 17.5% to 38.2% at 3 and 12 months, respectively (53). Lower rates were reported in the LOCF analysis (53). The rates for the achievement of a PASI 90 response are well in line with data from a Spanish cohort, but lower than rates for PASI 100 and PASI 90 4 months after treatment start, as reported from Greece (73,74).

The 12-months treatment survival in the biologic cohort was observed highest for ustekinumab (89.0%), followed by ixekizumab (86.0%), secukinumab (78.1%), adalimumab (76.5%) and etanercept (66.0%), with ustekinumab being significantly superior to all other biologics in post-hoc analysis (37). Furthermore, ustekinumab and secukinumab were the only biologics not reaching the median survival rate during the 4-year observation (ixekizumab observation was only three years as the drug had just been introduced to the Austrian market) (37). In this study, previous-biologic treatment was identified as a factor significantly decreasing drug survival (HR 2.10, $p < 0.001$), irrespective of the prescribed treatment (37). However, the superiority of ustekinumab diminished after considering the high rates of non-naïve patients in patients treated with ixekizumab and secukinumab and adjusting for biologic naivety (37). Moreover, analysing drug survival prior to and after introduction of ixekizumab in Austria revealed a treatment independent increased risk for treatment discontinuation in the latter patient cohort (HR 1.60, $p = 0.0013$) (37). This indicates that drug survival per se is influenced by dynamic changes in the availability of highly effective treatment alternatives. Therefore, drug survival should be studied with regard to the available biologic treatment options (37). Moreover, female gender (HR 1.50, $p = 0.01954005$) was identified as a factor significantly decreasing biologic drug survival, while concomitant psoriatic arthritis was not (HR 0.89, $p = 0.21$) (37). An increased risk for treatment discontinuation in female patients (HR 1.28, $p < 0.05$) was also reported from a British cohort (75). However, in this study only patients receiving adalimumab, secukinumab and ustekinumab were analysed (75). In contrast to our findings, the British study observed an increased risk for treatment discontinuation in patients with concomitant psoriatic arthritis treated with ustekinumab (HR 1.42, $p < 0.05$), but the exact opposite for adalimumab (HR 0.67, $p < 0.05$), and no difference in secukinumab patients (HR 0.70, $p > 0.05$) (37, 75). A similar constellation was reported for patients with previous biologic treatment with an increased risk for treatment discontinuation in patients receiving ustekinumab (HR 1.54, $p < 0.05$), no significant effect on secukinumab patients (HR 1.49, $p > 0.05$), and a decreased risk in adalimumab patients (HR 0.71, $p < 0.05$) (75). Female gender

as risk factor for treatment discontinuation was also reported from another British cohort, analysing drug survival in adalimumab, etanercept, infliximab and ustekinumab (76). The hazard ratio for female gender was 1.22 in the multivariate analysis, however, after adjusting for the reason for treatment discontinuation (either discontinuation due to ineffectiveness or adverse events) the hazard ratio further increased for discontinuation due to adverse events (1.79, $p < 0.05$), while it was not significantly altered in female patients discontinuing treatment due to ineffectiveness (HR 1.02, $p > 0.05$) (76). These findings highlight differences in perception of treatment safety between male and female patients (76). In contrast to our study, psoriatic arthritis was associated with a decreased risk for treatment discontinuation (HR 0.82, $p < 0.05$) (37,76).

Lower drug survival rates were observed for patients treated with apremilast with a 12-months survival rate of 57.3% and a median survival time of 15.7 months (53). In contrast to drug survival in the biologic cohort, drug survival of apremilast was not altered by gender (HR 0.885, $p = 0.4077$) (53). However, similar to drug survival in biologics, the drug survival of apremilast significantly decreased in patients with previous biologic treatment (HR 1.662, $p = 0.002$), while it appeared not to be influenced by concomitant psoriatic arthritis (HR 0.893, $p = 0.5126$), fitting well in line with the results from our biologic cohort (37,53,55). Furthermore, we identified age < 40 years at treatment start as a factor significantly decreasing the drug survival of apremilast (HR 1.493, $p = 0.007918$) (53,55). Of note, the involvement of sensitive or difficult-to-treat body sites (scalp, palms and/or soles, nails, inverse areas) did not alter the risk of treatment discontinuation in apremilast patients. This also accounts for obese patients, though, this result is limited by the low number of obese patients (53,55). The results of this study have been confirmed from a Japanese cohort, reporting no significant differences in drug survival regarding gender, concomitant psoriatic arthritis, or involvement of sensitive body-sites (77). However, treatment duration was slightly lower in the Japanese cohort compared to the Austrian (53,77). No significant differences in the risk for treatment discontinuation in apremilast patients with previous biologic treatment have been observed in a Spanish study (HR 0.97, $p > 0.05$) (78). Furthermore, the authors of that study stated that no significant differences in drug survival were observed regarding female gender, concomitant psoriatic arthritis, or scalp, nail, or palmar and/or plantar involvement (78). However, that study only reported data on 41 patients, of whom 6 were suffering from other dermatologic conditions, limiting the results of that study (78). Finally, no significant differences in drug survival were found in a

Japanese cohort regarding concomitant psoriatic arthritis or previous systemic treatment (79).

Limitations

There are several limitations to the presented studies from PsoRA: Firstly, the data collected in PsoRA derives mainly from tertiary treatment centres and only to a small amount from private practices (37). Furthermore, PsoRA mainly collects data from patients with moderate-to-severe plaque psoriasis receiving systemic and/or phototherapeutic treatment (54). Therefore, patient and disease characteristics, as well as findings regarding drug survival, treatment effectiveness and safety cannot automatically be attributed to patients visiting primary and secondary care private practices, or patients with mild disease (37,54). Moreover, direct comparisons between single drugs in psoriasis registries are difficult to draw, as patients are not randomized to treatment cohorts, which could result in differences in patient and disease characteristics between the cohorts (80). Additionally, the data stored in PsoRA derives from clinical routine and not clinical trials, therefore, relevant clinical data could be missing (including PASI), which was also reported from other registries (53). The data reported to PsoRA does not exclude any licensed anti-psoriatic systemic drug. However, most psoriasis registries are supported by pharmaceutical industry, and some are designed to address specific research questions, which could result in the selection of specific treatment classes or single drugs to be included instead of all available treatment options (81). Finally, some of the data collected in psoriasis registries might be difficult to compare between registries, as assessment instruments are not harmonized (i.e. using different questionnaires to assess health-related quality of life) (81).

Conclusion

The introduction of biologics has sustainably changed the treatment of moderate-to-severe plaque psoriasis. However, all clinical improvements aside, there is still a considerable number of patients, who are not responding sufficiently to anti-psoriatic treatment. Previous biologic treatment and female gender are risk factors for an increased risk of biologic treatment discontinuation. Moreover, treatment effectiveness is reduced in patients, who received previous biologic treatments.

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Appendix

The following publications are appended (in order of appearance):

- Graier T, Salmhofer W, Jonak C, et al. Biologic drug survival rates in the era of anti-interleukin-17 antibodies: a time-period-adjusted registry analysis. Br J Dermatol. 2021 Jun;184(6):1094-105. (Original article) (37)
- Graier T, Weger W, Sator PG, et al. Effectiveness and clinical predictors of drug survival in psoriasis patients receiving apremilast: A registry analysis. JAAD Int. 2020 Dec;2:62-75. (Original article) (53)
- Correction: JAAD Int. 2021;3:53. (55)
- Graier T, Weger W, Jonak C, et al. Real-world effectiveness of anti-interleukin-23 antibodies in chronic plaque-type psoriasis of patients from the Austrian Psoriasis Registry (PsoRA). Sci Rep. 2022 Sep;12(1):15078. (Original article) (50)
- Graier T, Salmhofer W, Jonak C, et al. Evolution of characteristics and biologic treatment effectiveness in patients of the Austrian psoriasis registry from 2004-2022. J Dtsch Dermatol Ges. 2023 Dec;21(12):1513–23. (Original article) (54)

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Biologic drug survival rates in the era of anti-interleukin-17 antibodies: a time-period-adjusted registry analysis*

T. Graier,[1] W. Salmhofer,[1] C. Jonak,[2] W. Weger,[1] C. Kölli,[3] B. Gruber,[4] P.G. Sator,[5] K. Prillinger,[6] A. Mlynek,[7] M. Schütz-Bergmayr,[8] L. Richter,[9] G. Ratzinger,[10] C. Painsi,[11] S. Selhofer,[12] N. Häring,[13] K. Wippel-Slupetzky,[14] H. Skvara,[3] H. Trattner,[2] A. Tanew,[2] M. Inzinger,[1] R. Tatarski,[12] C. Bangert,[2] C. Ellersdorfer,[9] R. Lichem,[1] A. Gruber-Wackernagel,[1] A. Hofer,[1] F. Legat,[1] E. Schmiedberger,[15] R. Strohal,[13] B. Lange-Asschenfeldt,[11] M. Schmuth,[10] I. Vujic,[9] W. Hoetzenecker,[8] F. Trautinger,[6] W. Saxinger,[4] R. Müllegger,[3] F. Quehenberger[15] and P. Wolf[1]

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Linked Comment: Gniadecki. *Br J Dermatol* 2021; **184**:996–997.

Summary

Background Drug survival rates reflect efficacy and safety and may be influenced by the availability of alternative treatment options. Little is known about time-dependent drug survival in psoriasis and the effect of increasing numbers of biologic treatment options.

Objectives To determine whether drug survival is influenced by the availability of treatment options and by factors such as gender, psoriatic arthritis or previous biologic treatment.

Methods This observational, retrospective, multicentre cohort study analysed data from patients registered in the Austrian Psoriasis Registry (PsoRA) who were treated with biologics between 1 January 2015 and 30 November 2019.

Results A total of 1572 patients who received 1848 treatment cycles were included in this analysis. The highest long-term Psoriasis Area and Severity Index improvement was observed after treatment with ixekizumab, followed by ustekinumab and secukinumab, adalimumab and etanercept. Overall, ustekinumab surpassed all other biologics in drug survival up to 48 months. However, when adjusted for biologic naïvety, its superiority vanished and drug survival rates were similar for ixekizumab (91·6%), secukinumab (90·2%) and ustekinumab (92·8%), all of them superior to adalimumab (76·5%) and etanercept (71·9%) at 12 months and beyond. Besides biologic non-naïvety (2·10, $P < 0·001$), the introduction of a new drug such as secukinumab or ixekizumab (relative hazard ratio 1·6, $P = 0·001$) and female gender (1·50, $P = 0·019$) increased the risk of treatment discontinuation overall, whereas psoriatic arthritis did not (1·12, $P = 0·21$).

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Accepted for publication
28 November 2020

Funding sources
The Austrian Psoriasis Registry (PsoRA) was supported by unrestricted research grants or educational grants from the following pharmaceutical companies: AbbVie (2015–2019), Almirall (2017–2020), Amgen GmbH (2019–2020), Celgene (2016–2018), Eli Lilly (2015–2020), Janssen (2014–2016), Leo Pharma (2014–2020), Merck Sharp & Dohme (2014), Novartis (2019), Pfizer (2008–2018) and Sandoz (2020). The study was also supported by the Austrian Society for Dermatology and Venereology.

Conflicts of interest
Full details are given in the Appendix.

*Plain language summary available online

DOI 10.1111/bjd.19701

Conclusions The time-dependent availability of drugs should be considered when analysing and comparing drug survival. Previous biologic exposure significantly influences drug survival. Women are more likely to stop treatment.

What is already known about this topic?

- Female gender and previous biologic exposure have been discussed as predictors for decreased drug survival in patients with psoriasis, but it remains unknown whether a time-dependent increased availability of treatment options alters biologic drug survival.

What does this study add?

- The increased availability of alternative biologic treatments over time leads to an elevated risk for treatment discontinuation overall; therefore, drug survival analysis has to be time adjusted.
- Moreover, the study reveals that the impact of previous biologic treatment on drug survival is tremendous and confirms worse drug survival in female patients.

Biologics have revolutionized the treatment of psoriatic disease. In clinical trials, the latest classes of biologics [targeting interleukin (IL)-17 and IL-23] have proved to be effective antipsoriatics, promising complete clearance of plaques for a large number of patients.[1–5] However, their effectiveness, safety and drug persistence in real-life settings may not match those in clinical trials. Recent registry studies suggest that between 14·6% and 58·6% of patients with psoriasis on biologics would not have been eligible for a clinical trial and that safety and efficacy – but not risk of treatment discontinuation – would have been worse.[6,7]

Drug persistence is considered to be an indirect predictor of efficacy and safety,[8,9] and in general, dermatologists consider prolonged drug survival a favourable goal of systemic antipsoriatic treatment both clinically and economically.[10,11] However, this cannot automatically be applied to biologic treatment. A drug may be discontinued for many reasons (both related and unrelated to the drug's performance). These include safety reasons (i.e. adverse events),[12,13] pregnancy, complete remission or lack of improvement, denial of reimbursement, availability of alternative treatment options, and increasing expectations of physicians and patients or unconsidered patient needs[14–16] as more and more drugs become available. This is best reflected in drug survival, which encompasses all these reasons and factors. Indeed, in rheumatology, prolonged drug survival has been associated with the insufficient availability of effective alternative treatments.[17,18] Therefore, it is not surprising that recent studies have aimed at identifying patient characteristics that can predict drug survival.

So far, female gender and obesity have been identified as factors in decreased persistence of biologic therapy, while psoriatic arthritis is a factor associated with prolonged persistence in patients receiving antitumour necrosis factor-α or anti-IL-12/23 treatment.[12,19] Biologic non-naïvety is another well-known factor influencing drug persistence and it even seems that persistence is getting worse with the number of biologics that patients have received previously.[20,21] Whereas the impact of gender and concomitant psoriatic arthritis on biologic-specific drug survival has already been studied for adalimumab, etanercept and ustekinumab,[12,21–27] it has not been studied for the IL-17 inhibitors secukinumab and ixekizumab.

Therefore, we aimed to investigate the time-dependent drug survival rates of biologics, taking into account that they may be influenced by the overall number of available biologics, and then determine drug survival rates in the era of anti-IL-17 antibodies. Additionally, we aimed to determine whether the introduction of new biologics such as secukinumab and more recently ixekizumab have independently lowered drug survival rates for the remaining biologics.

Methods

Study design

This was an observational retrospective multicentre analysis of clinical data extracted from the Psoriasis Registry Austria (PsoRA). The design of this registry has been described in previous studies.[28–32] This nationwide Austrian database contains data on treatment cycles from patients with psoriasis treated under real-life conditions at six university dermatology departments, eight non-university dermatology departments and 12 dermatology practices. A list of all PsoRA centres is available at www.psoriasisregistry.at.

In the registry, treatment cycle is defined as the time period after a patient's allocation, followed by at least one visit, until last observation or discontinuation of treatment. Continuous prescription of a drug has to be confirmed for every visit recorded in the registry. End of treatment is defined as end of a biologic treatment cycle, which has to be entered in the

database along with the reason for treatment discontinuation. Interrupting a biologic treatment for longer than 12 weeks after the regular drug application interval is considered treatment discontinuation, and restarting thereafter on the same biologic is considered a new treatment cycle (for ustekinumab 24 weeks after last administration). The registry has been approved by the ethics committee of the Medical University of Graz (application number 21-094 ex 09/10), and the present analysis was conducted in accordance with the principles of the Declaration of Helsinki.

Data analysis and statistics

The study population included patients older than 18 years of age who had chronic plaque psoriasis, started a biologic therapy (adalimumab, etanercept, ustekinumab, secukinumab or ixekizumab) after January 2015 (after the introduction of secukinumab into clinical practice), and continued therapy until November 2019, and had at least one follow-up visit with the same treatment, irrespective of previous systemic treatment, psoriatic arthritis or any comorbidities. In addition, data from patients who received ustekinumab before 2015 were analysed to study its drug survival over time. Drug survival for each biologic treatment was calculated using Kaplan–Meier estimates. Treatment cycles for which no end of treatment was recorded were censored. Cox regression analysis was used to test for treatment effects, risk factors and interaction. The relative hazard ratio (HR) for gender, concomitant psoriatic arthritis, biologic naïvety and introduction of new treatments was calculated. Patients in whom the presence of concomitant arthritis was unknown were considered not to have psoriatic arthritis for the purposes of this analysis. To detect time-period effects from the release of new drugs, observation times were divided into the time at risk spent before the release of a new drug (period 1, January 2015 to July 2016) and after the release of the new drug (period 2, July 2016 to November 2019). A cycle extending over both periods was censored at the end of period 1 and considered to have entered period 2 not at time zero but at the time from the beginning of treatment (i.e. the time at which it was censored for period 1) and continuing in period 2 until end of treatment or censoring. Additionally, drug survival of ustekinumab was calculated for the time periods before and after the introduction of secukinumab (19 March 2015) as well as after the initiation of the first ixekizumab treatment (13 July 2016), to determine differences in the drug's survival in the presence of more available treatment options. Survival rates of all available biologics were calculated for the period before and the period after the first patient with ixekizumab treatment had been entered into the registry. The effectiveness of treatment was evaluated in terms of monitoring absolute Psoriasis Area and Severity Index (PASI) values with regard to values reported at each visit (as observed) and per last observation carried forward (LOCF). The chi-squared test was used to determine treatment allocation concerning gender, psoriatic arthritis and biologic naïvety. Calculations were performed by R 3·6·2 (www.r-project.org) using the package 'survival 3·1-8'.

Results

General patient characteristics

At the time of data extraction (30 November 2019), the PsoRA contained data on 4348 patients who had undergone a total of 7002 systemic treatment cycles. Of these, 1572 patients [573 (36·5%) women and 999 (63·5%) men] who had undergone a total of 1848 cycles of biologic treatment beginning after 1 January 2015 were eligible for the current analysis (Table S1; see Supporting Information). Overall, 547 (34·8%) patients had concomitant psoriatic arthritis (Table S1); for 80 patients (84 cycles) the presence of arthritis was unknown. Concomitant arthritis was significantly more frequent in women than men (38·2% vs. 32·8%, $P = 0·035$) (Table S1). The total number of treatment cycles for each biologic is depicted in Table 1, ranging from 96 cycles for etanercept to 662 cycles for ustekinumab. The mean (SD) age at the start of the treatment for a specific cycle in those patients was 45·6 (14·7) years (Table 1). Other patient characteristics at the start of the treatment cycle such as disease duration, weight, body mass index, presence of arthritis and biologic naïvety are also shown in Table 1. Furthermore, differences in treatment allocation dependent on whether a patient had concomitant arthritis or not were observed, with patients with arthritis receiving adalimumab, etanercept, ixekizumab and secukinumab much more frequently than ustekinumab (40·6–57·3% vs. 18·0%) ($P < 0·001$) (Table S2; see Supporting Information). Comorbidity rates among patients treated with ixekizumab or secukinumab were similar, except for hyperlipidaemia (14·3% vs. 20·3%) and obesity (18·5% vs. 12·1%) (Table S3; see Supporting Information). There was no statistically significant difference in treatment allocation for a specific drug between women and men (Tables S4, S5; see Supporting Information). A total of 1028 (55·6%) of the treatment cycles in this study were received by biologic-naïve patients and 820 (44·4%) cycles were administered to patients who had already been treated with at least one biologic (Table S6; see Supporting Information). The IL-17 inhibitors secukinumab and ixekizumab were more frequently administered to biologic non-naïve patients than were adalimumab, etanercept and ustekinumab (62·3% and 52·2% vs. 30·6%, 40·6% and 35·6%, respectively; overall P-value < 0·001) (Table S6).

Drug effectiveness

PASI values at treatment start were documented for 1126 (60·9%) treatment cycles. There were differences in PASI values at treatment start, with patients taking ixekizumab (mean 9·65) and secukinumab (9·60) having the highest PASI followed by ustekinumab (8·20), adalimumab (7·23) and etanercept (6·07) ($P = 0·028$) (Figure 1 and Table S7; see Supporting Information). Ixekizumab showed the highest PASI

Table 1 Characteristics of treated patients (n = 1572) with regard to initiation of a cycle (n = 1848)

Treatment cycles and characteristics	Adalimumab	Etanercept	Ixekizumab	Secukinumab	Ustekinumab	All treatment cycles
Total number of treatment cycles	294	96	406	390	662	1848
Characteristic at start of treatment cycle						
Number (%) of treatment cycles in male patients	189 (64·3)	56 (58·3)	277 (68·2)	229 (58·7)	407 (61·5)	1158 (62·7)
Mean age (SD), years	44·8 (14)	47·5 (14·8)	45·2 (13·7)	47·5 (14·7)	44·7 (15·3)	45·6 (14·7)
Mean PASI (SD) in biologic-naïve patients	7·6 (6·5)	7·2 (8·5)	9·87 (7·33)	9·95 (8·9)	8·47 (6·4)	8·9 (7·3)
Mean PASI (SD) in biologic-non-naïve patients	6·8 (6·7)	7·9 (11·4)	9·6 (6·7)	8·6 (7·9)	9·3 (7·3)	8·95 (7·4)
Number (%) of cycles in patients with arthritis	149 (50·7)	55 (57·3)	165 (40·6)	164 (42·1)	119 (18·0)	652 (35·3)
Mean years (SD) of disease duration	16·5 (12·6)	21 (15·7)	16·4 (11·1)	16·7 (12·2)	16·2 (12·5)	16·6 (12·4)
Mean weight in kg (SD)	85·9 (21·6)	80·1 (22·5)	91·3 (21·1)	84·2 (17·5)	85·8 (20)	86·1 (20·2)
Mean BMI (SD)	28·4 (6·4)	27·9 (8·6)	28·9 (6·1)	27·5 (5·2)	27·5 (6·2)	27·9 (6·1)

PASI, Psoriasis Area and Severity Index; BMI, body mass index.

improvement 3 months after treatment start in patients analysed as observed or with LOCF. The highest long-term PASI improvement (at least until 24 months) was also observed for treatment with ixekizumab, followed by ustekinumab and secukinumab, adalimumab and etanercept (Figure 1 and Table S7).

Drug survival

There were significant differences in drug survival for the different biologics ($P < 0·001$). Overall, the drug survival rate was highest for ustekinumab (Figure 2 and Tables S8, S9; see Supporting Information). In fact, drug survival at 12 months in patients treated with ustekinumab was 89·0%, compared with 86·0% for ixekizumab, 78·1% for secukinumab, 76·5% for adalimumab and 66·0% for etanercept (Table S8). The differences were statistically significant (Table S9) and were sustained or increased up to 48 months (Figure 2). The median survival rate of 50% was reached for etanercept at 27·0 months, for adalimumab at 30·8 months, and for secukinumab at 34·3 months (Figure 2), but not for ixekizumab at its maximum follow-up of 36 months or for ustekinumab at its maximum follow-up of more than 48 months. Of note, the dosage regimen was reported for 599 treatment cycles (32·4%) (Table S10; see Supporting Information). While most of those cycles were initiated with in-label dosage, irrespective of treatment allocation, off-label dosage change was most frequently observed in patients treated with ustekinumab (14·1%) (higher dosage of 90 mg vs. 45 mg subcutaneously and/or shorter administration intervals) (Table S10). Furthermore, when adjusted for time period in the overall cohort, the superiority of ustekinumab vs. ixekizumab vanished

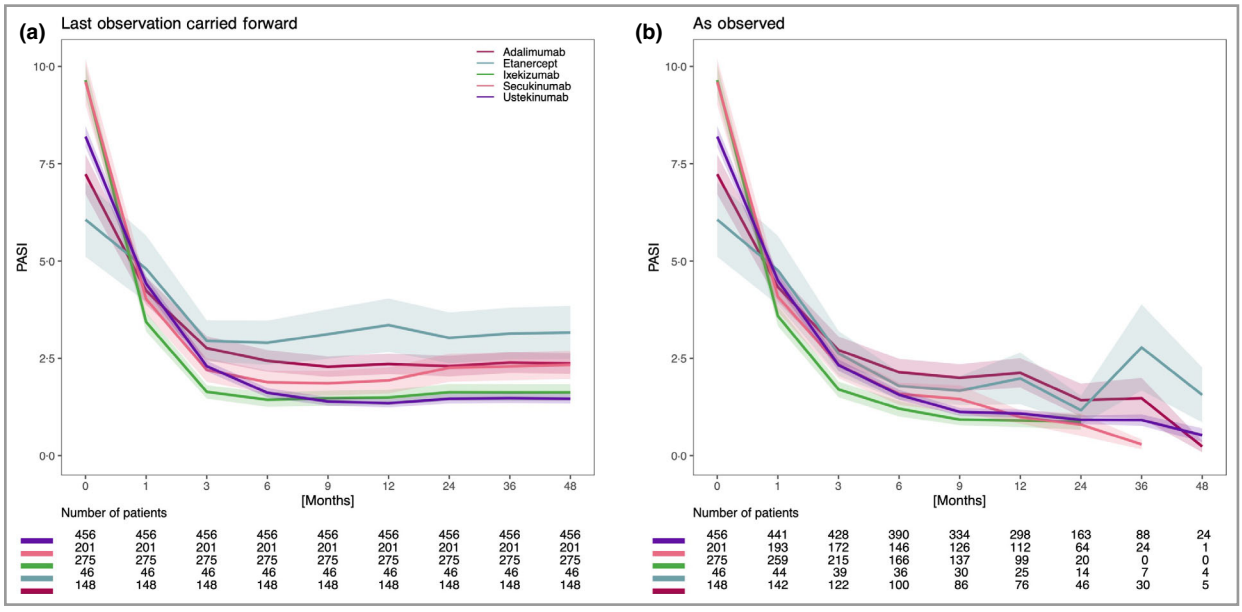

Figure 1 Effectiveness of biologics. Psoriasis Area and Severity Index (PASI) values and 95% confidence interval (see Table S7; Supporting Information) for treatment cycles analysed as last observation carried forward (a) and as observed (b).

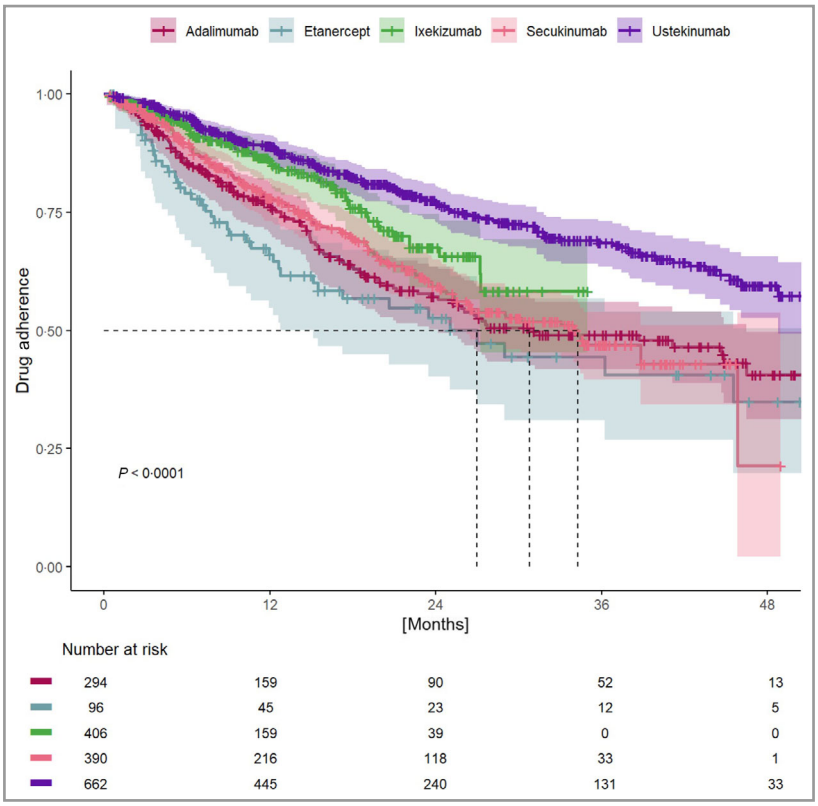

Figure 2 General drug survival rates. Relative drug survival rates (± 95% confidence intervals) of a specific biologic with regard to treatment cycles (n = 1848) using Kaplan–Meier estimates and log-rank tests. Dotted lines indicate timepoints at which 50% of cycles have been stopped for a respective biologic. The dotted lines indicate timepoints at which half of the patients have discontinued a respective treatment.

statistically (P = 0·075) (Figure S1; see Supporting Information). Indeed, ustekinumab's drug survival continuously declined over time (when comparing the periods before secukinumab initiation and before and after ixekizumab initiation) (Figures 3 and 4). Similar declines in drug survival over time were observed for adalimumab, etanercept and secukinumab (Figure 3 and Table S11; see Supporting Information). Overall, the probability that a treatment was discontinued significantly increased after the initiation of ixekizumab (relative HR 1·6, P = 0·001), irrespective of the treatment that had been administered (P = 0·858) (Table S12; see Supporting Information). Analysing drug survival with regard to gender revealed a treatment-independent (P = 0·392) increased risk (relative HR 1·50, P = 0·019) for drug discontinuation in women in overall (Figure 5). Previous biologic treatment also significantly increased the risk for treatment discontinuation (relative HR 2·10, P < 0·001), irrespective of the drug administered (P = 0·367) (Figure 6 and Table S12). After adjustment for biologic naïvety, the gap in drug survival between secukinumab (90·2%) and both ixekizumab (91·6%) and ustekinumab (92·8%) closed at 12 months and beyond (Table S8). The presence of psoriatic arthritis did not significantly influence the risk of treatment discontinuation in patients treated with biologics (P = 0·261) (relative HR 1.12, P = 0·21) (Figure S2 and Table S12; see Supporting Information). The drugs that were administered after initial treatment was stopped are listed in Table S13 (see Supporting Information). Of note, there were a substantial number of intraclass switches in anti-IL-17 drug from secukinumab to ixekizumab, as well as a number of switches to a new class of anti-IL-23-p19 antibodies (guselkumab, risankizumab and tildrakizumab) (Table S13). However, intraclass switching in IL-17 inhibitors is not uncommon, as it may restore clinical efficacy.[33] Overall, the rate at which a previously administered drug was restarted (after an interval of at least 12 weeks after the regularly scheduled administration as defined in the methods) ranged from 2·6% to 19·0% for etanercept, adalimumab, secukinumab, ustekinumab and ixekizumab (Table S13).

Reasons for treatment discontinuation

In total, 544 (29·4%) of 1848 treatment cycles were discontinued. The main reasons for discontinuation were no remission (20·0%) or partial remission (10·3%) (i.e. primary therapeutic failure), loss of efficacy (26·1%) and side-effects (17·3%) in the overall cohort (Table S14; see Supporting Information). However, there were differences in drug discontinuation in the drug-specific analysis (Table S15; see Supporting Information). The treatment stopped most frequently for primary treatment failure (with regard to total cycle number) was etanercept (18·8%), followed by secukinumab (10·8%), adalimumab (10·5%), ustekinumab (9·1%) and

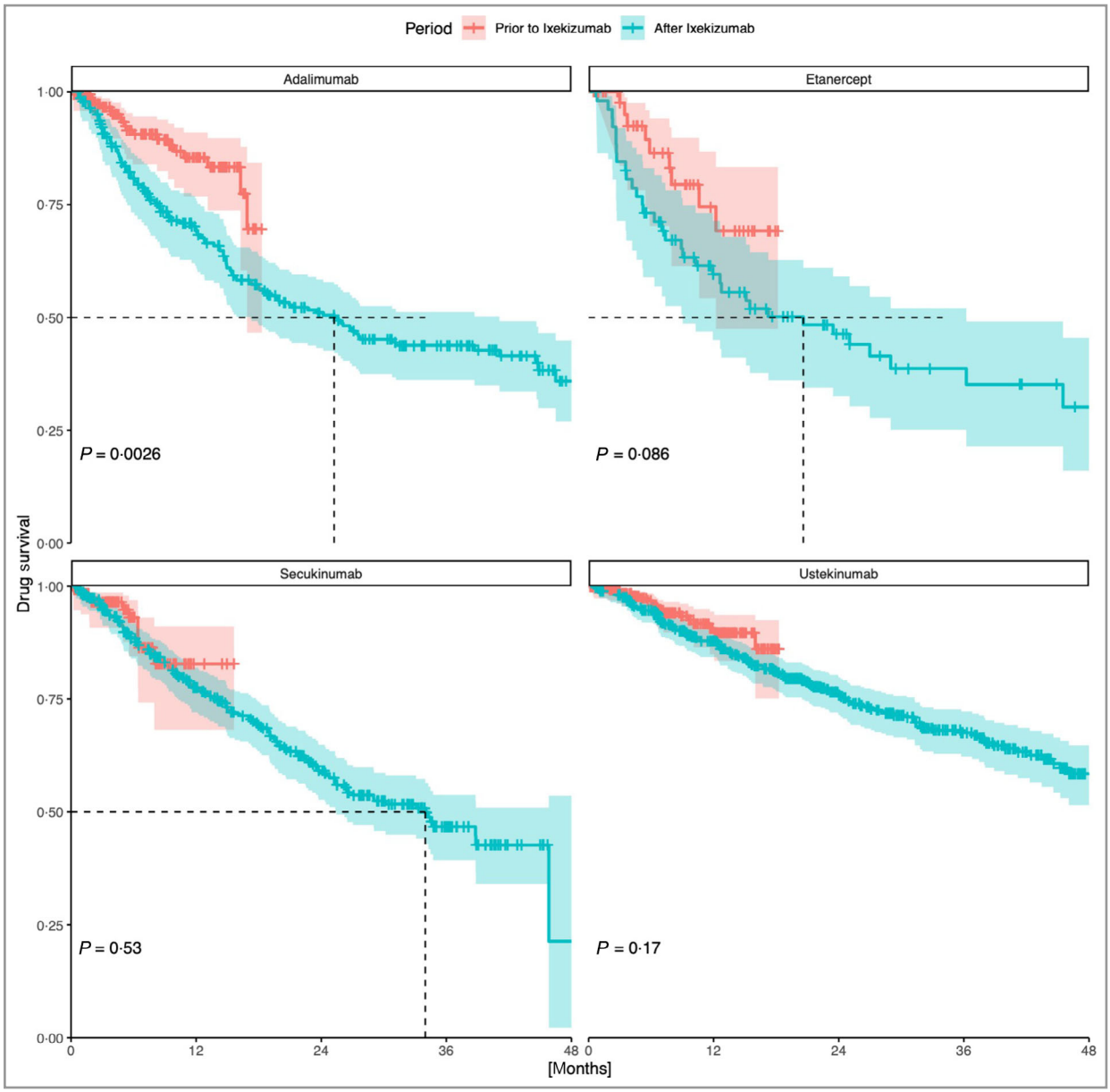

Figure 3 Drug survival prior to and after release of ixekizumab. Relative drug survival rates [± 95% confidence intervals (CIs)] of a specific biologic with regard to treatment cycles that were started prior to or after the initiation of ixekizumab in Austria (13 July 2016) and reported to PsoRA, using Kaplan–Meier estimates and log-rank tests. The red line and its CI represent treatment cyclesin patients in whom treatment was started, administered and stopped between 1 January 2015 and 13 July 2016. The blue line and its CI represent treatment cycles in patients in whom treatment was started any time after 1 January 2015, and continued or stopped after 13 July 2016. Respective P-values are plotted in the graphs. For number of treatment cycles with a specific biologic see Table S11 (Supporting Information). The dotted lines indicate timepoints at which half of the patients have discontinued a respective treatment.

ixekizumab (3·4%) (Table S15). The treatment stopped most frequently for loss of efficacy (with regard to total cycle number) was adalimumab (12·9%); the one stopped least frequently for the same reason was ixekizumab (3·9%) (Table S15). The treatment stopped most frequently because of side-effects (with regard to total cycle number) was secukinumab (6·9%), followed by adalimumab (6·5%), etanercept (5·2%), ixekizumab (4·9%) and ustekinumab (3·5%) (Table S15). The side-effects leading to discontinuation that were reported most frequently were infections, ranging from 0·6% for ustekinumab to 3·1% for secukinumab (Table S16; see Supporting Information). These infections included candida infection in 1·0% of ixekizumab cycles and 0·3% of secukinumab cycles. From a relative point of view, infections were also the most common cause for stopping treatment, ranging from 17·4% for ustekinumab to 45·0% for ixekizumab considering the discontinued cycles per drug only (Table S17; see Supporting Information).

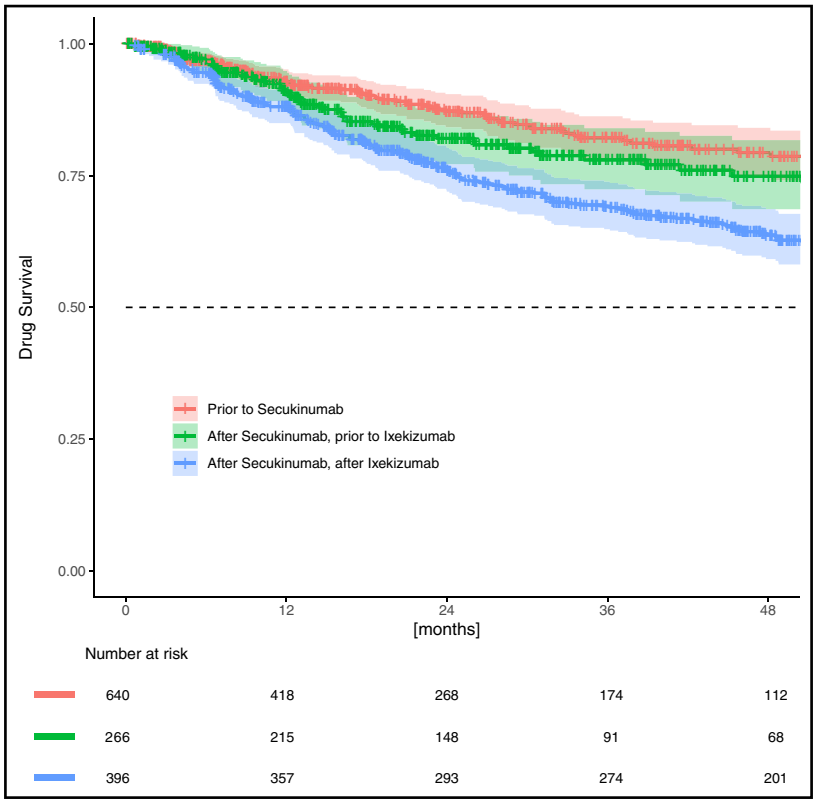

Figure 4 Drug survival of ustekinumab over time. Relative drug survival rates (± 95% confidence intervals) of ustekinumab (n = 1302) with regard to treatment cycles that were started prior to or after the first treatment initiation with secukinumab (19 March 2015) or ixekizumab (13 July 2016) reported in the Austrian Psoriasis Registry (PsoRA), using Kaplan–Meier estimates and log-rank tests. The drug survival rate for ustekinumab was significantly lower (P = 0·006) for the time period after ixekizumab introduction (blue) compared with the time periods prior to ixekizumab (green) and secukinumab (red) introduction (P = 0·305). Note that this analysis contains, besides the 662 ustekinumab cycles administered since January 2015, an additional 640 ustekinumab treatment cycles initiated prior to January 2015, resulting in a total of 1302 cycles. The dotted lines indicate timepoints at which half of the patients had discontinued a respective treatment.

Discussion

This study of 1572 patients and 1848 treatment cycles is one of the larger registry studies that have examined the effect of gender, psoriatic arthritis and biologic naïvety on biologic drug survival, especially with regard to the IL-17 inhibitors.[21,22,24–27,34] It is also one of the largest registry studies so far to compare drug survival for ixekizumab, secukinumab and ustekinumab head to head. Our analysis unambiguously indicates that the time-dependent availability of drugs must be considered when analysing drug survival. When taking into account the IL-17 inhibitor era (i.e. the timespan since the clinical introduction of secukinumab), ustekinumab apparently surpassed all other biologics in drug survival (Figure 2). However, most of the off-label dosage changes were reported for ustekinumab (14·1%). Furthermore, when comparing drug survival rates before and after the release of ixekizumab, the superiority of ustekinumab vanished (Figure S1), well in line with the general decline in drug survival rates of ustekinumab since its introduction in 2009 (Figure 4). Similarly, drug survival rates of adalimumab, etanercept and secukinumab also declined over time at an overall relative HR of 1·60 (P = 0·001) (Figure 3 and Table S12). In agreement with these findings, the drug survival rates of adalimumab and etanercept after the release of ixekizumab that we noted in the present study appeared to be slightly lower than in one of our previous studies for the period between 2004 and 2013·[29] After adjustment for biologic naïvety, the drug survival rates for ustekinumab (92·8%), ixekizumab (91·6%) and secukinumab (90·2%) were closer at 12 months and beyond in biologic-naïve patients.

Overall, the drug-specific survival rates for ustekinumab, adalimumab and etanercept that we have observed in this study compare favourably with previously reported findings.[12,24–27,34] However, the rates for ixekizumab and secukinumab in this study (Table S8) appear to be higher.[20,35,36] Notably, comorbidity rates among patients treated with ixekizumab or secukinumab were similar, except for hyperlipidaemia (14·3% vs. 20·3%) and obesity (18·5% vs. 12·1%) (Table S3). Compared with our findings, a recent Swedish registry study observed a similar median drug survival rate for adalimumab but a worse median discontinuation rate for etanercept (17·5 months vs. 27·0 months).[37] A recent analysis of a smaller dataset from the Slovenian psoriasis registry (with

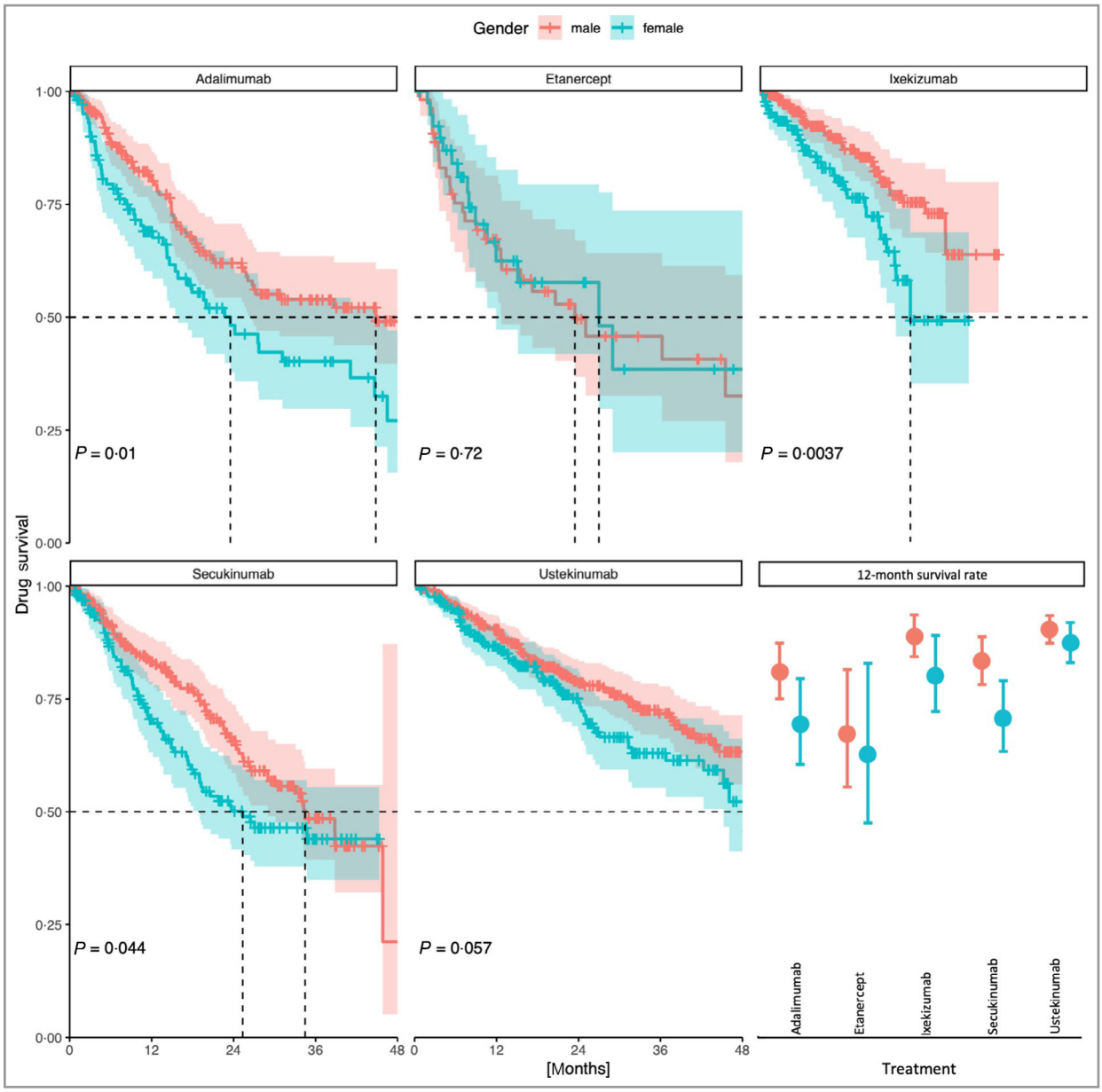

Figure 5 Drug survival rates regarding gender. Relative drug survival rates (± 95% confidence intervals) of a specific biologic with regard to treatment cycles (n = 1848) comparing women and men using Kaplan–Meier estimates and log-rank tests. Respective P-values are plotted in the graphs. Interdependence analysis revealed that the significant influence of gender on drug survival was independent from the administered biologic (see Table S12; Supporting Information). The dotted lines indicate timepoints at which half of patients have discontinued a respective treatment.

regard to IL-17 inhibitors) also found a similar drug survival rate for ustekinumab but lower rates for ixekizumab and secukinumab.[38] Likewise, a recent Italian study found a relatively high survival rate of ustekinumab,[39] similar to the rate for secukinumab, but much higher than the rates for adalimumab, infliximab and etanercept (ixekizumab was not included in the study). Overall, our findings are also consistent with those of a US study (which did not take into consideration time period of application) in which the drug survival rate was higher for ixekizumab than for secukinumab, but in which the rates for both were lower than in our study.[35] Similar results were obtained in a smaller Danish cohort with relatively short follow-up times of 12 months.[20]

According to a recent meta-analysis, previous studies have already identified female gender as an independent risk factor for stopping biologic treatment in psoriasis,[12,19,21,22,27,40] with HRs of 1·22 overall, 1·53 for adalimumab and 1·56 for etanercept.[19] In comparison, the gender HR in our present study was 1·50 (P = 0·019), indicating that women were more likely than men to discontinue biologic treatment. We

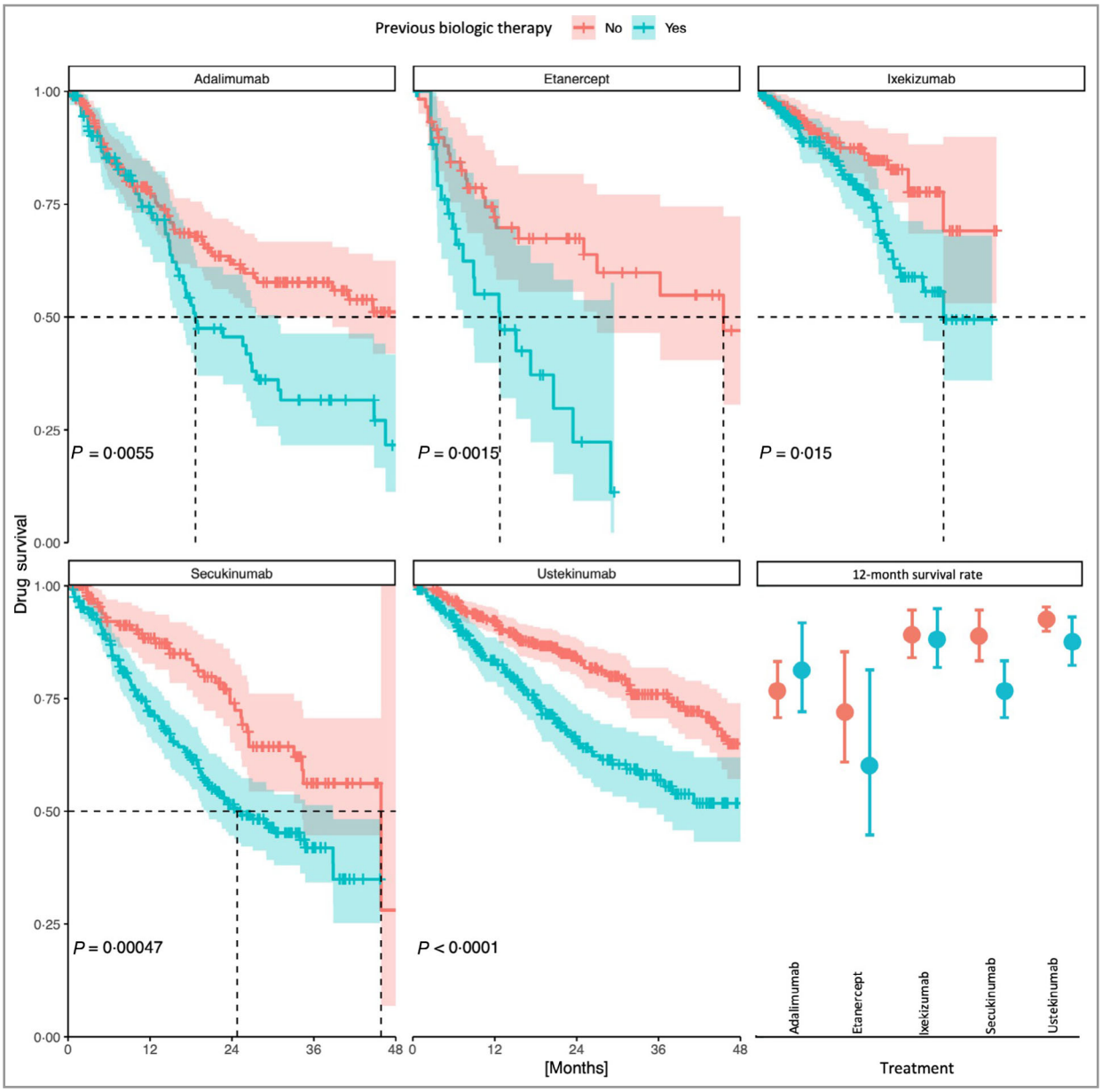

Figure 6 Drug survival rates regarding previous biologic treatment. Relative drug survival rates (± 95% confidence intervals) of a specific biologic with regard to treatment cycles (n = 1848) comparing naïve and non-naïve patients using Kaplan–Meier estimates and log-rank tests. Respective P-values are plotted in the graphs. Note the relative drug survival rate at 12 months for patients entering a cycle naïvely was 76·7% for adalimumab, 72·1% for etanercept, 89·1% for ixekizumab, 88·8% for secukinumab and 92·5% for ustekinumab, respectively (see also Table S8; Supporting Information). The dotted lines indicate timepoints at which half of patients have discontinued a respective treatment.

also observed a slightly increased HR of 1·12 for stopping treatment in patients with psoriatic arthritis; however, this was not statistically significant (Figure S2 and Table S12).[19,41]

Previous biologic treatment is a well-known risk factor for drug discontinuation[42] and appears to be increasing the rate of drug discontinuation as patients receive more and more drugs.[20] For instance, a study from 2015 revealed an increased HR of 1·24 for biologic-naïve patients remaining on biologic treatment.[42] However, in a recent British registry analysis, previous biologic treatment strongly influenced drug survival. While previous exposure to a biologic predicted discontinuation in secukinumab- and ustekinumab-treated patients, it was linked to increased drug survival in adalimumab-treated patients.[41] In comparison, the risk of treatment discontinuation after previous biologic exposure in our present study was 2·10 (P < 0·001), irrespective of the treatment given (Figure 6 and Table S12).

Therefore, it is very likely that the relatively worse drug survival rate for secukinumab overall seen in our study (Figure 1) was due to the high percentage (62·3%) of non-naïve patients being treated with it (compared with 30·6% receiving adalimumab, 35·6% receiving ustekinumab, 40·6% receiving

etanercept, and 52.2% receiving ixekizumab) (Table S6). Consistent with this notion, the loss of efficacy rate for secukinumab was 10·2% compared with 3·9% for ixekizumab (Table S15). The similar drug survival rates for secukinumab and ustekinumab seen in our study compare favourably with those reported in a British study (72·9% biologic-naïve treatment cycles of secukinumab and 74·8% of ustekinumab).[41]

The main reasons for treatment discontinuation in the present study were primary treatment failure, secondary loss of efficacy, side-effects and patient request. However, the frequency of those reasons for treatment discontinuation differed slightly depending on the drug used. The rate of primary treatment failure was highest for etanercept (18·8%); that of secondary loss of efficacy, highest for adalimumab (12·9%); and that of side-effects, highest for secukinumab (6·9%) (Table S15). A recent meta-analysis revealed worse tolerability of ixekizumab compared with secukinumab.[43] Analysis of confounding factors in our study revealed hardly any differences among patient characteristics; however, treatment discontinuation due to side-effects was relatively low across all drugs (Table S15). Overall, the most common side-effect was infection (0·6% for ustekinumab, 1·0% for etanercept, 2·0% for adalimumab, 2·2% for ixekizumab and 3·1% for secukinumab) (Table S16).

Regarding study limitations, beside the registry's retrospective design, most of the data reported to PsoRA come from tertiary treatment centres caring for patients with moderate-to-severe psoriasis. Thus, drug survival among patients with psoriasis in Austria might differ slightly. Because this analysis included data from patients treated through November 2019, it is possible that IL-23p19 inhibitors, clinically introduced in Austria in early 2019, may have influenced drug survival rates. However, this was not taken into consideration in this analysis. This may have some implications for our analysis of ixekizumab drug survival rates as IL-23p19 inhibitors are the most common drugs administered in patients failing ixekizumab (32·8%), while ixekizumab was the most frequently prescribed drug after failing adalimumab (25·7%), ustekinumab (28·4%) and secukinumab (41·1%) (Table S13).

In conclusion, this study contributes to the understanding of biologic drug survival in psoriasis. In Austria, biologics approved as first-line therapy for moderate-to-severe psoriasis are usually reimbursed only after conventional (systemic) treatments have been tried. However, until very recently, there have been no economic restrictions on the selection of biologic drug once the decision is made to move from conventional to biologic antipsoriatic treatment. Because this may not be the case in other countries,[44] our results offer a nonbiased, real-world analysis of outcome and the persistence of biologic treatments independent of insurance guidelines. The fact that gender and biologic non-naïvety affects drug survival rates in a similar fashion for all biologic treatments (independent of the type of drug) may help both patients and clinicians in treatment decision-making. Most importantly, because the availability of alternative treatment options strongly affects drug survival rates of biologics, the timepoints at which newer biologics become available must be considered when analysing and comparing drug survival rates.

Acknowledgments

We thank the patients participating in PsoRA and all members of PsoRA (see https://psora.medunigraz.at/) who provided data for this analysis. Special thanks go to Matthias Wagner, Vienna, for development of the original electronic PsoRA database; Maximilian Errath for technical support; and Andrea Berghold, Department Chair, Institute for Medical Informatics, Statistics and Documentation for continuous support in further development of the PsoRA database. We also thank Martina Praszl-Posch and Kirsten Sommer for support of data entry into the PsoRA database, Honnavara N. Ananthaswamy, Houston, TX, for critical reading of the manuscript, and Jude Richard, Austin, TX, for editing of the manuscript. This work has been conducted as part of a doctoral thesis (T.G.).

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Appendix Conflicts of Interest

T.G. has received a travel grant from Novartis. W.S. has received speaker and consulting honoraria from Abbvie, Almirall and Novartis. C.J. has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Mallinckrodt/Therakos, Novartis, Pfizer and 4SC. W.W. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Galderma, Janssen, Leo Pharma, Merck Sharp & Dohme, Novartis, Pelpharma, Pfizer, Sandoz and UCB. C.K. has received travel refunds from Almirall, Celgene, Janssen and Pelpharma and consulting honoraria from Lilly and Novartis. P.G.S. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Actelion, ALK, Almirall, Amgen, Celgene, Eli Lilly, Galderma, Gilead, Janssen, Leo Pharma, Maruho, Merck Sharp & Dohme, Novartis, Pfizer, Sandoz and UCB. K.P. has received speaker and consulting honoraria from AbbVie, Eli Lilly, Janssen and Novartis; and travel refunds from AbbVie, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma and Novartis. A.M. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Almirall, Amgen GmbH, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis and Pfizer. M.S.-B. has received speaker and consulting honoraria from AbbVie, Celgene, Lilly, Janssen and Novartis. L.R. has received speaker and/or consulting honoraria from AbbVie, Almirall, Janssen, Leo Pharma, Lilly, MSD, Novartis and Pfizer. G.R. reports personal fees from AbbVie, Eli Lilly, Janssen, Novartis and Pfizer, and grants and personal fees from Leo Pharma, all during the conduct of the study as well as outside the submitted work. K.W.-S. received speaker and/or consulting honoraria and/or travel refunds from AbbVie, Amgen GmbH, Eli Lilly, Janssen, Leo Pharma, Novartis and Pfizer. H.S. received honoraria/travel refunds as speaker/consultant from AbbVie, Almirall, Celgene, Janssen, Leo, Lilly, Novartis, Pfizer and UCB. M.I. has received speaker and consulting honoraria and travel refunds from AbbVie, Eli Lilly, Janssen, Novartis and Pfizer. B.L.-A. reports personal fees for advisory board meetings from AbbVie, Eli Lilly, Leo and Novartis, outside the submitted work. I.V. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Almirall, Amgen GmbH, Celgene, Eli Lilly, Janssen, Leo Pharma, Merck Sharp & Dohme, Novartis, Pfizer and Sandoz. W.H. has received research grants, speaker and consulting honoraria from AbbVie, Almirall, Amgen GmbH, Bencard, Celgene, Eli Lilly, Janssen, Leo Pharma and Novartis. F.T. reports personal fees from AbbVie, Almirall, Amgen, Eli Lilly, Janssen-Cilag, Leo Pharma and Novartis, from outside the submitted work. W.S. reports personal fees from AbbVie, Almirall and Novartis. P.W. has received research grants, speaker and/or consulting honoraria and/or travel refunds from AbbVie, Almirall, Amgen GmbH, Celgene, Eli Lilly, Janssen, Leo Pharma, Merck Sharp & Dohme, Novartis, Pfizer and Sandoz. The remaining authors have nothing to disclose.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Gender prevalence of psoriatic arthritis.

Table S2 Treatment allocation in patients with psoriatic arthritis.

Table S3 Comorbidities in treatment cycles with interleukin (IL)-17 inhibitors.

Table S4 Treatment allocation regarding gender.

Table S5 Gender allocation regarding treatment.

Table S6 Treatment allocation regarding biologic naïvety status.

Table S7 Treatment effectiveness.

Table S8 Drug survival at 12 months with regard to different characteristics.

Table S9 Statistical comparison of drug survival.

Table S10 Dosage regimen of biologic treatments.

Table S11 Treatment cycles prior to and after ixekizumab initiation.

Table S12 Interdependence analysis of prescribed biologics.

Table S13 Treatment after stop of initial therapy.

Table S14 Drug-specific reason for drug discontinuation.

Table S15 Reason for drug discontinuation.

Table S16 Reason for treatment discontinuation due to side-effect.

Table S17 Drug-specific reason for treatment discontinuation due to side-effect.

Figure S1 Drug survival of ixekizumab and ustekinumab.

Figure S2 Drug survival regarding concomitant psoriatic arthritis.

Effectiveness and clinical predictors of drug survival in psoriasis patients receiving apremilast: A registry analysis

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Background: Little is known about the effectiveness and drug survival associated with apremilast under real-world conditions.

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Funding sources: Psoriasis Registry Austria (PsoRA) was supported by unrestricted research grants or educational grants from the following pharmaceutical companies: AbbVie (2015-2020), Amgen GmbH (2019-2020), Almirall (2017-2020), Celgene (2016-2018), Eli Lilly (2015-2020), Janssen (2014-2016), Leo Pharma (2014-2020), Novartis (2019), Merck Sharp & Dohme (2014), Sandoz (2019-2020), and Pfizer (2008-2018).

Conflicts of interest: Dr Wolf has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Amgen GmbH, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz, and Pfizer. Dr Graier has received a travel grant from Novartis. Dr Jonak has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Almirall, Celgene, Eli Lilly, Janssen, LEO Pharma, Mallinckrodt/Therakos, Novartis, Pfizer, and 4SC. Dr Hoetzenecker has received research grants and speaker and consulting honoraria from AbbVie, Amgen GmbH, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, and Bencard. Dr Ratzinger reports personal fees from Eli Lilly, personal fees from AbbVie, personal fees from Novartis, grants and personal fees from Leo, personal fees from Janssen, personal fees from Pfizer; personal fees from Eli Lilly, AbbVie, Novartis, Janssen, and Pfizer; and grants and personal fees from Leo, outside the submitted work. Dr Prillinger has received speaker and consulting honoraria from AbbVie, Eli Lilly, Janssen, and Novartis and travel refunds from AbbVie, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, and Novartis. Dr Sator has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Actelion, Amgen, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz, Maruho, ALK, Galderma, UCB, Gilead, and Pfizer. Dr Skvara received honoria/travel refunds as speaker/consultant from AbbVie, Almirall, Celgene, Janssen, Leo, Lilly, Novartis, Pfizer, and UCB. Dr Mlynek has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Amgen GmbH, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, and Pfizer. Dr Vujic has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Amgen GmbH, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz, and Pfizer. Dr Saxinger has received speaker and consulting honoraria from Almirall, AbbVie, and Novartis. Dr Kölli has received travel refunds from Janssen, Celgene, Almirall, and Pelpharma and consulting honoria from Novartis and Lilly. Dr Schütz-Bergmayr has received speaker and consulting honoria from AbbVie, Celgene, Lilly, Janssen, and Novartis. Dr Weger has received speaker and/or consulting honoraria and/or travel refunds from AbbVie, Amgen GmbHm Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz, and Pfizer.

IRB approval status: The registry was approved by the ethics committee of the Medical University of Graz (application number 21-094 ex 09/10).

Accepted for publication October 18, 2020.

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2666-3287

https://doi.org/10.1016/j.jdin.2020.10.012

Objective: To investigate the influence of patient and disease characteristics on drug survival associated with apremilast and to elucidate clinical effectiveness with regard to the psoriasis area and severity index (PASI) reduction.

Methods: This was an observational, retrospective, multicenter analysis from the Austrian Psoriasis Registry.

Results: Data from 367 patients were eligible for analysis. The 12-month drug survival rate associated with apremilast (ie, the proportion of patients on the drug) was 57.3% and decreased significantly in patients younger than 40 years (relative hazard ratio = 1.49, P = .007918). Sex; concomitant arthritis; previous biologic therapy; obesity; and palmoplantar, scalp, nail, and intertriginous involvement did not significantly affect drug survival. At 12 months, the response rates in patients receiving apremilast per protocol with a PASI of 50, 75, 90, and 100 were 80.0%, 56.4%, 38.2%, and 22.7%, respectively.

Limitations: Inclusion of a substantial number of patients with no record of absolute PASI at study entry and lack of PASI reduction follow-up data of 103 patients (28.1%) after starting apremilast treatment.

Conclusion: Apremilast is a robust antipsoriatic drug for which the drug survival is not strongly influenced by most patient- or disease-related factors except age. Drug survival is significantly shorter in patients younger than 40 years. (JAAD Int 2021;2:62-75.)

Key words: apremilast; drug survival; psoriasis.

INTRODUCTION

Since its introduction in Europe in 2015, the antipsoriatic drug apremilast has become a valuable treatment option for both moderate-to-severe plaque psoriasis and psoriatic arthritis.[1-4] It is especially useful for patients in whom the use of biologic drugs is to be avoided (eg, those with cancer, latent tuberculosis infection, or infective hepatitis)[5-7] or in those with psoriasis-related diseases such as palmoplantar pustulosis.[8] However, little is known about the drug survival associated with apremilast (ie, the proportion of patients on apremilast treatment at certain time points), effectiveness, and safety in real-world patients.[9-14] Biologic treatments for psoriasis tend to perform more poorly in real-world settings than in clinical trials. Therefore, it is important to evaluate the long-term effectiveness and drug survival of small molecules such as apremilast.[15-18]

We use the term "drug survival" as it best reflects real-life outcomes by encompassing many reasons for treatment discontinuation that are both related and unrelated to the drug performance, including safety reasons[19,20] (ie, adverse events), pregnancy, complete remission or lack of improvement, denial of reimbursement, availability of alternative treatment options, increasing expectations of physicians and patients, or unconsidered patient needs.[21-23]

CAPSULE SUMMARY

- Little is known about the effectiveness and factors influencing the drug survival of apremilast.
- Apremilast drug survival is not strongly influenced by most patient or disease-related factors. However, drug survival is significantly shorter in patients younger than 40 years of age.

Most biologics have similar overall drug survival rates (per drug within a certain range), but the 12-month survival rates of apremilast range widely by study, from 2.6% to 55.4%.[24,25] Decreased biologic drug survival is associated with female sex, previous biologic exposure, and obesity.[26] For most biologics, metabolic conditions (ie, hypertension, diabetes, and metabolic syndrome and its associated comorbidities) increase the risk of treatment discontinuation, although this was not the case for apremilast in a previous study.[27] However, 1 study has shown that the risk of apremilast discontinuation does increase in obese patients receiving it [hazard ratio (HR): 1.2].[25] The risk of apremilast discontinuation also appears to increase in patients with palmoplantar pustulosis suffering from depression[8] but not in patients with concomitant psoriatic arthritis.[28] Note, however, that most studies of apremilast drug survival (except 1 study from Spain with 377 patients)[25] enrolled relatively few patients (ie, 35, 94, and 138 patients) and were therefore insufficiently powered to fully determine what parameters influence drug survival.[8,28,29]

Abbreviations used:

HR: hazard ratio
LOCF: last observation carried forward
PASI: psoriasis area and severity index
PP: per protocol
PsoRA: Psoriasis Registry Austria
SD: standard deviation

Therefore, we aimed to evaluate the influence of patient and disease characteristics on apremilast drug survival and the effectiveness of apremilast in reducing the extent and severity of psoriasis in a large psoriasis registry.

METHODS

Analytical design

This study was an observational retrospective multicenter analysis of clinical data extracted from the Austrian Psoriasis Registry (PsoRA) on November 30, 2019. The design of this nationwide Austrian database has been described previously.[30-34] Detailed information about PsoRA is available at www.psoriasisregistry.at. The registry defines 1 treatment as the time from a patient's allocation to a specific therapy, followed by at least 1 visit, until the last observation or discontinuation of treatment. For every visit entered in the registry, the continuous prescription of a drug has to be confirmed; otherwise, the reason for treatment discontinuation has to be entered. PsoRA also collects data on the psoriasis area and severity index (PASI), which can be entered at the start of treatment and at every recorded visit. This allows the automatic calculation of the percent PASI change from baseline, ranging from complete remission (PASI 100) to partial remission (PASI 90, PASI 75, PASI 50, and PASI <50) to worsening. For patients with a missing PASI at baseline (at treatment start), the PASI reduction category can be manually entered at each visit thereafter. The registry was approved by the ethics committee of the Medical University of Graz (application number 21-094 ex 09/10). The present analysis was conducted in accordance with the principles of the Declaration of Helsinki.

Data analysis and statistics

All patients >18 years of age who had psoriasis of any clinical type started apremilast before November 2019 and had at least 1 follow-up visit were eligible for this study, irrespective of previous systemic treatment, psoriatic arthritis, or comorbidities. Drug survival was calculated using Kaplan-Meier estimates and log-rank tests. Patients were censored at the last date of follow-up if the end of treatment had not occurred until then. Relative HRs were calculated for patient characteristics [sex, age at therapy start (<40 vs ≥40 years of age), body mass index (BMI, <30 vs ≥30), concomitant psoriatic arthritis, biologic naïvety], and disease characteristics (palmar and/or plantar, scalp, nail, or inverse involvement). For the purposes of this analysis, patients with an unknown history of concomitant arthritis were considered not to have psoriatic arthritis.

The effectiveness of apremilast treatment was evaluated in terms of the absolute change in PASI and reduction in PASI. The change in PASI was calculated and analyzed per protocol (PP) and per last observation carried forward (LOCF) together with worst-case analysis by considering all patients with no follow-up as treatment failures (ie <PASI 50). Patients included in the PP analysis received no concomitant systemic therapy or phototherapy; for those included in the LOCF analysis, we carried forward their PASI score from the last visit at discontinuing apremilast or starting concomitant systemic therapy or phototherapy. The chi-square test was used to test for differences in concomitant psoriatic arthritis prevalence by sex and for differences in treatment discontinuation by age at treatment start (<40 vs ≥40 years of age). Calculations were performed using R 3.6.2 (www.r-project.org) with the statistical analysis package survival 3.1-8.

Table I. Patient characteristics

Number of patients	367
Women (%)	138 (37.6)
Men (%)	229 (62.4)
Age (years), mean (SD)	50.0 (±15.0)
Age < 40 years (%)	103 (28.1)
Number (%) of patients with psoriatic arthritis*	89 (24.3)
BMI, mean (SD)	28.5 (±6.3)
PASI, mean (SD)	7.0 (±6.4)
PASI (non-naïve), mean (SD)	8.0 (±7.6)

BMI, Body mass index; *PASI*, psoriasis area and severity index; *SD*, standard deviation.
*For 20 (5.4%) patients, presence and/or history of psoriatic arthritis was unknown.

Table II. Prevalence of psoriatic arthritis*

	Number (%) of patients		
Sex	**All**	**Without arthritis**	**With arthritis**
Male	229	179 (78.2)	50 (21.8)
Female	138	99 (71.7)	39 (28.3)

*Prevalence numbers (percentages) of all patients (N = 367) regarding concomitant arthritis and sex. A chi-square test indicated no significant differences between patients with or without psoriatic arthritis with respect to sex ($P = .21$).

Table III. Psoriasis types

Psoriasis type	Plaque	Guttata	Erythrodermic	Pustular	Palmar and/or plantar	Inverse	Nails	Scalp
Plaque	**322***							
Guttata	11	**16**						
Erythrodermic	4	1	**4**					
Pustular	4	NA	NA	**10**				
Palmar and/or plantar	17	NA	1	10	**41**			
Inverse	34	3	1	1	2	**37**		
Nails	73	1	0	3	10	19	**91**	
Scalp	69	3	0	1	2	18	35	**74**

NA, Not applicable.
*Numbers in bold represent the total numbers of patients with certain types of psoriasis. Some patients had more than one type of psoriasis thus the total number of specific types of psoriasis exceeds the total number of patients (N = 367).

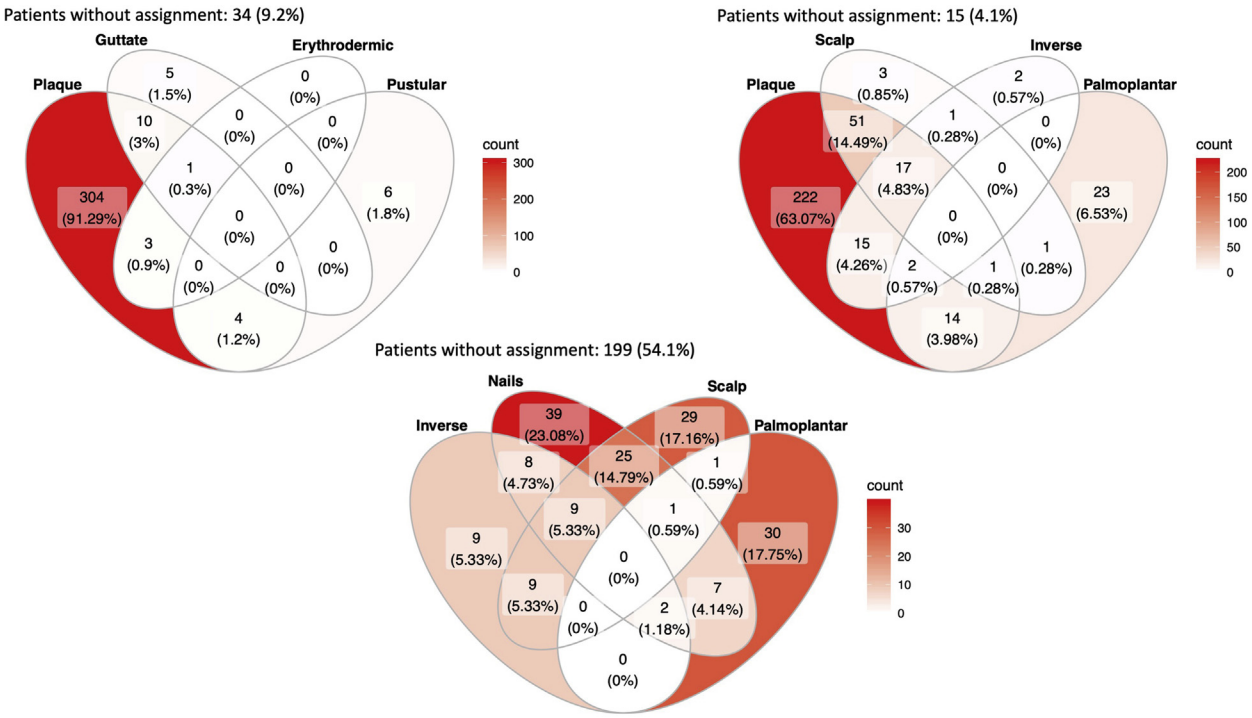

Fig 1. Distribution of psoriasis types. Distribution numbers (%) of patients regarding psoriasis types and body site involvement (N = 367).

RESULTS

General patient characteristics

At the time of data extraction, PsoRA contained data on 4348 patients who had undergone a total of 7002 systemic treatments. A total of 367 patients, including 138 (37.6%) women and 229 (62.4%) men, had received apremilast and were eligible for this analysis (Table I), and at least 1 follow-up visit had been recorded for 264 (71.9%) patients. Concomitant psoriatic arthritis was present in 89 (24.3%) patients and of unknown status in 20 patients (5.4%) (Table I). The prevalence of psoriatic arthritis did not differ by sex (P = .21) (Table II). At the start of apremilast treatment, the mean age (standard deviation, SD) was 50.0 years ± 15.0, and a large proportion of patients (28.1%) were <40 years of age (Table I). Other characteristics of the patients at the start of treatment, such as disease duration, weight, BMI, and concomitant psoriatic arthritis, are summarized in Table I. The most common psoriasis type was plaque (322 patients, 87.7%). Nail psoriasis or involvement was present in 91 (24.8%) patients, and scalp psoriasis or involvement was present in 74 (20.2%) (Table III and Fig 1). Previous treatments had been administered to 305 (83.1%) of patients, of which UVB phototherapy (20.3%), fumaric acid (19.6%), methotrexate (20.1%), and biologics (15.5%) were most frequent (Table IV).

Table IV. Previous treatments

Previous systemic treatment	Number (%) of patients with previous systemic treatment or not*	Type of treatment		Number (%) of administered treatments†
Yes	305 (83.1)	Phototherapy	UVB	87 (20.3)
			PUVA	49 (11.4)
		Conventional systemic	Cyclosporine	6 (1.4)
			Fumaric acid	84 (19.6)
			Methotrexate	86 (20.1)
			Retinoids	30 (7.0)
		Biologics	Adalimumab	16 (3.7)
			Etanercept	19 (4.4)
			Golimumab	1 (0.2)
			Infliximab	2 (0.5)
			Ixekizumab	1 (0.2)
			Secukinumab	10 (2.3)
			Ustekinumab	18 (4.2)
		Other		19 (4.4)
		Total number of treatments		428 (100)
No	62 (16.9)	NA		NA

NA, Not applicable; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.
*Percentages of patients with (N = 305, 83.1%) and without (N = 62, 16.9%) therapy before starting apremilast.
†Certain patients received more than one previous treatment; thus the total number of specific treatment (N = 428) for psoriasis exceeds the total number of patients who had received previous treatment.

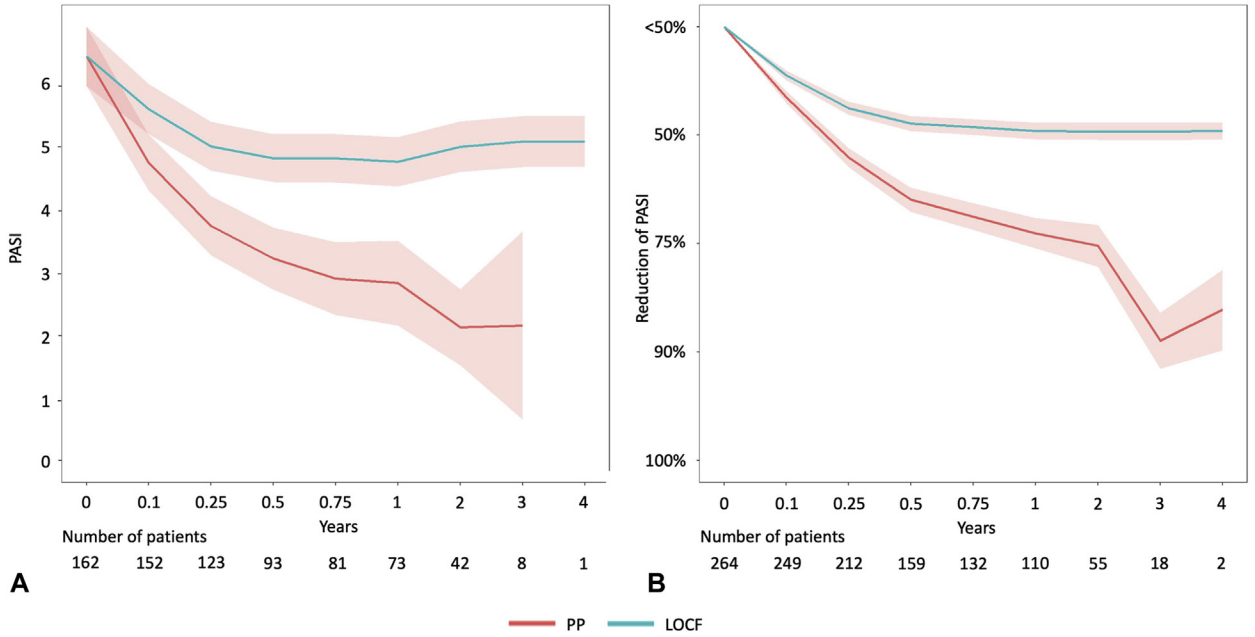

Fig 2. Effectiveness of apremilast. **A**, Absolute PASI value (± 95% confidence interval) and (**B**) mean PASI reduction score (± 95% confidence interval) plotted over time for patients analyzed in PP (*red line*) and LOCF (*blue line*). *LOCF*, Last observation carried forward; *PASI*, psoriasis area and severity index; *PP*, per protocol.

Effectiveness

PASI values at the start of treatment were documented for 162 (44.1%) patients. The mean (SD) PASI of those patients at treatment start was 6.48 (±6.37) (Fig 2 and Table V). In the PP analysis, the mean (SD) PASI was 3.76 (±5.58) at 3 months and improved to 2.84 (±6.13) at 12 months. In the LOCF analysis, the mean (SD) PASI was 5.04 (±5.96) at 3 months and did not improve much until 12 months and beyond (until last observation) (Fig 2 and Table V).

Table V. Effectiveness of apremilast

Timepoint (months)	PASI, mean (SD)		PASI reduction category, mean (SD)	
	PP	LOCF	PP	LOCF
0	6.48 (6.37)	6.48 (6.37)	NA	NA
3	3.76 (5.58)	5.04 (5.96)	3.79 (1.33)	4.25 (1.26)
6	3.24 (5.02)	4.85 (5.94)	3.40 (1.46)	4.07 (1.48)
12	2.84 (6.13)	4.79 (6.21)	3.09 (1.54)	4.03 (1.54)
24	2.14 (4.15)	5.03 (6.43)	2.98 (1.50)	4.03 (1.58)
36	2.16 (4.50)	5.12 (6.46)	2.11 (1.14)	4.03 (1.62)
48	NA	5.12 (6.48)	2.39 (0.55)	4.04 (1.61)

LOCF, Last observation carried forward/worst-case scenario; *NA*, not applicable; *PASI*, psoriasis area and severity index; *PP*, per protocol; *SD*, standard deviation. PASI reduction category is defined as follows: 5 (<50%), 4 (50% to <75%), 3 (75% to <90%), 2 (90% to <100%) and 1 (100%).

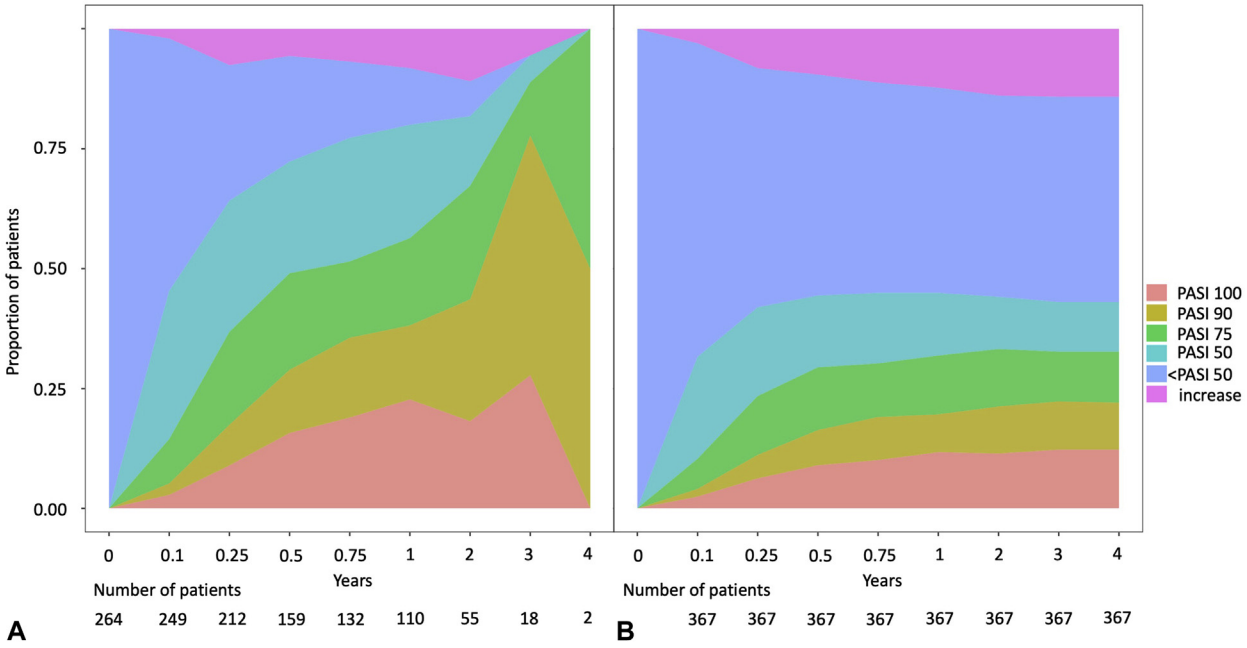

Fig 3. Achievement of skin goals. Relative number of PP (**A**) and LOCF/worst-case scenario (**B**) patient treatment cycles in which a certain PASI improvement was achieved, plotted over time. *LOCF*, Last observation carried forward; *PASI*, psoriasis area and severity index; *PP*, per protocol.

Table VI. Achievement of treatment goals

Timepoint (months)	Number of patients (PP/LOCF)	Percentage of patients achieving a certain PASI reduction (PP/LOCF)					
		PASI 100	>PASI 90	>PASI 75	>PASI 50	<PASI 50	Increase of PASI
3	212/367	9.0/6.3	17.5/11.2	36.8/23.5	64.2/42.0	28.3/49.9	7.5/8.2
6	159/367	15.7/9.0	28.9/16.4	49.0/29.5	72.3/44.5	22.0/46.0	5.7/9.5
12	110/367	22.7/11.7	38.2/19.6	56.4/31.9	80.0/45.0	11.8/42.8	8.2/12.3
24	55/367	18.2/11.4	43.7/21.2	67.3/33.2	81.8/44.1	7.3/42.0	10.9/13.9
36	18/367	27.8/12.3	77.8/22.4	88.9/32.8	94.5/43.2	NA/42.8	5.6/14.2
48	2/367	NA/12.3	50.0/22.1	100/32.7	NA/43.1	NA/42.8	NA/14.2

LOCF, Last observation carried forward; *NA*, not applicable; *PASI*, psoriasis area and severity index; *PP*, per protocol.

In the PP analysis, the mean (SD) PASI reduction score was 3.79 (±1.33) at 3 months, which improved to 3.09 (±1.54) at 12 months. In the LOCF analysis, the PASI reduction score was 4.25 (±1.26) at 3 months, which improved slightly to 4.03 (±1.54) at 12 months (Fig 2 and Table V). Three months after

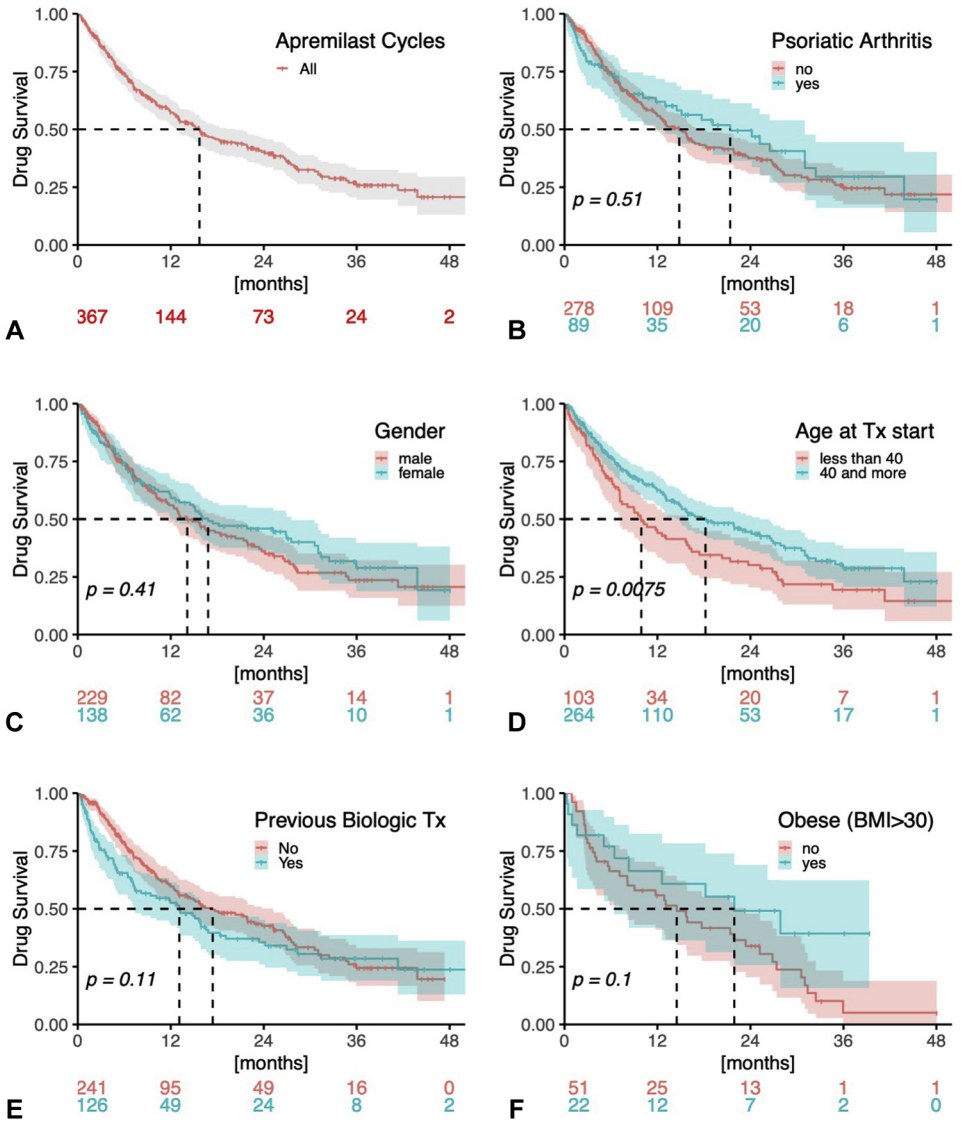

Fig 4. Drug survival of apremilast. Relative drug survival rates (± 95% confidence intervals) of apremilast (N = 367) with regard to different factors possibly influencing survival, using Kaplan-Meier estimates and log-rank tests.

the start of treatment, 9.0% of patients in the PP analysis had achieved a complete remission of psoriatic plaques and 36.8% had achieved a PASI 75 reduction (Fig 3 and Table VI). After the first treatment year, complete remission was observed in 22.7% of patients and partial remission (PASI 75) was observed in 56.4% of patients in the PP analysis (Fig 3 and Table VI).

Drug survival

The overall drug survival rate at 12 months was 57.3%, and the median survival was 15.7 months (Fig 4 and Table VIII). Five patients (1.4%) temporarily paused apremilast treatment (for up to several weeks) mainly to observe whether or not psoriasis would reoccur. Most of the patient characteristics (female sex, concomitant psoriatic arthritis, BMI, and biologic naïvety) and disease characteristics (scalp, nail, inverse or palmar, and/or plantar involvement) analyzed were not significantly associated with an increased risk of drug discontinuation (Figs 4 and 5 and Table VIII). However, an age <40 years at treatment start was significantly associated with an increased risk of treatment discontinuation [relative HR (CI): 1.493 (1.111-2.007), $P = .007918$) (Fig 4 and Table VIII)]. An analysis for confounding factors revealed that a significantly higher proportion of patients <40 years at treatment start suffered from inverse (48.7% vs 7.2%, $P = .004$) and scalp (33.0% vs 15.2%, $P = .000127$) involvement (Table IX). In

Table VII. Drug survival with regard to different characteristics

Characteristics	Drug survival rates [percentage (CI)] for a specific drug*			Median drug survival (CI)
	3 months	6 months	12 months	
Patient characteristics				
Sex				
Male	88.2 (83.1-91.8)	74.2 (67.6-79.6)	56.0 (48.4-62.9)	14.1 (11.5-20-3)
Female	83.0 (75.5-88.3)	74.1 (65.7-80.8)	59.1 (49.8-67.3)	16.8 (12.0-27.5)
Arthritis				
No	88.3 (83.6-91.7)	75.0 (69.0-80.1)	56.4 (49.4-62.8)	14.8 (11.9-17.4)
Yes	79.2 (69.1-86.4)	74.0 (63.2-82.1)	61.9 (49.9-71.8)	21.4 (11.8-31-1)
Age at therapy start				
≥40 years	87.8 (83.2-91.3)	76.7 (70.9-81.6)	62.6 (55.8-68.6)	18.2 (14.5-25.2)
<40 years	81.9 (72.8-88.2)	67.4 (56.9-75.9)	44.0 (3.3-54.2)	9.9 (7.1-15.8)
BMI				
<30	78.4 (64.4-87.4)	66.3 (51.5-77.5)	55.9 (41.0-68.4)	14.5 (7.1-23.4)
≥30	81.8 (58.5-92.8)	77.0 (53.2-89.7)	66.3 (41.8-82.5)	21.9 (6.5-NA)
Biologic naïvety				
No	76.2 (67.6-82.8)	65.5 (56.2-73.3)	52.5 (42.8-61.4)	13.1 (7.3-16.8)
Yes	91.4 (86.9-94.3)	78.6 (72.5-83.5)	59.6 (52.3-66.2)	17.4 (12.9-25.2)
Disease characteristics				
Palmar and/or plantar involvement				
No	86.4 (82.1-89.7)	74.3 (68.9-78.8)	57.5 (51.3-63.1)	15.7 (12.8-19.1)
Yes	82.5 (66.7-91.3)	71.2 (53.9-83.0)	54.0 (35.6-69.2)	15.0 (8.1-35.9)
Scalp involvement				
No	86.9 (82.4-90.4)	75.0 (69.4-79.8)	57.4 (50.9-63.4)	15.8 (12.4-22.8)
Yes	83.1 (72.2-90.1)	70.7 (58.2-80.0)	56.6 (43.4-67.9)	15.1 (7.2-21.8)
Nail involvement				
No	86.5 (81.8-90.1)	74.0 (68.2-79.0)	58.8 (52.2-64.8)	15.9 (13.1-21.9)
Yes	85.2 (75.9-91.1)	74.7 (63.8-82.8)	52.1 (39.5-63.2)	12.9 (9.5-21.8)
Inverse involvement				
No	87.1 (82.9-90.4)	74.7 (69.4-79.2)	57.6 (51.4-63.2)	15.8 (12.9-21.4)
Yes	78.0 (60.8-88.4)	69.1 (51.1-81.6)	54.7 (35.9-70.1)	15.7 (6.4-NA)
Overall survival per drug	86.2 (82.1-89.4)	74.1 (69.1-78.5)	57.3 (51.5-62.6)	15.7 (12.8-20.3)

CI, Confidence interval; *NA*, not applicable.
*Percentages (confidence interval) of drug survival at 12 months (N = 367).

addition, a higher percentage of patients ≥40 years had psoriatic arthritis (29.2% vs 11.7%, $P = .001$).

Reasons for treatment discontinuation

Treatment was stopped early in 195 (53.1%) patients (Table X). In an analysis by the number of stopped treatments, the most common reasons for treatment discontinuation were primary therapeutic failure (ie, no skin improvement at all, 32.3%), side effects (31.3%), and secondary loss of efficacy (ie, relapse after initial skin improvement, 20.5%) (Table X). In an analysis by patient number, gastrointestinal symptoms (8.7%) were the most frequently occurring side effects with regard to the total patient number. Eleven patients (2.9%), including 5 women and 6 men, stopped treatment because of depression (including potential signs of depression such as dysthymia, energy loss, and sleeping changes) (Table XI). Ten of those patients (90.9%) were >40 years of age. One patient in whom depression had been previously diagnosed reported suicidal ideation. Other common side effects leading to treatment discontinuation were headache (2.1%) and infection (1.1%). Seven (1.9%) patients discontinued treatment due to ≥2 side effects (Table XI). An analysis of the reason for treatment discontinuation (ie, primary and secondary treatment failure, side effects, patient request, denial of reimbursement) with regard to patients age (<40 vs ≥40 years at treatment start) revealed no differences (Table XII).

Most patients who discontinued apremilast treatment were subsequently treated with biologics (61.6%). Those most frequently used were ustekinumab (29.2%), ixekizumab (11.3%), and secukinumab (10.3%) (Table XIII).

DISCUSSION

This analysis of 367 patients is one of the largest registry-based studies of effectiveness and drug

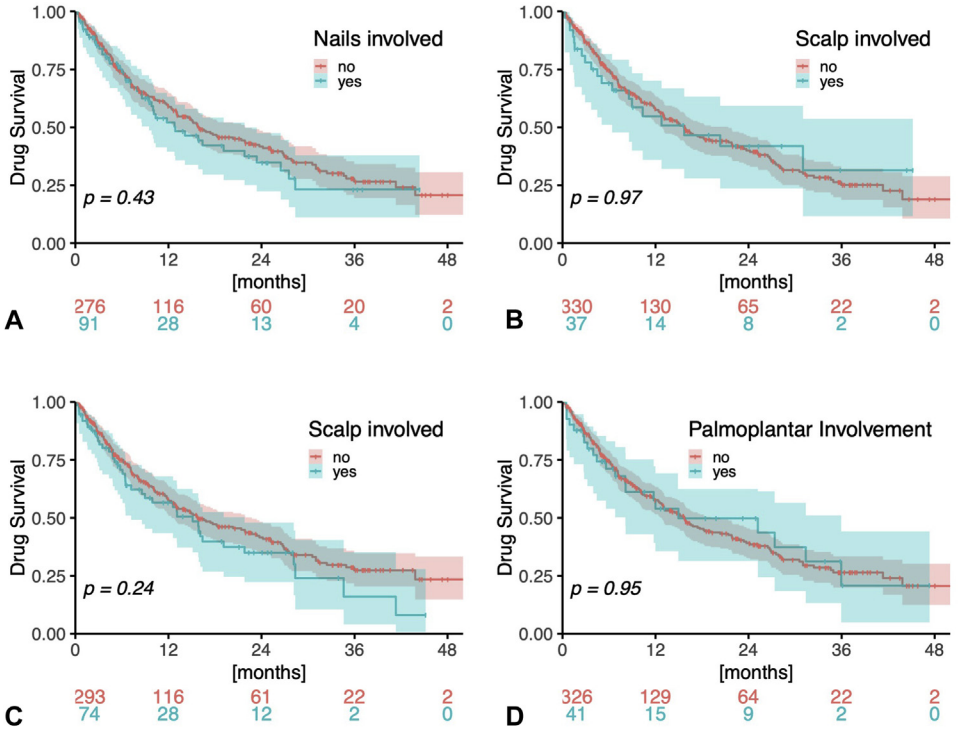

Fig 5. Drug survival regarding body site involvement. Relative drug survival rates (± 95% confidence intervals) of apremilast (N = 367) with regard to the involvement of body sites that possibly influence survival, using Kaplan-Meier estimates and log-rank tests.

Table VIII. Risk ratios for apremilast discontinuation

Risk factor	Relative risk (CI)	*P* value
Female sex	0.885 (0.662-1.182)	.4077
Concomitant psoriatic arthritis	1.095 (0.777-1.542)	.6046
Age <40 years at start of treatment	1.493 (1.111-2.007)	**.007918***
BMI ≥30	0.576 (0.294-1.128)	.1075
Previous biologic treatment	1.269 (0.949-1.696)	.1083
Palmar and/or plantar involvement	0.986 (0.627-1.551)	.9526
Scalp involvement	1.228 (0.872-1.729)	.2396
Nail involvement	1.143 (0.821-1.593)	.4288
Inverse involvement	0.989 (0.616-1.590)	.9662

BMI, Body mass index; *CI*, confidence interval.
*Significant *P* values are in bold.

survival in patients treated with apremilast. Our analysis of treatment sequences helped us to evaluate the role of apremilast in psoriasis treatment. UVB-phototherapy (20.3%) and PUVA (11.4%), as well as fumaric acid (19.6%) and methotrexate (20.1%) as traditional systemic agents were the most frequently administered treatments before apremilast (Table IV); biologic therapy (61.6%) was the most frequently administered treatment after apremilast discontinuation (Table XIII).

As shown by PP analysis, apremilast was clinically effective when evaluated in terms of PASI reduction. At 3 months after treatment start, PASI 100 had been achieved in 9.0% of patients, PASI 90 in 17.5%, PASI 75 in 36.8%, and PASI 50 in 64.2% (Table VI). At 12 months, the rates had increased to PASI 100 in 22.7%, PASI 90 in 38.2%, PASI 75 in 56.4%, and PASI 50 in 80.0% (Table VI). Similar findings for PASI 75 and PASI 90 responses at 3 and 12 months were recently reported from Spanish and Italian cohorts.[25,35] However, in our LOCF/worst-case scenario analysis, the clinical effectiveness of apremilast plateaued at 3 to 6 months after treatment start (Figs 2 and 3), in accordance with recently published guidelines

Table IX. Patient and disease characteristics regarding age

Characteristics	Number (%) of patients/mean value (SD) <40 years (N = 103)	Number (%) of patients/mean value (SD) ≥40 years (N = 264)	*P* value
Patient characteristics			
Sex			
Male	68 (66.0)	161 (61.0)	.403
Female	35 (34.0)	103 (39.0)	
Arthritis			
No	91 (88.3)	187 (70.8)	**.001***
Yes	12 (11.7)	77 (29.2)	
PASI at therapy start	6.9 (5.5)	7.0 (6.7)	.929
BMI	26.6 (7.5)	29.3 (5.6)	.095
Biologic naïvety			
No	69 (67.0%)	172 (65.2)	.807
Yes	34 (33.0)	92 (34.8)	
Disease characteristics			
Palmar and/or plantar involvement			
No	94 (91.3)	232 (87.9)	.368
Yes	9 (8.7)	32 (12.1)	
Scalp involvement			
No	69 (67.0)	224 (84.8)	**.000127***
Yes	34 (33.0)	40 (15.2)	
Nail involvement			
No	77 (74.8)	199 (75.4)	1.000
Yes	26 (25.2)	65 (24.6)	
Inverse involvement			
No	19 (51.3)	245 (92.8)	**.004***
Yes	18 (48.7)	19 (7.2)	

BMI, Body mass index; *PASI*, psoriasis area and severity index; *SD*, standard deviation.
*Significant *P* values are in bold. N = 367

Table X. Reason for drug discontinuation*

Reason for treatment discontinuation	Number (%) of discontinued treatment cycles per stopped/ per total treatments
Remission	
Complete	NA
None	43 (22.1/11.7)
Partial	20 (10.3/5.5)
No and partial	63 (32.3/17.2)
Loss of efficacy	40 (20.5/10.9)
Denial of reimbursement	2 (1.0/0.5)
Patient request	13 (6.6/3.5)
Pregnancy	NA
Side Effect	61 (31.3/16.6)
Other	16 (8.2/4.4)
All	195 (100/53.1)

NA, Not applicable.
*Total number of patients and treatments (N = 367).

Table XI. Reason for treatment discontinuation due to side effects*

Type of side effect	Number (%) of discontinued treatments* (per total number of stopped treatments†/ per total treatments‡)
Depression	11 (5.6/2.9)
Gastrointestinal symptoms	32 (16.3/8.7)
Headache	8 (4.1/2.1)
Infection	4 (2.0/1.1)
Liver toxicity	1 (0.5/0.3)
Kidney toxicity	1 (0.5/0.3)
Neurological symptoms	2 (1.0/0.5)
Sleep disorder	2 (1.0/0.5)
Rash	1 (0.5/0.3)
Skin cancer	1 (0.5/0.3)
Other cancer	1 (0.5/0.3)
Other	5 (2.5/1.3)

*Number of patients (N = 61) who discontinued apremilast due to side effects (N = 69).
†Total number of stopped treatments (N = 195).
‡Total number of patients and treatments (N = 367). Note that treatment was stopped due to 2 side effects in 6 patients and due to 3 side effects in 1 patient.

suggesting that drug effectiveness should be evaluated at 16 weeks after the start of treatment.[5]

Overall, the drug survival rate at 12 months in our study was 57.3%. This is in the upper range of

Table XII. Reason for treatment discontinuation regarding age

Reason for treatment discontinuation	Number (%) of discontinued treatment cycles per stopped stopped/per total treatments*	
	<40 years	≥40 years
Remission		
Complete	NA	NA
None	13 (19.4/12.6)	30 (23.4/11.3)
Partial	9 (13.4/8.7)	11 (8.6/4.2)
No and partial	22 (32.8/21.3)	41 (32.9/15.5)
Loss of efficacy	15 (22.4/14.6)	25 (19.5/9.5)
Denial of reimbursement	1 (1.5/0.9)	1 (0.8/0.4)
Patient request	5 (7.5/4.8)	8 (6.3/3.0)
Pregnancy	NA	NA
Side Effect	20 (29.9/19.4)	41 (32.0/15.5)
Other	4 (6.0/3.9)	12 (9.4/4.5)
All	67/103	128/264

NA, Not applicable.
*Prevalence numbers (percentages) of all patients (N = 367) regarding the reason for treatment discontinuation in patients < or ≥40 years of age at the start of therapy. The chi-square test indicates no significant differences in patients with or without psoriatic arthritis regarding sex (P = .21).

Table XIII. Treatments after apremilast discontinuation

Treatment discontinuation	Number (%) of patients with systemic treatment or not*	Type of treatment		Number (%) of treatments
Yes	195 (53.1)	Phototherapy	UVB	1 (0.5)
			PUVA	2 (1.0)
		Conventional systemic	Fumaric acid	4 (2.1)
			Methotrexate	12 (6.2)
			Retinoids	3 (1.5)
		Biologics	Adalimumab	9 (4.6)
			Brodalumab	6 (3.1)
			Etanercept	4 (2.1)
			Guselkumab	7 (3.6)
			Ixekizumab	22 (11.3)
			Risankizumab	3 (1.5)
			Secukinumab	20 (10.3)
			Tildrakizumab	1 (0.5)
			Ustekinumab	57 (29.2)
			All biologics	120 (61.6)
		Other		1 (0.5)
		No treatment specified		43 (22.1)
No	172 (46.9)	NA		NA

NA, Not applicable; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.
*Percentages of patients starting with another treatment after apremilast discontinuation. Certain patients received more than one biologic treatment after apremilast discontinuation, therefore the total number of biologics (N = 129) exceeds the total number of patients who had received a biologic (N = 120).

previously published results (Table VII), which vary widely due to presumed differences in the methodical approaches used by the groups reporting them. For instance, lower 12-month survival rates were detected in insurance claims databases from France (30.7%) and the United States (2.6%)[24,36] and in the Slovenian psoriasis registry (20.0%).[13] However, rates similar to ours were seen in retrospective observational studies from Spain (54.9%)[25] and Japan (53.4%),[28] although the apremilast-treated cohorts in most of those studies were smaller than ours.

Furthermore, our analysis indicates that apremilast is a robust antipsoriatic drug for which drug survival is not strongly influenced by most patient or disease-related factors (Figs 4, 5, and Tables VII, VIII). For instance, previous studies of biologics identified female sex as an independent risk factor for treatment discontinuation; however, this was not the case for apremilast in our study. Moreover, the drug survival of apremilast was not influenced by previous biologic exposure, obesity, concomitant psoriatic arthritis, or clinical psoriasis type in our study (Figs 4, 5, and Tables VII, VIII). However, drug survival was significantly influenced by the age at treatment start. When compared with patients aged ≥40 years, those <40 years at the start of treatment had an increased risk of treatment discontinuation (relative HR: 1.49, $P = .007918$) (Fig 4 and Table VIII) and had a significantly higher rate of inverse (48.7% vs 7.2%) and scalp (33.0% vs 15.2%) involvement (Table IX). However, a statistical subgroup analysis of a potential interaction between age and psoriasis type would have been underpowered, and therefore, we did not perform this investigation. Although data on the effects of age on biologic and nonbiologic drug survival are limited,[26] it is well known that younger patients place more importance on clinical efficacy than do older patients, as this enables the former group to lead normal working lives, feel comfortable being in public, be less burdened in partnerships and have normal sex lives[23]; therefore, younger patients may be tempted to discontinue apremilast more quickly for a lack of effectiveness. Furthermore, the increased inverse and scalp involvement in younger patients may have additionally contributed to worse drug survival in patients <40 years old (Table IX). Moreover, a significantly higher percentage of patients ≥40 years of age had psoriatic arthritis (29.2% vs 11.7%), which possibly contributed to prolonged drug survival in this group, as increased drug survival was previously observed for patients with psoriatic arthritis and biologic treatment.[26] Overall, the age-dependent decrease in drug survival among conventional systemic therapies in younger patients was described in a retrospective database analysis for psoriasis patients receiving acitretin (HR: 0.992 per year) and methotrexate (HR: 0.99 per year) in Israel.[37]

The main reasons for drug discontinuation in our analysis were primary treatment failure (32.3%), secondary loss of efficacy (20.5%), and side effects (31.3%) (Table X). While the observed rates of primary and secondary treatment failure are in the ranges of previously published results, the rate of drug discontinuation due to side effects is higher (31.3% vs 5.1-26.9%).[25,28,38-43] Gastrointestinal symptoms (8.7%) were the most common side effects, followed by headache (2.1%) and infection (1.1%) (Table XI). Eleven patients (2.9%) stopped apremilast because of signs of depression, beginning depression, or worsening depression, and 1 patient reported suicidal ideation. When we compared the treatment discontinuation rates for apremilast in this analysis with those in previously reported studies, we observed similar rates of discontinuation due to depression and headache[44,45] but a lower rate of discontinuation due to gastrointestinal symptoms in our study (8.7% vs 13.0-19.2%).[44,45]

Limitations

No PASI follow-up data were available for 28.1% of patients after the start of apremilast (Fig 2, *B*). Our analysis of effectiveness included a substantial number of patients who had no record of absolute PASI at therapy start (Fig 2, *A*). However, a much higher proportion of patients had documented PASI reduction values throughout our follow-up period (Fig 2, *B*).

CONCLUSIONS

Apremilast is a robust antipsoriatic drug for which the drug survival is not strongly influenced by the psoriasis subtype; female sex; obesity; psoriatic arthritis; previous biologic exposure; or palmoplantar, nail, scalp, and inverse involvement. However, drug survival is decreased in patients <40 years of age. Furthermore, apremilast seems to be an effective treatment option, although it does not target a specific cytokine or receptor. However, factors predicting the therapeutic response remain to be identified.

We thank the patients participating in PsoRA and all members and investigators of PsoRA (see https://psora.medunigraz.at/) who provided data for this analysis. Special thanks go to Matthias Wagner, Vienna, for development of the original electronic PsoRA database; Maximilian Errath for technical support; and Andrea Berghold, Department chair, Institute for Medical Informatics, Statistics, and Documentation, for continuous support in further development of the PsoRA database. We also thank Martina Praszl-Posch and Kirsten Sommer for support of data entry in the PsoRA database and Jude Richard, Austin, Texas, for editing of the manuscript. This work has been conducted as part of a dissertation thesis (TG).

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CORRECTION

Graier T, Weger W, Sator P-G, et al. Effectiveness and clinical predictors of drug survival in psoriasis patients receiving apremilast: A registry analysis. *JAAD Int.* 2021;2:62-75.

On behalf of our coauthors, we write to report errors that occurred in the original article "Effectiveness and clinical predictors of drug survival in psoriasis patients receiving apremilast: A registry analysis." The errors were elucidated when one author manually extracted data for a new independent analysis from the Psoriasis Registry Austria and tried to merge it with automatically extracted data from the electronic data files of the registry. We discovered an inconsistency regarding biologic naïve and biologic non-naïve patients, due to two coding errors. One error caused previous treatment with some non-biologics to be considered as a biologic treatment. The second error caused that some treatments with biologics or non-biologic treatments were not or not correctly identified. Together these errors caused a total of 48 of 367 patients to be wrongly considered as biologic non-naïve. In fact, only 78 (21.3%) of patients had received previous biologic treatment, instead of 126 (34.3%) as depicted in Fig 4E.

The errors also caused wrong patient numbers in Table IX: 17 (16.5%) of 103 patients under 40 years of age were biologic non-naïve instead of 34 (33.0%) patients. For patients ≥40 years of age at treatment start 61 (23.1%) patients were biologic non-naïve instead of 92 (34.8%) patients. Furthermore, this led to an underestimation of patients that had received previous treatments and the total number of previous treatments as depicted in Table IV. In fact, 308 (83.9%) patients instead of 305 (83.1%) patients had received previous treatments. The total number of previous treatments was 622, instead of 428.

Our study had revealed that drug survival of apremilast decreased significantly in patients younger than 40 years (relative hazard ratio [confidence interval, CI], 1.493 [1.111-2.007], $P = .008$). Based on the corrected data we now identified previous biologic treatment as an additional factor significantly decreasing drug survival of apremilast treatment with a relative hazard ratio of 1.662 (CI, 1.198-2.305, $P = .002$) instead of 1.269 (CI, 0.949-1.696, $P = .108$) as depicted in Table VIII. This also led to slightly different drug survival rates (CI) for biologic naïve and non-naïve patients in Table VII: naïve 89.2% (85.0-92.4) instead of 91.4% (86.9-94.3), 77.9% (72.4-82.4) instead of 78.6% (72.5-83.5) and 60.2% (53.6-66.1) instead of 59.6% (52.3-66.2), at 3, 6 and 12 months respectively; non-naïve 74.6% (63.1-83.0) instead of 76.2% (67.6-82.8), 60.0% (47.7-70.3) instead of 65.5 (56.2-73.3), 46.2% (33.7-57.7) instead of 52.5% (42.8-61.4), at 3, 6 and 12 months respectively. The median drug survival (CI) in months for biologic naïve patients changed from 17.4 (12.9-25.2) to 18.2 (13.11-25.2), and for biologic non-naïve patients from 13.1 (7.3-16.8) to 11.8 (5.1-15.1). These findings are consistent with results from a recently published study, reporting an increased risk for drug discontinuation in biologic non-naïve patients receiving apremilast (hazard ratio of 3.86).[1] Furthermore, we noticed that the impact of arthritis on drug survival in the Kaplan-Meier plot of Fig 4B did not match with the relative hazard ratio in Table VIII. This was caused by the interchange of numerator and denominator in the study's programming code compared to the code of the database, leading to the output of the reciprocal value. However, this error remains without statistical significance. By cross checking the rest of the manuscript, we noticed a few additional minor rounding errors in Tables X, XI, and XII, and a duplicate labeling in Fig 5 (the labeling of Fig 5B should read inverse involvement).

Besides all other major conclusions of the study remain unchanged and valid. This includes psoriasis area and severity index response rates, reasons for treatment discontinuation and side effects as well as post apremilast treatments. Furthermore the relative hazard ratios for gender, obesity or nail, palmoplantar, scalp and intertriginous involvement remain also unchanged as reported in the paper.

We sincerely apologize for the errors we made, and the inconvenience this *caused JAAD International* and its readership.

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Real-world effectiveness of anti-interleukin-23 antibodies in chronic plaque-type psoriasis of patients from the Austrian Psoriasis Registry (PsoRA)

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With the introduction of the latest class of biologic drugs targeting interleukin (IL)-23p19, three new, highly effective drugs can be used for the treatment of chronic plaque psoriasis. However, poorer skin improvement as well as higher rates of serious adverse events have been reported for patients under real-world conditions (outside clinical trials). This accounts especially for patients who have already been treated with biologic drugs. We therefore aimed to determine effectiveness and safety of IL-23p19 inhibitors in real-world patients by analysing data from the Psoriasis Registry Austria (PsoRA) in this observational, retrospective, multicentre cohort study. Data for 197 patients (52.3% biologic-non-naïve), who were treated with anti-IL-23p19 antibodies (127 guselkumab, 55 risankizumab and 15 tildrakizumab) for at least 3 months, were eligible for analysis. In general, biologic-non-naïve patients displayed a less favourable response to anti-IL-23 treatment as compared to biologic-naïve patients. However, after correction for previous biologic exposure, few differences in PASI improvement were detected among biologic-naïve and -non-naïve patients treated with different IL-23p19 inhibitors. This indicates that treatment effectiveness is not related to the class of the previously administered therapy in biologic-non-naïve patients. Therefore, IL-23p19 inhibitors represent a promising treatment alternative for patients who have not responded to previous biologics. However, as with other biologic agents (including IL-17 inhibitors), we did not observe an entirely satisfactory treatment response (i.e. PASI < 3 and/or PASI 75) to anti-IL-23 treatment in one out of four to five patients. Adverse events (mainly non-severe infections) were observed in 23 (11.7%) patients with no major differences regarding the administered IL-23 inhibitor or previous biologic exposure.

With the introduction of the latest class of biologic drugs targeting interleukin (IL)-23p19, three new, highly effective drugs, i.e. guselkumab, risankizumab and tildrakizumab, can be used for the treatment of chronic plaque psoriasis[1–3]. However, 14.6–58.6% of patients with psoriasis treated in daily routine would not have been eligible for clinical trials; indeed, poorer skin improvement as well as higher rates of serious adverse events have been reported for those patients under real-world conditions[4,5]. Previous biologic exposure is a well-known risk factor for decreased drug survival, and it appears that clinical effectiveness is also reduced in these patients, including patients treated with IL-17 and IL-23 inhibitors[6–10]. These considerations are especially pertinent in order to select a new treatment, if treatment has been discontinued due to insufficient skin improvement, whereas the occurrence of adverse events often leads to a switch in biologic class or conventional systemic treatment[11,12]. Thus, recently developed non-invasive tools which might help predict the patients' responses to biologic treatment

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could become a milestone in anti-psoriatic treatment[12]. Clinical trials of these tools are ongoing, and they will hopefully soon enable physicians to more efficiently select the most promising biologic drug for biologic-naïve and -non-naïve patients. Nevertheless, treatment selection depends on a variety of factors including disease severity, involvement of sensitive body sites, quality of life, response to previous therapies, comorbidities (including chronic infections), patient`s scheme of life, (and physician's) and patient's treatment preferences[13,14]. Thus, psoriasis patients need an individually tailored treatment selection[13,14].

Recent case series have shown that intra-class switching within the group of IL-17 or IL-23 inhibitors can be a promising therapeutic option in patients exhibiting treatment failure[15,16]. However, little is known at this time about the impact of previous biologic exposure on subsequent treatments, not allowing physicians to draw conclusions regarding the advisability of intra- or inter-class biologic treatment switching[15,16]. Therefore, we evaluated both the treatment effectiveness in patients treated with guselkumab, risankizumab, or tildrakizumab and the influence of previous biologic exposure in these patients.

Methods

Study design. This study was carried out as an observational retrospective multicentre analysis of clinical data extracted from the Psoriasis Registry Austria (PsoRA). The design of this registry has been described in previous studies[7,17–19]. Further information about PsoRA and participating centres is available at www.psoriasisregistry.at. In the registry, one treatment is defined as the time from a patient`s allocation to a specific therapy, followed by at least one visit, until last observation or discontinuation of treatment. For every visit entered into the registry, the continuous prescription of a drug has to be confirmed; otherwise, the reason for treatment discontinuation has to be entered. The registry has been approved by the Ethics Committee of the Medical University of Graz (application number 21-094 ex 09/10), and the present analysis was conducted in accordance with the principles of the Declaration of Helsinki and informed consent has been obtained from the patients according to prerequisites of the study approval.

Data analysis and statistics. The study population included patients > 18 years of age who had chronic plaque psoriasis and started a biologic therapy with guselkumab, risankizumab, or tildrakizumab. These patients had at least one follow-up visit (and a treatment duration of at least 3 months) with the same treatment, irrespective of their previous systemic treatment, psoriatic arthritis, or any comorbidities. Data extraction was performed on February 4, 2021, and covered the period from March 23, 2018, to February 4, 2021. The Psoriasis Area and Severity Index (PASI) score prior to therapy start and at least one PASI score during the follow-up (at 3, 6, or 12 months) had to be documented in order to include a patient in the analysis. The effectiveness of the IL-23 inhibitors was evaluated in terms of absolute PASI change and PASI reduction (defined as categories ranging from complete remission, i.e. PASI 100, to partial remission, i.e. PASI 90, PASI 75, PASI 50, PASI < 50 to worsening) with regard to biologic naivety, as well as in terms of the class of previous biologic therapy (i.e. tumour necrosis factor-TNF-alpha, IL-12/23, IL-23 and IL-17 inhibitors). The change in PASI was calculated and analysed as observed and with respect to the last observation carried forward (LOCF) worst-case scenario (considering the last known PASI or PASI reduction response to be continued or otherwise patients to be non-responders, i.e. PASI < 50 response) for further analysis, irrespective of treatment discontinuation.

The chi-square test was used to determine the treatment allocation concerning gender, psoriatic arthritis, and biologic naivety, as well as to analyse differences in the achievement of PASI reduction categories and to detect the occurrence of adverse events regarding the (class of) previous biologic exposure. Two sample *t*-tests and analysis of variances or the Kruskal–Wallis test were used to compare the PASI regarding the drug and (class of) previous biologic exposure. A post hoc analysis was performed pairwise using the Bonferroni correction. Calculations were performed with IBM® SPSS® Statistics 26.0 (Armonk, New York, IBM Corporation). *P*-values < 0.05 were considered to be statistically significant.

Results

General patient characteristics. Nine patients were excluded from the analysis due to treatment discontinuation prior to 3 months, and only two of these patients received more than one treatment dosage. Reasons for treatment discontinuation included patient requests due to lack of skin improvement ($n = 4$), side effects ($n = 1$) (skin abscess) and worsening of another skin disease (*acne inversa*) ($n = 1$), and other reasons ($n = 3$). PASI or PASI reduction was not available for these 9 patients. Data from 197 patients (34.0% women) and their administered treatments (127 cycles of guselkumab, 55 of risankizumab and 15 cycles of tildrakizumab) were eligible for analysis (Table 1). Psoriatic arthritis was present in 51 (25.9%) patients, and 94 (47.7%) of the treatments were administered in biologic-naïve patients (Table 1). In biologic-non-naïve patients, Il-17 and Il-12/23 inhibitors were the most frequently administered drugs (Table 1). Furthermore, 12.7% of patients had already received at least three (3) biologic treatments. No differences existed in allocation to treatment with regard to gender, age, BMI, PASI, biologic naivety, or class of previous biologic therapy (Table 1). All patients received standard dosage at treatment start. An off-label dosage change was performed in one man receiving risankizumab (in whom the risankizumab administration interval was reduced to 10 weeks) and in another man receiving tildrakizumab (in whom the dosage was increased to 200 mg tildrakizumab every 12 weeks). Fifty-two patients (26.4%) had a PASI ≤ 3 at treatment start (Table 1). Concomitant psoriatic arthritis was present in 24 of these patients (46.2%), and 35 patients (67.3%) were switched from another biologic to anti IL-23 treatment for various reasons (data not shown). Forty-eight (92.3%) patients suffered from the involvement of at least one difficult-to-treat or psychologically incriminating body site: 21 (40.4%) scalp, 17 (32.7%) nails, 14 (26.9%) inverse, 11 (21.2%) palmar and/or plantar region; 2 (3.8%) patients had additional palmoplantar involvement with pustules and plaques. Previous biologic treatment had been discontinued due to primary treatment failure ($n = 10$), secondary treat-

Treatment characteristics		Treatment				p-value
		Guselkumab	Risankizumab	Tildrakizumab	All treatments	
Total number of treatments/patients		127	55	15	197	
Characteristic at start of treatment	Number (%) of females	44 (34.6)	19 (34.5)	4 (26.7)	67 (34.0)	0.891
	Mean age (SD)	46.0 (14.2)	47.9 (11.6)	45.9 (14.1)	46.5 (13.5)	0.668
	Mean PASI (SD) in biologic naïve patients	9.63 (6.59)	11.13 (6.67)	11.67 (11.08)	10.25 (7.23)	0.545
	Mean PASI (SD) in biologic non-naïve patients	7.80 (7.52)	9.13 (8.10)	9.13 (5.22)	8.01 (7.44)	0.700
	Number (%) of patients with PASI ≤ 3	37 (29.1)	12 (21.8)	3 (20.0)	52 (26.4)	0.496812
	Number (%) of cycles in patients with arthritis	31 (24.4)	19 (34.5)	1 (6.7)	51 (25.9)	0.077
	Mean weight in kg (SD)	92.0 (19.2)	88.9 (13.4)	94.4 (11.8)	91.3 (17.4)	0.736
	Mean BMI (SD)	30.0 (6.5)	29.3 (4.4)	29.9 (2.3)	29.8 (5.6)	0.914
Number (%) of patient with the last previous biologic treatment	None	54 (42.5)	29 (52.7)	11 (73.3)	94 (47.7)	0.068
	TNF-alpha	14 (11.0)	6 (10.9)	0 (0)	20 (10.2)+	
	IL-12/23	33 (26.0)	5 (9.1)	2 (13.3)	40 (20.3)*	
	IL-17	26 (20.5)	15 (27.3)	2 (13.3)	43 (21.8)#	
Number (%) of previous biologic therapies	1	41 (55.4)	13 (50.0)	2 (50.0)	56 (53.8)	0.767
	2	14 (18.9)	8 (30.8)	1 (25.0)	23 (22.1)	
	≥ 3	19 (25.7)	5 (19.2)	1 (25.0)	25 (24.0)	

Table 1. Patient characteristics. Analysis of variances and chi-square test did not reveal differences in allocation to treatment regarding sex, age, PASI, psoriatic arthritis, or (type of) previous biologic exposure. Chi-square test results revealed that a previous treatment with TNF-alpha and IL-12/23 inhibitors were the first biologic treatments for a significantly higher proportion of patients ($p = 0.000778$). +Seven patients (35.0%) were biologic-non-naïve when treated with TNF-alpha inhibitors. *Ten patients (25.0%) were biologic-non-naïve when treated with IL-12/23 inhibitors. #Twenty-eight patients (65.1%) were biologic-non-naïve when treated with IL-17 inhibitors. BMI, body mass index; IL, interleukin; PASI, Psoriasis Area and Severity Index; SD, standard deviation; TNF, tumour necrosis factor.

ment failure (i.e. loss of efficacy) ($n = 15$), side effects ($n = 4$), patient request ($n = 3$), denial of reimbursement ($n = 1$), start of the COVID-19 pandemic ($n = 1$) and unknown reasons ($n = 1$) (data not shown).

Effectiveness. The mean (SD) PASI at treatment start was 8.42 (7.13), 10.07 (7.28) and 11.0 (9.74) for patients treated with guselkumab, risankizumab and tildrakizumab, respectively (Table S1). PASI (SD) continuously declined over 12 months to 1.22 (2.84)/1.93 (3.64) for guselkumab, 0.93 (1.80)/1.03 (1.94) for risankizumab and 5.40 (6.79)/3.93 (6.57) for tildrakizumab regarding the analysis as observed/LOCF (Fig. 1, Table S1). In general, biologic-naïve patients had a significantly higher disease severity at treatment start with a mean PASI (SD) of 10.25 (7.23) as compared to 8.01 (7.44) in biologic-non-naïve patients ($p = 0.033$) (Table 2). However, biologic-naïve patients achieved significantly lower mean absolute PASI values (SD) as compared to -non-naïve patients at 3 months (1.27 [3.01] versus 2.35 [3.83]; $p = 0.048$) and 6 months (0.53 [0.82] versus 2.86 [4.45]; $p = 0.001$). Furthermore, a trend toward lower PASI at 12 months was detected in biologic-naïve patients as compared to -non-naïve patients ($p = 0.07$) (Table 2). However, PASI values were similar for each timepoint within the groups of biologic-naïve and -non-naïve patients, irrespective of the currently administered Il-23 inhibitor, except for PASI values at 12 months in biologic-non-naïve patients ($p = 0.006$) (Table 3). The class of the previously administered biologic drug had no significant influence on PASI effectiveness in patients treated with IL-23p19 inhibitors at 3 months ($p = 0.312$), 6 months ($p = 0.535$), or 12 months ($p = 0.999$) after treatment initiation, despite the significant differences observed in PASI at treatment start regarding class of previous biologic treatment ($p = 0.001$) (Table 4).

After 3 months of treatment, the observed PASI 50, 75, 90 and 100 (complete response) rates were 80.6%, 60.2%, 39.8% and 27.8% for guselkumab, 93.6%, 74.5%, 63.9% and 42.6% for risankizumab, and 66.7%, 50.0%, 50.0% and 8.3% for tildrakizumab, respectively. These values ultimately reached 83.4%, 76.7%, 61.7% and 46.7% for guselkumab, 96.0%, 84.0%, 72.0% and 60.0% for risankizumab and 50.0%, 50.0%, none (not available) and none (not available) for tildrakizumab after 12 months of treatment (Fig. 2, Table 5). In general, a significantly higher proportion of biologic-naïve patients achieved PASI 75, PASI 90 and PASI 100 responses at 3 ($p = 0.0049$), 6 ($p = 0.0041$) and 12 months ($p = 0.0413$) after treatment initiation compared to non-naïve patients. However, these findings could only be statistically confirmed in the subgroup analysis for risankizumab at 6 months ($p = 0.0001$), and for tildrakizumab at 3 months ($p = 0.0013$) after treatment initiation (Table S2).

Safety. Adverse events were documented in 23 patients (11.7%), with infections being the most commonly seen side effects in 18 patients (9.1%), taking all IL-23 inhibitors together (Table 6). No differences were identified in the incidence of adverse events with regard to the administered drug ($p = 0.159$) (Table S3). Furthermore, the rates of adverse events were similar in biologic-naïve and -non-naïve patients ($p = 0.368294$) (Table 6).

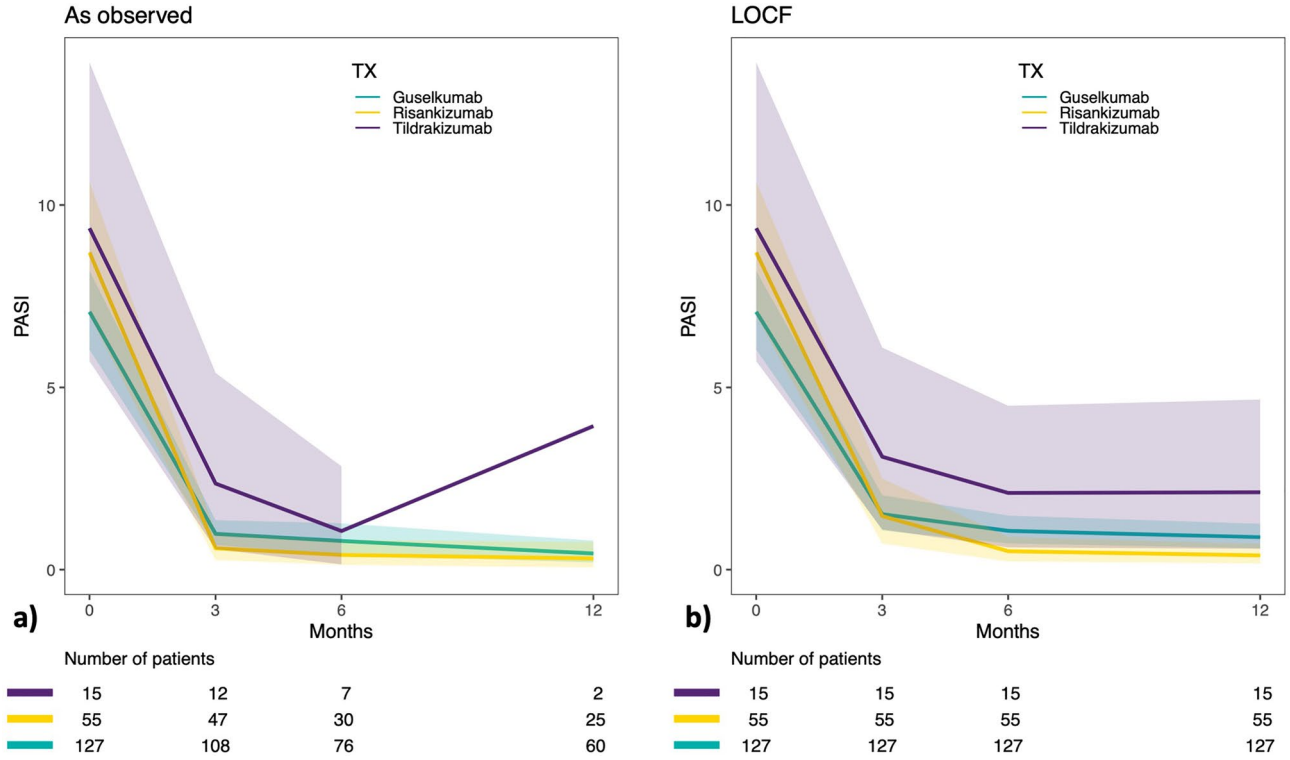

Figure 1. Effectiveness of IL-23 inhibitors in terms of absolute PASI. Absolute Psoriasis Area and Severity Index (PASI) value (±95% confidence interval) plotted over time for patients analysed as observed (**a**) and per last observation carried forward (LOCF) (**b**).

Timepoint	Mean PASI (SD) in biologic-naïve/-non-naïve patients as observed		*p*-value
	Biologic naive	Biologic non-naive	
Baseline	10.25 (7.23)	8.01 (7.44)	**0.033**
3 months	1.27 (3.01)	2.35 (3.83)	**0.048**
6 months	0.53 (0.82)	2.86 (4.45)	**< 0.001**
12 months	0.71 (2.68)	1.77 (2.69)	0.07

Table 2. Treatment effectiveness regarding biologic naivety. A two-sample *t*-test revealed significantly higher PASI values in biologic naïve patients at treatment start, as well as significantly higher PASI values in biologic-non-naïve patients at 3 and 6 months after treatment initiation. Significant *p*-values are in bold. PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Treatment discontinuation. A total of 22 (11.2%) out of 197 patients discontinued treatment within the first treatment year (guselkumab, 12.6%; risankizumab, 5.5%; tildrakizumab, 13.3%). Reasons for treatment discontinuation included primary treatment failure ($n = 7$, 3.6%), secondary treatment failure (i.e. loss of efficacy) ($n = 5$, 2.5%), insecurities due to the COVID-19 pandemic (n = 5, 2.5%), side effects ($n = 3$, 1.5%) and patient request ($n = 2$, 1.0%).

Discussion

This study of 197 patients is one of the larger registry studies conducted so far to examine the effectiveness and safety of real-world patients receiving IL-23p19 inhibitors, as well as the impact of previous biologic exposure on these parameters. The rate of off-label dosage changes were relatively low, i.e. 1.0% in this study as compared to that of 14.1% for the IL-12/23 inhibitor ustekinumab, which was been reported from this registry previously[7]. Taking all anti-IL-23 inhibitors together, the observed/LOCF response rates at 3 months with a PASI 100 were 29.9%/25.4%; for PASI 90, 47.3%/40.1%; and for PASI 75, 63.5%/53.8%. After 12 months, the values for PASI 100 reached 49.4%/38.6%; for PASI 90, 63.2%/53.3%; and for PASI 75, 78.2%/69.0%.

Treatment effectiveness in terms of the PASI reduction category for guselkumab observed in this study was within the lower range or was slightly lower than that reported in clinical trials. Three months after treatment start, the PASI 75 response was 60.2% (as compared to 69.8–91.2%), the PASI 90 response was 39.8% (as compared to 69.0–73.3%), and the PASI 100 response was 27.8% (as compared to 27.0–37.4%). Fifty-two weeks

Timepoint	Treatment	Biologic naïve patients		Biologic-non-naïve patients	
		PASI (SD)	*p*-value	PASI (SD)	*p*-value
Baseline	Guselkumab	9.63 (6.59)	0.545	7.80 (7.52)	0.700
	Risankizumab	11.13 (6.67)		9.13 (8.10)	
	Tildrakizumab	11.67 (11.08)		9.13 (5.22)	
3 months	Guselkumab	1.02 (1.55)	0.085	2.59 (4.44)	0.200
	Risankizumab	0.95 (1.59)		2.08 (2.76)	
	Tildrakizumab	3.56 (7.78)		6.47 (3.56)	
6 months	Guselkumab	0.54 (0.86)	0.745	3.25 (5.07)	0.798
	Risankizumab	0.42 (0.75)		2.48 (3.22)	
	Tildrakizumab	0.74 (0.86)		4.20 (2.55)	
12 months	Guselkumab	1.01 (3.34)	0.609	1.42 (2.41)	**0.006**
	Risankizumab	0.107 (0.29)		2.76 (3.29)	
	Tildrakizumab	0.60 (NA)		10.20 (NA)	

Table 3. Treatment effectiveness as observed regarding biologic naivety in patients treated with different IL-23 inhibitors. Analysis of variances revealed no statistically significant differences in PASI for any timepoint among biologic-naïve or -non-naïve patients with regard to the administered drug, except for PASI at 12 months in biologic-non-naïve patients. However, post hoc analysis was not feasible due to the low number of patients at 12 months in the tildrakizumab group ($n = 2$). Significant *p*-values are bold. NA, not applicable (none); PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Timepoint (total number of patients)	Type of biologic	Number (percentage) of patients that received a certain class of previous biologic therapy	Biologic-non-naïve patients	
			PASI (SD)	*p*-value
Baseline (103)	TNF-α	20 (19.4)	7.36 (5.52)	**0.001**
	Il-17	43 (41.7)	11.12 (8.94)	
	Il-12/23	40 (38.8)	4.99 (4.86)	
3 months (91)	TNF-α	17 (18.7)	2.17 (3.29)	0.312
	Il-17	34 (37.4)	3.12 (5.23)	
	Il-12/23	38 (41.6)	1.74 (2.24)	
6 months (55)	TNF-α	10 (18.2)	1.56 (2.32)	0.535
	Il-17	28 (50.9)	3.40 (5.05)	
	Il-12/23	17 (30.9)	2.72 (4.40)	
12 months (43)	TNF-α	5 (11.6)	1.80 (2.00)	0.999
	Il-17	19 (44.2)	1.78 (2.89)	
	Il-12/23	19 (44.2)	1.75 (2.78)	

Table 4. Treatment effectiveness as observed with regard to class of previous biologic therapy. Analysis of variances revealed statistically significant differences in disease severity (as measured in PASI) regarding the class of previous biologic treatment at baseline. Post hoc analysis results show significantly higher PASI in patients treated with IL-17 inhibitors as compared to those treated with IL-23 inhibitors ($p < 0.001$), but not TNF- α inhibitors ($p = 0.147$). There was no difference regarding PASI at baseline between TNF- α inhibitors and IL-12/23 inhibitors at baseline ($p = 0.655$). Significant *p*-values are in bold. IL, interleukin; PASI, Psoriasis Area and Severity Index; SD, standard deviation; TNF, tumour necrosis factor.

after treatment start, the PASI 75 response was 76.7% (as compared to 77.8–87.8%), the PASI 90 response was 61.7% (as compared to 76.3–84.0%), and the PASI 100 response was 46.7% (as compared to 46.7–58.0%) (Fig. 2, Table 5)[20–22]. In general, these response rates are also in the range (or slightly lower) as those recently published from Italian real-world patient cohorts[23–25].

Treatment results for risankizumab were also within the lower range or slightly lower than results from a clinical trial. PASI 75 responses at 12 weeks were 74.5% (as compared to 91.0–94.5%), PASI 90 responses were 63.9% (as compared to 72.0–74.8%), and PASI 100 responses were 42.6% (as compared to 32.7–40.0%). Fifty-two weeks after treatment start, the PASI 75 response was 84.0% (as compared to up to 96.4%), the PASI 90 response was 72.0% (as compared to 80.6–92.7), and the PASI 100 response was 60.0% (as compared to 41.8–60.0%) (Fig. 2, Table 5)[1,26]. Similar data regarding treatment effectiveness has been obtained in recently published real-world studies[27,28].

However, it is noteworthy that the efficacy endpoints in most of these clinical trials (of guselkumab and risankizumab) were measured 16 weeks after treatment initiation, whereas this study analysed treatment effectiveness 12 weeks after treatment initiation[1,21,22,26,29]. Furthermore, the rate of biologic-non-naïve patients in this

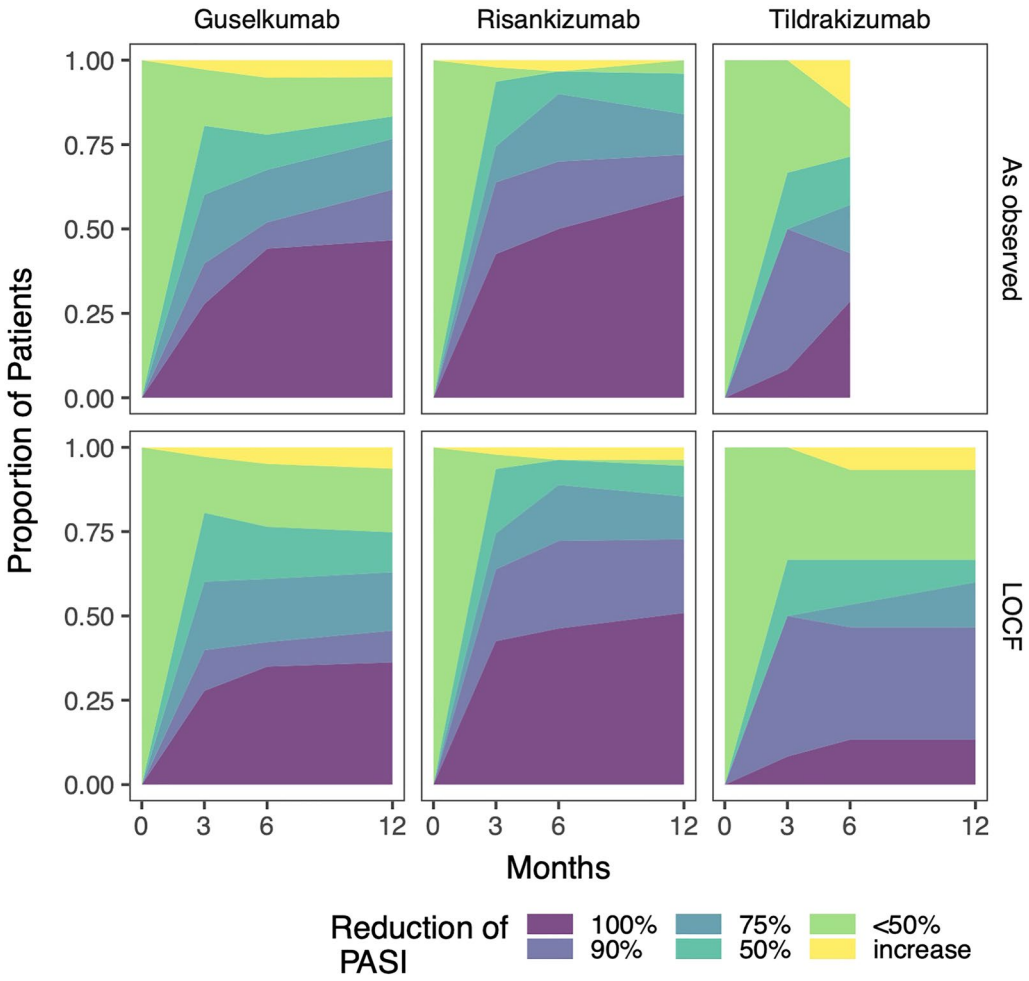

Figure 2. Achievement of skin goals. Relative number of patients analysed as observed and per last observation carried forward (LOCF), in whom a certain Psoriasis Area and Severity Index (PASI) was achieved, plotted over time.

study was higher than that in clinical trials, namely, 57.5% and 47.3% biologic-non-naïve patients for guselkumab and risankizumab, respectively, as compared to a range of 17.5–29.0% in guselkumab trials and 29.0–39.0% in risankizumab trials (Table 1)[1,20–22,26].

Patients receiving tildrakizumab had treatment responses that mostly fell well within the range of results cited from clinical trials, with a PASI 75 response 12 weeks in this study of 50% (as compared to 41.2–64.0%), a PASI 90 response of 50.0% (as compared to 35.0–73.2%), and a PASI 100 response of 8.3% (as compared to 14.0–34.4%). Meanwhile, twenty-six weeks after treatment initiation, a PASI 75 response of 57.2% was recorded (as compared to 73.0–80.0%), a PASI 90 response of 42.9% (as compared to 52.0–56.0%), and a PASI 100 response of 28.6% (as compared to 23.0–24.0%) (Fig. 2, Table 5)[30–32]. However, better reals-word response rates have been recently reported in Italian patient cohorts[25,33]. Like the rates for biologic-non-naïve patients seen in the clinical trials of guselkumab and risankizumab, the rates seen for biologic-non-naïve patients receiving tildrakizumab were 26.7% in this study; thus, this rate was slightly higher than the rate seen in its clinical trials (13.0–23.0%) (Table 1). However, the PASI < 50 response rates at 6/12 months after treatment initiation were relatively high in patients treated with guselkumab (21.3%/18.9%) and tildrakizumab (26.7% and 26.7%, respectively) as compared to risankizumab (1.8%/1.8%) in the LOCF analysis. Significantly better skin improvement as measured by absolute PASI was also observed at 12 months for risankizumab as compared to tildrakizumab (Table S1). It is important to note, however, that PASI reduction is not the most appropriate method to measure treatment effectiveness in patients with low PASI at baseline[34]. Notably, 52 patients (26.4%) included in this study started treatment with PASI ≤ 3 (Table 1). After excluding these patients, the LOCF analysis results reveal that 80.0% of the patients achieved a PASI ≤ 3 at 12 months, which is considered as achieving the therapeutic treatment goal (Table 5)[35]. On the other hand, this finding indicates that 1 out of 5 patients did not display an entirely satisfactory treatment response (Table 5). With regard to PASI reduction, 23.4% did not reach a PASI 75 response, and 13.1% (i.e. one out of eight patients) remained below a PASI 50 improvement level or their skin manifestations even worsened (Table 5). Notably, similar PASI reduction rates were observed when patients starting with PASI ≤ 3 were not excluded from analysis (Table 5).

Treatment	Timepoint (months)	Number of patients (as observed/LOCF)	Percentage of patients achieving a certain PASI reduction (as observed/LOCF)						Number (%) of patients of patients achieving ≤ PASI 3 (as observed /LOCF)
			PASI 100	> PASI 90	> PASI 75	> PASI 50	< PASI 50	Increase in PASI	
Guselkumab	3	108/127	27.8/23.6	39.8/33.8	60.2/51.1	80.6/68.4	16.7/29.1	2.8/2.4	89 (82.4)/94 (74.0)
	6	77/127	44.2/33.9	52.0/41.0	67.6/59.1	78.0/74.1	16.9/21.3	5.2/4.7	65 (84.4)/104 (81.9)
	12	60/127	46.7/36.2	61.7/45.6	76.7/62.9	83.4/74.7	11.7/18.9	5.0/6.3	53 (88.3)/105 (82.7)
Risankizumab	3	47/55	42.6/36.4	63.9/54.6	74.5/63.7	93.6/80.1	4.3/18.2	2.1/1.8	41 (87.2)/41 (74.5)
	6	30/55	50.0/45.5	70.0/71.0	90.0/87.4	96.7/94.7	NA/1.8	3.3/3.6	27 (90.0)/48 (87.3)
	12	25/55	60.0/50.9	72.0/72.7	84.0/85.4	96.0/94.5	4.0/1.8	NA/3.6	22 (88.0)/48 (87.3)
Tildrakizumab	3	12/15	8.3/6.7	50.0/40.0	50.0/40.0	66.7/53.3	33.3/46.7	NA/NA	9 (75.0)/10 (66.7)
	6	7/15	28.6/13.3	42.9/46.6	57.2/53.3	71.5/66.6	14.3/26.7	14.3/6.7	6 (85.7)/11 (73.3)
	12	2/15	NA/13.3	NA/46.6	50.0/59.9	50.0/66.6	NA/26.7	50.0/6.7	1 (50.0)/11 (73.3)
All treatments ($N = 197$)	3	167/197	29.9/25.4	47.3/40.1	63.5/53.8	82.0/70.6	14.4/27.4	2.4/2.0	139 (83.2%)/145 (73.6%)
	6	114/197	44.7/35.5	56.1/49.7	72.8/66.5	82.5/79.2	12.3/16.2	5.3/4.6	98 (86.7%)/163 (82.7%)
	12	87/197	49.4/38.6	63.2/53.3	78.2/69.0	86.2/79.7	9.2/14.7	4.6/5.6	76 (87.4%)/164 (83.3%)
Patients with PASI > 3 at treatment start ($n = 145$)	3	131/145	30.5/27.6	51.1/46.2	64.1/57.9	80.9/73.1	9.9/25.5	1.5/1.4	94 (77.7%)/94 (64.8%)
	6	86/145	50.0/37.9	62.8/55.2	81.4/48.3	91.9/85.5	5.8/11.7	2.3/2.8	75 (87.2%)/116 (80.0%)
	12	63/145	55.6/41.4	71.4/59.3	85.7/76.6	93.7/86.9	4.8/9.7	1.6/3.4	54 (85.7)/116 (80.0%)

Table 5. Achievement of treatment goals. In 52 patients, the PASI at baseline was ≤ 3, of whom 9 had a PASI ≤ 1 at baseline. The number (%) of those patients achieving a PASI ≤ 1 as observed/LOCF was 32 (69.6)/32 (61.5), 16 (59.3)/34 (65.4), 18 (75.0)/35 (67.3) at 3, 6 and 12 months, respectively. In 2/4 patients, the PASI increased to > 3 at 12 months with regard to the analysis as observed/LOCF, while the remaining patients had a stable disease (continued having PASI ≤ 3). LOCF, last observation carried forward; NA, not applicable (none); PASI, Psoriasis Area and Severity Index.

Type of adverse event	Number (%) of patients reporting an adverse event once per drug			
	All ($N = 197$)	Guselkumab ($n = 127$)	Risankizumab ($n = 55$)	Tildrakizumab ($n = 15$)
Gastrointestinal symptoms	2 (1.02)+	1 (0.79)	1 (1.82)	NA
Infection	18 (9.14)*	16 (12.60)	2 (3.64)	NA
Neurological symptoms	2 (1.02)#	1 (0.79)	NA	1 (6.67)
Rash	1 (0.05)	1 (0.79)	NA	NA
All	23 (11.67)	19 (14.96)	3 (5.45)	1 (6.67)

Table 6. Occurrence of adverse events under treatment with Il-23 inhibitors. Fisher's exact test results indicate no significant differences in the occurrence of adverse events regarding drug ($p = 0.159$). $N = 197$. NA, not applicable (none). +Included two patients with diarrhoea. *Included seven patients with common cold, two patients with coronavirus disease 2019 (COVID-19), two patients with cellulitis, one patient with influenza, one patient with herpes zoster, one patient with skin abscess, one patient with angina tonsillaris, one patient with tooth abscess, and two patients with unspecified infections. #Included one patient with headache and one patient with headache and paraesthesia.

Analysing the treatment outcomes of the whole cohort with regard to previous biologic exposure revealed higher rates of PASI 50, PASI 75, PASI 90 and PASI 100 responses in biologic-naïve patients as compared to in biologic-non-naïve patients at 3, 6 and 12 months after treatment initiation (Table S2). These findings are consistent with results from clinical trials and first real-world data, which show a better treatment outcome in biologic-naïve patients or patients directly randomized to the IL-23p19 arm instead of the biologic crossover arm[9,23,26,30,32,36,37]. However, it appears as though the class of the previously administered biologic does not influence the effectiveness of the IL-23p19 inhibitors (Table 4). It is noteworthy, that patients previously treated with IL-17 inhibitors had the highest PASI values at baseline among the biologic-non-naïve patients (Table 4). This may indicate a more difficult-to-treat patient cohort, as significantly more patients had already received more than one previous biologic treatment in the IL-17 group (65.1%) as compared to those in the TNF-alpha (35.0%) and IL12/23 (25.0%) groups (Table 1). This finding is consistent with those of another analysis of data from the Austrian registry, whereby patients treated with IL-17 inhibitors were significantly more often biologic-non-naïve patients[7]. The findings indicate that switching from IL-17 inhibitors to IL-23 inhibitors might be a promising therapeutic alternative if treatment with IL-17 inhibitors fails. Nevertheless, biologic-naïve patients showed

a significantly higher PASI improvement for all measured timepoints, despite having a higher skin burden at treatment start (Table 2). However, after correcting for previous biologic exposure, no major differences in PASI improvement could be detected in PASI for any timepoint among biologic-naïve or -non-naïve patients with regard to the administered drug, except for PASI at 12 months in biologic-non-naïve patients. (Table 3). These findings indicate that all IL-23 inhibitors are promising drugs for the subsequent treatment of biologic-non-naïve patients.

In general, the rate of adverse events (11.67%) observed in this study is much lower than that reported in clinical trials, as well as real-world patients (Table 6)[20,24,28,29,31]. The rates of adverse events found in this study were also similar to previously published rates between biologic-naïve and non-naïve patients (Table S3)[38].

Limitations. The registry`s retrospective design aside, the limitations of this study include the fact that only a low number of patients received tildrakizumab, limiting the validity of results reported for this drug. Furthermore, more patients than usual could have deviated from the regular administration of the prescribed drug due to the ongoing pandemic for several reasons (e.g. being placed under quarantine, waiting for vaccination, or worrying about developing a more severe course of COVID-19 while/due to taking immunomodulatory drugs).

Conclusion

IL-23 inhibitors are highly effective drugs for the treatment of chronic plaque psoriasis with biologic-naïve patients, enabling them to achieve better skin improvement than biologic-non-naïve patients. In biologic-non-naïve patients, the treatment effectiveness is not related to the class of the previously administered therapy. Therefore, IL-23p19 inhibitors represent a promising treatment alternative in patients for whom previous biologic treatment has failed. However, despite all of the improvements and progress made in the treatment of chronic plaque type psoriasis as reported from clinical studies and the fact that IL-23 inhibitors (together with anti-IL-17 inhibitors) are considered as the most effective class of anti-psoriatic drugs, the study also revealed that one patient out of four to five treated with these drugs under real-world conditions (i.e. outside of clinical studies) still does not achieve an entirely satisfactory treatment response (i.e. PASI < 3 and/or PASI 75). This makes the continued improvement of anti-psoriatic drugs desirable in order to provide a satisfactory response to all patients in need.

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Received: 7 March 2022; Accepted: 19 August 2022
Published online: 05 September 2022

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Acknowledgements

We thank the patients participating in PsoRA and all members of PsoRA (see grtps://psora.medunigraz.at/) who provided data for this analysis. Special thanks go to Matthias Wagner, Vienna, for development of the original electronic PsoRA database; Erich Schmiedberger, administrator of the newly developed electronic database; Maximilian Errath for technical support; and Andrea Berghold, Department chair, Institute for Medical Informatics, Statistics, and Documentation for continuous support in further development of the PsoRA database. We also thank Franz Trautinger, University Hospital of St. Poelten, Karl Landsteiner University of Health Sciences, Krems, Austria, for continuous support in promoting further development of PsoRA. Martina Praszl-Posch and Kirsten Sommer for support of data entry in the PsoRa database, Sara Crockett, Graz, Austria for editing of the manuscript. This work has been conducted as part of a doctoral thesis (T.G.).

Author contributions

T.G. conceived and designed the analysis, collected the data, performed the analysis and wrote the paper. W.W. collected and contributed the data, and edited the manuscript. C.J. collected and contributed the data, and edited the manuscript. P.S. collected and contributed the data. C. Z. collected and contributed the data. K.P. collected and contributed the data. C.S. collected and contributed the data. B.G. collected and contributed the data. W.S. collected and contributed the data. G.R. collected and contributed the data. C.P. collected and contributed the data. A.M. collected and contributed the data. N.H. collected and contributed the data. B.S. collected and contributed the data. H.T. collected and contributed the data, and edited the manuscript. R.M. collected and contributed the data. F.Q. performed the analysis and made graphical illustrations. W.S. collected and contributed the data, and edited the manuscript. P.W. conceived and designed the analysis, performed the analysis and wrote the paper. All authors have critically read the manuscript and approved its publication.

Funding

PsoRA has been supported by unrestricted research grants or educational grants from the following pharmaceutical companies: AbbVie, Amgen GmbH, Almirall, Astropharma, Boehringer-Ingelheim , BMS, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz, UCB Pharma and Pfizer.

Competing interests

PW has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Actavis, Amgen GmbH, Almirall, Boehringer-Ingelheim, BMS, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Merck Sharp & Dohme, Roche, Sandoz, Sanofi, Pfizer and UCB. TG has received a travel grant from Novartis, speaker honoraria from Amgen and Novartis, and consulting honoraria from Almirall. WS reports grants and personal fees from AbbVie, Almirall, Leo Pharma and Novartis. CJ served as PI (grant paid to institution), and/or received speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Almirall, Amgen, Eli Lilly, Janssen, Kyowa Kirin, LEO Pharma, Novartis, Pfizer, Recordati, Sandoz, Takeda UCB, and 4SC. WS reports grants and personal fees from Janssen, grants and personal fees from Amgen, grants and personal fees from Lilly, grants and personal fees from AbbVie, personal fees from Celgene, personal fees from Leo, personal fees from Novartis, outside the submitted work. NH has received honoraria for advisory boards from Eli Lilly, Almirall, Novartis and Leo Pharma. KP has received speaker and consulting honoraria from: Abbvie, Eli Lilly, Janssen and Novartis. Travel refunds from: Abbvie, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma and Novartis. WW has received speaker and/or consulting honoraria and/or travel refunds from AbbVie, Amgen GmbHm Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz and Pfizer. GR reports honoraria for training sessions or participation in advisory boards from Eli Lilly, Novartis, Janssen, UCB, Pelpharma, Abbvie, Leo Pharma. AM has received research grants, speaker and/or consulting honoraria, and/or travel refunds from AbbVie, Amgen GmbH, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, and Pfizer. BS reports industry grants/royalties from Abbott/Abbvie, Almirall, Celgene, Eli-Lilly, Galderma, Novartis, Pfizer, Trevi Therapeutics, UCB and Janssen Cilag. PS has received research grants, speaker and/or consulting honoraria, and/or travel refunds from Abbvie, Actelion, Amgen, Almirall, Janssen, Novartis, Leo Pharma, Pfizer, MSD, Celgene, Maruho, ALK, Galderma, Abbott, UCB, Gilead, Lilly.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-18790-9.

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Received: 22 January 2023 | Accepted: 21 July 2023

DOI: 10.1111/ddg.15213

ORIGINAL ARTICLE

Evolution of characteristics and biologic treatment effectiveness in patients of the Austrian psoriasis registry from 2004–2022

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Summary

Background and Objectives: This study analyzed the extent to which the recent introduction of more effective treatments has led to an improvement in real-world psoriasis patients.

Patients and Methods: Patient characteristics and the first-year treatment effectiveness in biologic-naive patients have been analyzed since 2004 until now, irrespective of treatment switches.
Results: Data from 2,729 patients were eligible for this analysis. The proportion of female patients increased significantly over the years from 29.9% to 36.2% ($p < 0.028$), while the number of patients with psoriatic arthritis declined from 36.6% to 30.0% ($p < 0.001$). Moreover, the duration of psoriatic disease and PASI at the start of the treatment significantly decreased. Last observation carrief forward (LOCF) analysis indicated that PASI 90 response increased from 18.9 to 44.6% at 3 months and from 32.9 to 66.8% at 12 months after treatment started. Similary, the PASI $\leq$ 3 rates increased from 33.2% to 66.0% at 3 months and from 41.9% to 78.9% at 12 months after the treatment started.
Conclusions: The continuous introduction of more efficient biologics has led to significant improvements in patient care and clinical outcomes. Though one out of three to five patients, depending on the endpoint selected, nowadays still does not achieve an entirely satisfactory treatment response (i.e., PASI 90 or PASI $\leq$ 3).

KEYWORDS
Psoriasis, psoriatic arthritis, psoriasis treatment, biologics

INTRODUCTION

The turn of the millennium ushered in a new therapeutic era as monoclonal antibodies and fusion proteins, also known as biologics, revolutionized the antipsoriatic treatment of patients with moderate to severe plaque psoriasis. Those patients have a high need for medical care.[1–3] In fact, psoriasis was reported to be the third most frequently treated disease in German dermatology clinics.[4] With the introduction of the interleukin (IL)-17 and IL-23p19 inhibitors for the treatment of plaque psoriasis, the efficacy has reached new heights, with more patients than ever achieving an excellent treatment response (i.e., $\geq$ 90% clearance of psoriatic lesions [Psoriasis Area and Severity Index, PASI 90 response], and full remission [PASI 100 response]) in clinical trials.[5–10] However, the efficacy of clinical trials cannot automatically be translated into the outcome of routine care, as real-world patients may differ from patients in clinical trials. Furthermore, real-world data registries have become recognized as crucial instruments that can be used to study biologic drug survival and drug effectiveness.[11,12] However, these studies have mostly examined the treatment effectiveness of specific drugs or in specific patient cohorts, irrespective of time-dependent dynamic changes in the use of anti-psoriatic drugs (or in the availability of treatment options).

In this study, we took the opportunity to scrutinize data from the Austrian Psoriasis Registry (PsoRA) to assess patient-focused anti-psoriatic treatment effectiveness in the years since the introduction of biologics (2003/2004) up to the current timepoint, irrespective of the prescribed treatment or treatment switches.

PATIENTS AND METHOD

This study was performed as an observational retrospective multicenter analysis of clinical data extracted from the Austrian Psoriasis Registry (PsoRA) on February 10, 2022. The design of this nationwide Austrian database has been described previously.[13–17] Detailed information about PsoRA is available at www.psoriasisregistry.at. The registry was approved by the Ethics Committee of the Medical University of Graz (application number 21–094 ex 09/10). The present analysis was conducted in accordance with the principles of the Declaration of Helsinki.

Data analysis and statistics

Data collected from adult patients with chronic plaque psoriasis who were biologic-naive and started biologic treatment in the period from April 30, 2004 (the first documented biologic treatment in the registry) to February 10, 2022 (data extraction) and who had at least one follow-up visit were eligible for this analysis. The assessment of PASI reduction was made based on data collected at 3, 6, and 12 months after the treatment started, irrespective of the administered biologic treatment or treatment switches to phototherapeutic, conventional systemic, or other biologic therapies. However, if a treatment switch was done, it had to be performed within 12 months of the initial treatment start, and a new therapy had to be initiated within 3 months of the discontinuation of the first administered treatment; otherwise, the treatment was considered to be terminated (end of treatment, EOT). The change in PASI

and PASI reduction was always analyzed in relation to the baseline PASI for all subsequent timepoints (i.e., 3, 6, and 12 months after the treatment started), irrespective of whether patients switched treatment or not (including multiple switches). The changes in the PASI and PASI reduction were analyzed as observed (ASOB) and as a last observation carried forward (LOCF) worst-case scenario, which considered the last known PASI or PASI reduction to be continued for further analysis. Otherwise, patients were considered non-responders, i.e., PASI < 50 response. For purposes of the analysis, patients were assigned to biologic generation eras by referring to the timepoint of biologic treatment initiation. Specifically, the first biologic generation era was initiated on April 30, 2004 with infliximab, alefacept, efalizumab, etanercept, and adalimumab; the second-generation era began with the first PsoRA-documented prescription of ustekinumab (March 26, 2009) as the first second-generation biologic; the third-generation era began on March 18, 2015 (first prescription of secukinumab), followed by ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab.

Patients whose visits spanned across two eras were allocated for the analysis to the first era of treatment. The PASI and PASI reduction referred to the closest visit to the simulated timepoints of 3, 6, or 12 months (with maximum grey periods of ± 4 weeks for 3 months and 8 weeks for 6 and 12 months, respectively).

Statistical analysis

A Kruskal-Wallis H test or Pearson's chi-square test was used to determine differences between treatment eras regarding patient characteristics or treatment goal achievement. Smooth interpolating curves were obtained by running generalized additive models using smoothing splines and applying the generalized cross-validation criterion. The R software package (version 4.1.3, www.r-project.org) was used to perform calculations and graphical interpretation. The post hoc analysis was performed by calculating pairwise comparisons using the Bonferroni correction. Statistical significance was set at $p < 0.05$.

RESULTS

Study participants

At the time of data extraction (February 10, 2022), PsoRA contained data on 4,731 patients. Of these, 2,729 patients were eligible for analysis, including 928 female patients (34.0%) and 1,801 male patients (66.0%) across all three eras (Table 1; Figure S1, online supplement). Overall, concomitant psoriatic arthritis was present in 874 patients (32.0%). Significant differences were observed across the three treatment eras regarding the number of female patients, with a continuous increase seen in female patients over time (29.9% in the first-generation era, 32.6% in the second-generation era, and 36.2% in the third-generation era) ($p = 0.028$) (Table 1). However, the number of patients with psoriatic arthritis significantly declined over time (36.6% in the first-generation era, 33.0% in the second-generation era, and 30.0% in the third-generation era) ($p < 0.001$). The proportion of patients with at least one comorbid disease was found to be highest in the third-generation treatment era (54.1% vs. 49.9% and 42.0% in the former eras) (Table 1). In addition, the mean duration of the psoriatic disease prior to starting biologic treatment became significantly shorter over time, as depicted in Table 1 ($p < 0.001$).

Treatment prescriptions

The most frequently used biologic drugs based on data extracted from our registry at the extraction date were: 1) etanercept (46.5%), efalizumab (21.5%), and adalimumab (15.7%) in the first-generation era. 2) adalimumab (44.6%), ustekinumab (31.5%), and etanercept (22.1%) in the second-generation era, and 3) ustekinumab (32.0%), adalimumab (18.7%), ixekizumab (18.0%), and secukinumab (13.1%) in the third-generation era (Table S1, online supplement). Treatment adherence increased from 60.4% in the first-generation era to 85.0% in the third-generation era (Table 1). However, the number of patients for whom data were not completely documented in the 12-month observational period was much higher in the third-generation era than in the preceding eras (32.6% vs. 1.3–4.7%) ($p = 0.001$) (Table 1). Furthermore, differences in the number of patients who permanently discontinued anti-psoriatic treatment were observed, with patients discontinuing biologic treatment in the first-generation era much more frequently than in later eras (23.7% vs. 5.5–10.9%) ($p < 0.001$) (Table 1). Significant differences in the proportions of patients who switched the initial treatment were reported, with the highest number of switches occurring in the first-generation era (15.9%) as compared to the second- (9.4%) and third-generation eras (9.4%) ($p < 0.001$) (Table 1). IL-17 inhibitors were the most frequently prescribed drugs (43.0%) among patients who discontinued the initial treatment in the third-generation era, followed by IL-23p19 inhibitors (25.2%), IL-12/23p40 inhibitors (11.9%), and TNF-α inhibitors (11.1%) (Table S1, online supplement; Figure 1).

Evolution of PASI at treatment start

The mean PASI (SD) at the start of biologic treatment decreased continuously from 17.9 (8.4) in the first-generation era to 9.0 (7.4) in the third-generation era ($p < 0.001$) (Table 1, Figure 2). Overall, 293 patients (16.7%) had a PASI ≤ 3 documented at the beginning of treatment out of the total number of patients (n = 1759) documented with a PASI at treatment start (see Table 1). However,

TABLE 1 Patient characteristics in the different biologic treatment eras. Pearson's chi-square test or Kruskall-Wallis H test, whatever was appropriate, was used to determine statistical significance among the different biologic treatment eras. Post hoc analysis shows significantly lower baseline PASI in patients in the third-generation era as compared to those in the first ($p < 0.001$) and second-generation eras ($p < 0.001$), and in the second-generation as compared to the first-generation era ($p < 0.001$). Significant p-values are bold.

Patient characteristics at treatment start are depicted as means (SD) or number (%)	Biologic treatment era*			p-value
	1st generation	*2nd generation*	*3rd generation*	
Total number of patients (n = 2729)	**465**	**834**	**1,430**	
Age (in years)	46.5 (12.6)	45.4 (13.6)	44.8 (14.8)	0.096
PASI**	17.9 (8.4)	13.9 (8.2)	9.0 (7.4)	< **0.001**
PASI ≤ 3**	1 (0.2)	26 (3.1)	266 (18.6)	< **0.001**
BMI	29.2 (6.6)	29.1 (6.1)	28.4 (6.2)	0.054
Weight (in kilogram)	87.9 (19.6)	90.5 (19.8)	86.3 (20.3)	**0.025**
Duration of psoriatic disease (in years)	20.5 (11.0)	25.4 (13.5)	15.9 (12.9)	< **0.001**
Female gender	139 (29.9)	272 (32.6)	517 (36.2)	**0.028**
Concomitant arthritis	170 (36.6)	275 (33.0)	429 (30.0)	< **0.001**
Patients with ≥ 1 comorbid disease	232 (49.9)	350 (42.0)	773 (54.1)	**0.00182**
Smoking***	2 (40.0)	31 (51.7)	224 (46.9)	< **0.001**
Continuation of initial treatment	275 (59.1)	626 (75.1)	750 (52.4)	< **0.001**
Discontinuation of initial treatment	110 (23.7)	91 (10.9)	79 (5.5)	< **0.001**
Switch to another treatment	74 (15.9)	78 (9.4)	135 (9.4)	< **0.001**
Observation period shorter than one year	6 (1.3)	39 (4.7)	466 (32.6)	< **0.001**

Abbr.: BMI, body mass index; PASI, Psoriasis Area and Severity Index; SD, standard deviation

*For definition of biologic treatment eras, please see the methods section.

**Baseline PASI (n = 1,759) was reported for 210, 443, and 1,106 patients in the first-, second-, and third-generation era, respectively.

***Smoking status was known for 5, 60, and 478 patients in the first-, second-, and third-generation era, respectively.

there were notable dissimilarities in the percentage of patients beginning treatment with a PASI ≤ 3 across the treatment eras. The majority of these patients were identified in the third-generation era (18.6%), whereas only 0.2% were reported in the first-generation era and 3.1% in the second-generation era. Differences in characteristics in patients with a PASI ≤ 3 and a PASI > 3 at treatment start in the third-generation treatment era were observed, with a significantly higher proportion of females (42.5% vs. 33.7%, $p = 0.011$) and presence of concomitant arthritis (42.5% vs. 25.7%, $p < 0.001$), as well as a higher proportion of palmar and/or plantar involvement (39.1% vs. 16.0, $p = < 0.001$) in the lower PASI group (Table S3, online supplement).

PASI response

The mean PASI response (SD) to treatment improved continuously and significantly over time (Figures 2, 3; Tables 2; Table S2, online supplement). More patients exhibited PASI 75, PASI 90, and PASI 100 responses at all timepoints in the third-generation era than in the preceding eras (Figure 3, Table 2). Likewise, the proportions of observed patients with a PASI ≤ 3 or PASI ≤ 1 increased continuously from 46.2% to 77.2%, and from 20.9% to 71.9% at 3 months, from 76.7% to 92.9%, and from 51.1% to 79.0% at 6 months, as well as from 56.5% to 92.8%, and from 41.3% to 76.9% at 12 months after the treatment started over the eras ($p = 0.117794$ and $p = 0.023164$) (Table S4, online supplement). Similar findings were observed in the LOCF analysis (Table S4, online supplement).

DISCUSSION

This is the first study to analyze the effectiveness of antipsoriatic treatments in biologic-naive patients who were treated with biologics in a treatment- and treatment-switch-independent manner. It is noteworthy that biologic allocation in Austria is commonly based on the German S3-guidelines for the treatment of plaque psoriasis.[18,19] Therefore, photo(chemo)-therapy, or non-biologic treatment options such as retinoids, methotrexate, ciclosporin, or fumaric acid should be used prior to biologic treatment initiation. However, for patients with severe disease, significantly impaired quality of life, severe itching, or involvement of hard-to-treat areas, biologic treatment may be initiated directly. Authorization for reimbursement from the patient's social insurance institution needs to be obtained prior to the initiation of biologic treatment prescriptions except for adalimumab, etanercept, or infliximab,

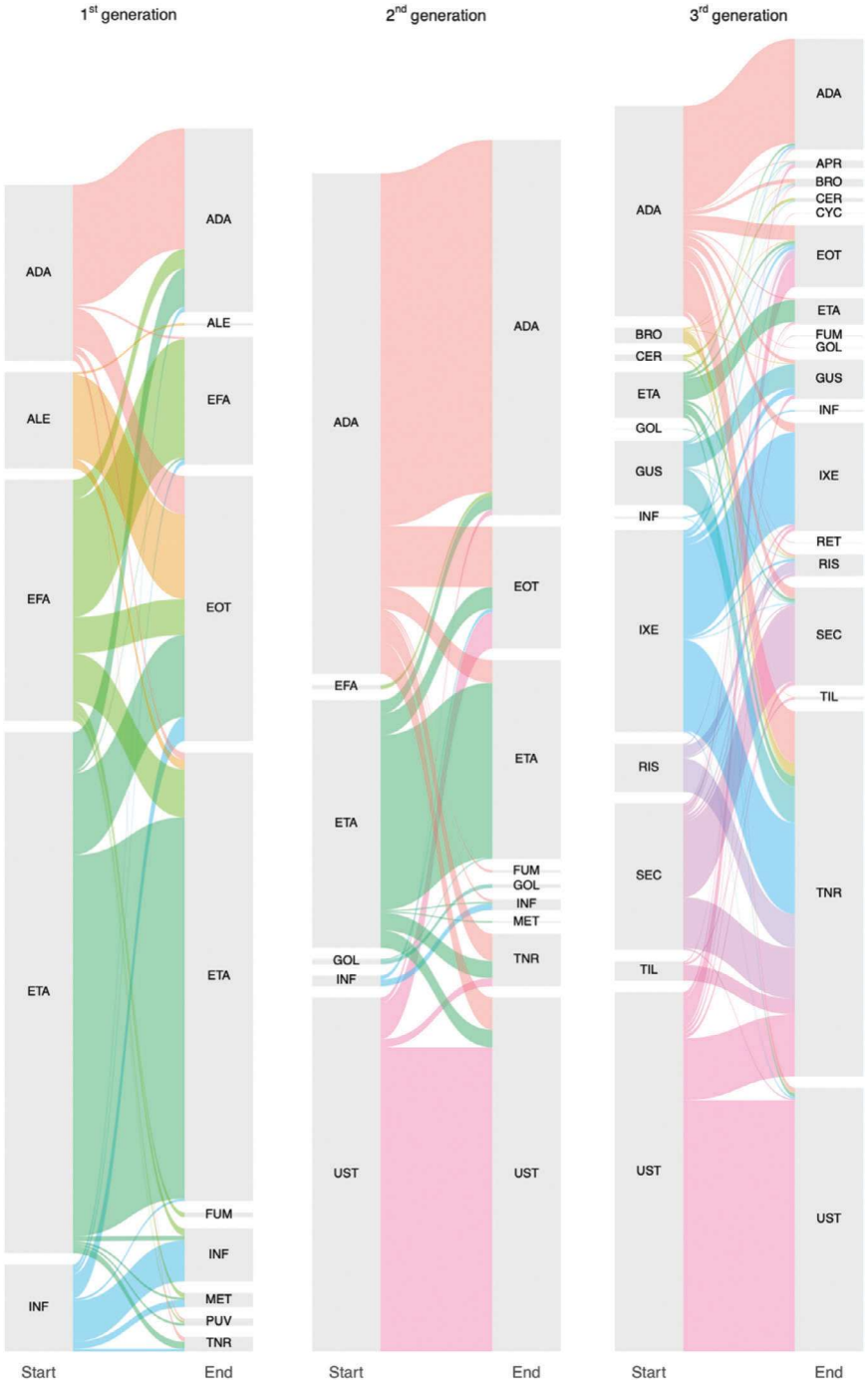

FIGURE 1 Prescription course in the three eras. The flow chart shows the proportion of patients who had started treatment on a specific drug and the respective treatment course during the observation period (1 year). Patients who continued a specific treatment during the whole observation period are depicted in the same flow stream in which they had started (i.e., ADA to ADA). Patients who were lost to follow-up (outcome unknown) or who had no reported visit at 12 months prior to the end of the observation period are depicted in the 12-month timepoint not reached (TNR) flow stream. Patients who permanently discontinued treatment prior to the end of the observation period are presented in the end of treatment (EOT) flow stream. To maintain readability, only the initial biologic and the biologic at the first treatment switch are displayed. *Abbr.*: ADA, adalimumab; ALE, alefacept; APR, apremilast; BRO, brodalumab; CER, certolizumab pegol; CIC, ciclosporin; EFA, efalizumab; EFA, efalizumab; ETA, etanercept; FUM, fumaric acid; GOL, golimumab; GUS, guselkumab; INF, infliximab; IL, interleukin; IXE, ixekizumab; MTX, methotrexate; PUVA, psoralen plus ultraviolet-A treatment; RET, retinoids; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab.

according to the Refund Code (i.e., EKO) of the Association of the Austrian Social Security Institutions.

An examination of the study findings, based on data from 2,729 patients, enables us to describe changes that took place in pre-treatment patient characteristics over time and to assess the treatment effectiveness, irrespective of the prescribed treatment or treatment switches that frequently occur in real-world patients.

This study is among the earliest to conduct time-dependent analysis, which considers the changing availability and diversity of biologic drugs. The results show that the PASI at the start of treatment significantly declined and that the clearance rates of psoriatic plaques continuously improved over time. Regarding patient characteristics, the proportion of female patients treated with biologics increased over time, while the overall duration of the disease decreased from the first report of disease symptoms to the start of treatment with biologics. Moreover, the number of reports of concomitant arthritis in patients treated with biologics filed in the Austrian Psoriasis Registry (PsoRA) decreased over time. The increase in the proportion of female patients observed over time in this study (from 29.9% in the first-generation era to 36.2% in the third-generation era) is consistent with findings from studies on

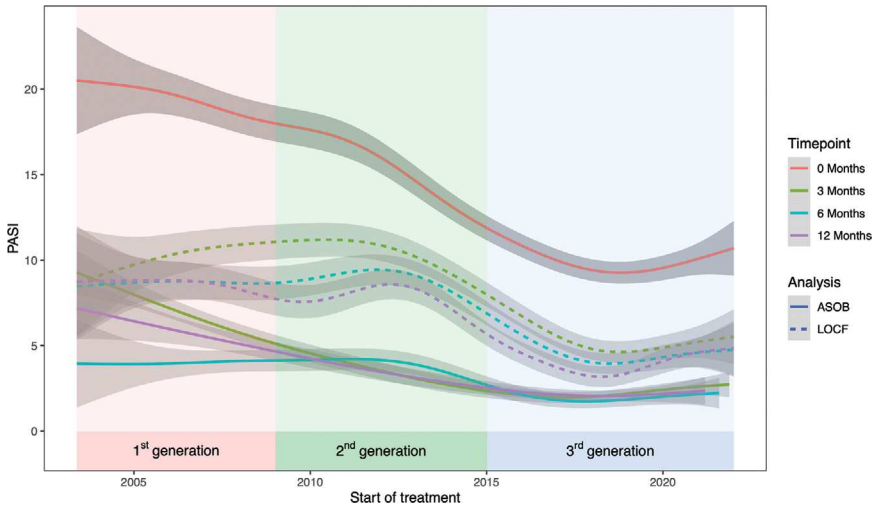

FIGURE 2 Treatment effectiveness in terms of absolute PASI in the three eras. Absolute Psoriasis Area and Severity Index (PASI) value (± 95% confidence interval) plotted over time for patients analyzed as observed (ASOB) and as last observation carried forward (LOCF).

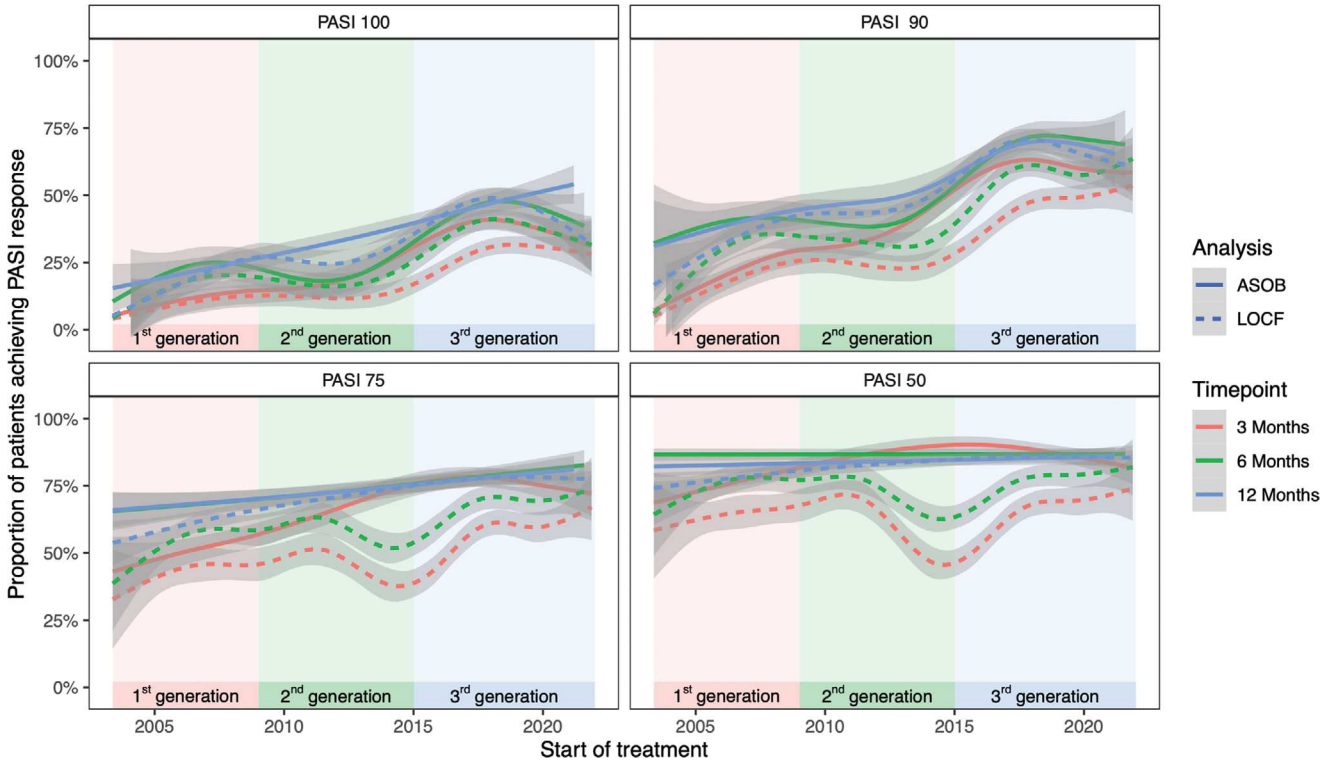

FIGURE 3 Achievement of treatment goals in the three eras. Relative number of patients analyzed as observed (ASOB) and as last observation carried forward (LOCF), for whom a certain Psoriasis Area and Severity Index (PASI) was achieved, is plotted over time.

data from other psoriasis registries. These analyses reported even higher proportions of female patients, namely, an increase in a German cohort from 42.2% to 45.2% (comparing data from 2004/2005 to 2016/2017) and in a Spanish cohort from 38.0 to 46.0% (comparing data from 2008 to 2018).[20,21] The decrease seen in the proportion of patients with psoriatic arthritis in this study (from 36.6% in the first-generation era to 30.0% in the third-generation era) is consistent with findings from studies on data from other registries. These analyses reported even lower proportions of patients with psoriatic arthritis, namely, a decrease in a German cohort from 20.6% to 17.4% (comparing data from 2004/2005 to 2013/2014) and in a Spanish cohort from 19.0% to 14.0% (comparing data from 2008 to 2018).[20–24] In this study, a reduction in disease duration prior to biologic treatment initiation was observed from 20.5 years in the first-generation era to 15.9 years in the third-generation era. These findings are similar to findings from a study on data from the Spanish psoriasis registry, namely, a reduction from 16.9 years to 13.9 years from 2008 to 2018.[20]

TABLE 2 Achievement of PASI reduction categories in the three eras. Pearson's chi-square test results indicate statistically higher PASI 100, PASI > 90, and PASI > 75 responses in the third-generation era. Significant p-values are bold.

Timepoint	PASI reduction category	Number (percentage) of patients achieving a certain PASI reduction in the respective treatment era* (ASOB/LOCF)						p-value	
		1st generation		*2nd generation*		*3rd generation*			
		ASOB	*LOCF*	*ASOB*	*LOCF*	*ASOB*	*LOCF*	*ASOB*	*LOCF*
3 months	Number of patients	359	419	383	547	767	1049	< **0.001**	< **0.001**
	PASI 100	42 (11.7)	42 (10.0)	67 (17.5)	67 (12.2)	295 (38.5)	295 (28.1)		
	PASI 90	79 (22.0)	79 (18.9)	131 (34.2)	131 (23.9)	468 (61.0)	468 (44.6)		
	PASI 75	186 (51.8)	186 (44.4)	242 (63.2)	242 (44.2)	593 (77.3)	593 (56.5)		
	PASI 50	272 (75.8)	272 (64.9)	329 (85.9)	329 (60.1)	676 (88.1)	676 (64.4)		
	< PASI 50	87 (24.2)	147 (35.1)	54 (14.1)	218 (40.0)	91 (11.9)	373 (35.6)		
6 months	Number of patients	246	419	287	547	504	1049	< **0.001**	< **0.001**
	PASI 100	59 (24.0)	74 (17.7)	56 (19.5)	95 (17.4)	224 (44.4)	392 (37.4)		
	PASI 90	100 (40.7)	125 (29.8)	112 (39.0)	176 (32.2)	350 (69.4)	599 (57.1)		
	PASI 75	170 (69.1)	233 (55.6)	197 (68.6)	309 (56.5)	407 (80.6)	714 (68.1)		
	PASI 50	214 (87.0)	318 (75.9)	240 (83.6)	387 (70.7)	445 (88.3)	800 (76.3)		
	< PASI 50	32 (13.0)	101 (24.1)	47 (16.4)	160 (29.3)	59 (11.7)	249 (23.7)		
12 months	Number of patients	299	419	335	547	630	1049	< **0.001**	< **0.001**
	PASI 100	68 (22.7)	80 (19.1)	98 (29.3)	146 (26.7)	300 (47.6)	470 (44.8)		
	PASI 90	119 (39.8)	138 (32.9)	161 (48.1)	249 (45.5)	426 (67.6)	701 (66.8)		
	PASI 75	202 (67.6)	251 (59.9)	233 (69.6)	380 (69.5)	503 (79.8)	826 (78.7)		
	PASI 50	242 (80.9)	318 (75.9)	277 (82.7)	455 (83.2)	547 (86.8)	905 (86.3)		
	< PASI 50	57 (19.1)	101 (24.1)	58 (17.3)	92 (16.8)	83 (13.2)	144 (13.7)		

Abbr.: ASOB, as observed; LOCF, last observation carried forward; PASI, Psoriasis Area, and Severity Index
*For definition of biologic treatment eras, please see the methods section.

An analysis of treatment prescriptions revealed that the implementation of newly introduced drugs in biologic-naive patients progressed slowly. This can be observed in the second-generation era, when adalimumab (n = 372) became the most frequently prescribed drug by far, followed by ustekinumab (n = 263), and then etanercept (n = 184). A similar pattern appears in the third-generation era, when ustekinumab (n = 458) became the predominant prescribed drug, followed by adalimumab (n = 268), then ixekizumab (n = 258), and finally secukinumab (n = 187). However, the exact opposite pattern is observed for biologic non-naive patients, who displayed higher rates of IL-17 and IL-23 inhibitor use than TNF-α inhibitor and ustekinumab use, as reported in our previous studies.[11,25]

Slightly lower prescription rates for IL-17 inhibitors were recently reported from a multinational observational study (39.0% vs. 32.5% in this study).[26] Differences in biologic treatment prescription were also observed compared to German medical claims data, with TNF-α inhibitors being the most frequently prescribed biologic treatment in patients with prevalent psoriasis (44.1% vs. 23.6% in this study), followed by IL-12/23p40 and IL-23p19 inhibitors (28.6% vs. 43.8% in this study) and IL-17 inhibitors (27.3% vs. 32.5% in this study), possibly reflecting different reimbursement guidelines and/or prerequisites.[27]

Treatment adherence was highest in the third-generation era (85.0% vs. 60.4% in the first- and 79.7% in the second-generation eras). This result initially seems to conflict with the results of our previous studies, where we reported an overall decrease in drug survival due to the introduction of new highly effective biologic drugs targeting IL-17.[11] However, a high number of patients received alefacept or efalizumab in the first-generation era (30.1%), and, at the time, these drugs were used in the form of an intermediate treatment regimen for 12 weeks rather than as long-term medication. Furthermore, biologic-naive patients also exhibited superior drug adherence rates for IL-12/23p40, IL-17, and IL-23p19 inhibitors, as reported in our previous studies.[11,25] Taking these factors into account, the findings of the current study are well in agreement with our previous findings.

The mean PASI at the treatment start in this study decreased from 17.9 in the first-generation era to 9.0 in the third-generation era. This score was significantly lower than those reported for the earlier eras in a post hoc analysis ($p < 0.001$ for comparisons against the data from the first- and second-generation eras) (Table 1, Figure 1). This finding is similar to those recently reported from a

German study, which found a decrease in PASI from 11.4 in 2004/2005 to 7.1 in 2016/2017, and a Spanish study, which found a decrease in PASI from 14.0 in 2008–2010 to 10 in 2015–2018.[20,21] Accordingly, the proportion of patients with a PASI $\leq$ 3 at the treatment start increased significantly from 0.2% in the first-generation era to 18.6% in the third-generation era (Table 1). The lower PASI observed at treatment start and the higher number of patients who started biologic treatment with a PASI $\leq$ 3 in the third-generation era may be due to the individualized treatment approach taken, which enables patients with localized involvement of sensitive body sites or a high psychological burden to be considered eligible for biologic treatment.[18,28] This is supported by a higher proportion of female patients as well as a higher rate of concomitant arthritis and palmar and/or plantar involvement in individuals with a PASI $\leq$ 3 at treatment start (Table S3, online supplement). Additionally, the higher proportion of patients with at least one comorbid disease could result from international recommendations promoting screening of psoriasis patients for comorbid diseases.[29] Moreover, the use of highly efficient drugs in psoriasis patients may also be beneficial for comorbid diseases (including cardiovascular disease and depression).[30,31] Nevertheless, 59.3% of psoriasis patients recently reported being only moderately or even less satisfied with their treatment, despite a large choice of effective therapies.[32] Therefore, more research is needed to enable individualized treatment, taking into account the development of immunological memory, transcriptomic patterns, and epigenetic changes.[33]

The treatment effectiveness as measured by the PASI in these patients significantly improved from 5.6 to 1.2 at 3 months and 4.6 to 1.1 at 12 months after the treatment started, comparing the first- and third-generation treatment eras ($p < 0.001$). A similar improvement in the absolute PASI values was also observed as a result of the LOCF analysis (Table S2, online supplement). Furthermore, the proportion of patients with a PASI $\leq$ 3 at the aforementioned timepoints increased from 46.2% to 77.2% and from 56.5% to 92.8%, respectively ($p = 0.117794$). In the LOCF analysis, these proportions improved from 33.2% to 66.0% and from 41.9% to 78.9%, respectively ($p = 0.073877$) (Table S4, online supplement). Likewise, the proportion of patients with an absolute PASI $\leq$ 1 improved from 20.9% to 71.9% or 15.0% to 50.4% at 3 months and from 41.3% to 76.9% or 26.6% to 64.3% at 12 months after the treatment started, depending on whether the ASOB ($p = 0.023164$) or the LOCF analysis ($p = 0.019867$) was considered (Table S4, online supplement). Similar proportions of patients exhibiting a PASI $\leq$ 3 or PASI $\leq$ 1 at the respective timepoints were observed after analyzing only patients with a PASI > 3 at the treatment start (Table S4, online supplement). The proportions of patients who exhibited a PASI $\leq$ 3 in the third-generation era in this study are slightly higher than those reported in a recent study from a similar time period (but not including IL-23p19 inhibitors); this study reported that 52.0%, 64.0%, and 66.7% of patients exhibited a PASI $\leq$ 3 at 3, 6, and 12 months after the treatment started, respectively.[34] The improvement in treatment effectiveness resulted in an increased proportion of patients who exhibited a PASI 100 response over time (i.e., increasing from 11.7% to 38.5% and from 22.7% to 47.6%), a PASI 90 (i.e., increasing from 22.0% to 61.0% and from 39.8% to 67.6%), and a PASI 75 (i.e., increasing from 51.8% to 77.3% and from 67.6% to 79.8%) at 3 and 12 months after the treatment started when comparing the first- and third-generation treatment eras, respectively ($p < 0.001$). Overall, the proportions determined in the LOCF analysis were significantly lower but similarly improved comparing the first- and third-generation treatment eras (Table 2).

Previously reported results for PASI 90 and PASI 75 response rates at 6 and 12 months after the treatment start in patients treated with adalimumab, etanercept, and ustekinumab were 43.2% and 43.9% for PASI 90 and 66.2% and 66.8% for PASI 75, respectively.[35] These findings are similar to the ASOB findings of this study for the second-generation era, with a PASI 90 of 39.0% and 48.1% and a PASI 75 of 68.6% and 69.6% after 6 and 12 months, respectively. Furthermore, response rates for PASI 75 in a combined patient cohort from Switzerland and Germany (treated with adalimumab, etanercept, infliximab, secukinumab, and infliximab) were 47.1%, 58.2%, and 62.8% at 3, 6, and 12 months after the treatment started. Thus, these findings are lower than those for the third-generation era in this study (i.e., 77.3%, 80.6%, and 79.8%, respectively) (Table 2).[34] Finally, the response rates reported from a study on data from the Danish psoriasis registry 12 months after the treatment start were 63.7% (PASI 75), 50.4% (PASI 90), and 37.5% (PASI 100) as compared to the 79.8%, 67.6%, and 47.6% ASOB rates, respectively, found in the current study (Table 2).[12]

Limitations

Apart from the registry's retrospective design, most of the patient data were derived from tertiary treatment centers; thus, this study may not necessarily reflect treatment effectiveness in the entire Austrian population of patients with psoriasis. Furthermore, PsoRA is designed as a treatment registry; therefore, changes in the overall population of psoriasis patients cannot be monitored. We also observed that there was a high number of patients in the third-generation era for whom the treatment outcome was (still) unknown. However, this is an inevitable finding that is presumably related to the ongoing coronavirus pandemic and the fact that the third-generation era is still ongoing. Due to the registry's retrospective design, patient visits may not exactly reflect the aforementioned timepoints.

CONCLUSIONS

Although the clinical effectiveness of antipsoriatic treatment, and the quality of care have improved significantly over time, our study showed that one in three or five patients, depending on the endpoint (i.e., PASI 90 or PASI ≤ 3), still does not currently achieve an excellent treatment response. For this reason, continuous effort is still warranted to further develop and improve targeted treatments as well as patient care.

ACKNOWLEDGEMENTS

We thank the patients participating in PsoRA and all members of PsoRA (see https://psora.medunigraz.at/) who provided data for this analysis. Special thanks go to Matthias Wagner, Vienna, for development of the original electronic PsoRA database; Erich Schmiedberger und Maximilian Errath for technical support; and Andrea Berghold, Department Chair, Institute for Medical Informatics, Statistics and Documentation for continuous support in further development of the PsoRA database. We also thank Martina Praszl-Posch and Kirsten Sommer for support of data entry into the PsoRA database. This work has been conducted as part of a doctoral thesis (T.G.).

CONFLICT OF INTEREST

PW has received research grants from AbbVie, Amgen, Almirall, Astropharma, Boehringer-Ingelheim, BMS, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz, UCB Pharma, and Pfizer. Honoraria or fees from Eli Lilly, Celgene, travel grants from AbbVie and has served on the boards of Amgen, BMS, Boehringer-Ingelheim, Celgene, Janssen-Cilag, Leo Pharma, Eli Lilly, Novartis and UCB. TG has received travel grants from Novartis, Sanofi and Amgen, speaker fees from Amgen, Eli-Lilly, and Novartis, and consulting fees from Almirall. WS reports grants and honoraria from AbbVie, Almirall, BMS, Leo Pharma, MSD, and Novartis. WS reports grants and personal fees from Janssen, grants and personal fees from Amgen, grants and personal fees from Lilly, grants and personal fees from AbbVie, personal fees from Celgene, personal fees from Leo, personal fees from Novartis, outside the submitted work. KP has received speaker and consulting fees from: Abbvie, Amgen, BMS, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Sobi, and UCP. He has received travel reimbursement from: Abbvie, Amgen, BMS, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, and UCP. GR reports consulting fees from Almirall, Leo Pharma, Boehringer Ingelheim, Janssen-Cilag, Abbvie, Eli Lilly and Novartis. Honoraria from Almirall, Leo Pharma, Boehringer Ingelheim, Janssen-Cilag, AbbVie, Eli Lilly, and Novartis. Travel grants from Sanofi. Board service from Eli Lilly, Novartis Boehringer. CB has received consultancy fees and/or honoraria from Eli Lilly, Sanofi, Abbvie, Leo Pharma and Novartis. WH has received personal honoraria from Novartis and Abbvie. FL has received consultancy fees from AbbVie, Celgene, Eli Lilly, Galderma, Leo Pharma, Menlo Therapeutics, Novartis, Pfizer, Trevi Pharma, Vifor Pharma. Honoraria from Almirall, Celgene, Eli Lilly, Galderma, Leo Pharma, Menlo Therapeutics, Novartis, Pelpharma, Pfizer, Trevi Therapeutics, Vifor Pharma. Travel grants from AbbVie, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Leo Pharma, Novartis, Pelpharma, Pfizer. AM has received consulting fees from AbbVie, Eli Lilly, Janssen-Cilag, Novartis. Honoraria from AbbVie, Eli Lilly and Janssen-Cilag. Advisory board fees from Eli Lilly and Novartis. CP has received consultancy fees from Novartis, Eli Lilly, Almirall, Amgen, Leo Pharma, SOBI, Janssen, AbbVie, Pfizer. Honoraria from Novartis, Eli Lilly, Almirall, Amgen, Leo Pharma, SOBI, Janssen, AbbVie, Pfizer. Travel grants from Novartis, Eli Lilly, Almirall, Amgen, Leo Pharma, SOBI, Janssen-Cilag, AbbVie, Pfizer. LR has received consulting fees and/or honoraria from Eli Lilly, Novartis, AbbVie, Amgen, Leo Pharma, Janssen-Cilag, and Almirall. Payment for expert testimony from Amgen, Leo Pharma, Eli Lilly, and AbbVie. Travel grants from AbbVie, Janssen-Cilag, and Amgen. BS has received travel grants from Sanofi and Eli Lilly. CS has received consulting fees from Almirall, Janssen-Cilag, Novartis, UCB, Boehringer Ingelheim and/or served on their board. PS has received consultancy fees from AbbVie, Amgen, Almirall, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, UCB and Pfizer. Honoraria from AbbVie, Amgen, Celgene, Eli Lilly, Janssen-Cilag, and Novartis. Travel grants from Amgen. Board membership from Almirall. MS reports board participation for Biontech. Leadership or fiduciary role in the Austrian Society of Dermatology and Venereology, and in the European Society for Dermatological Research. MSB reports honoraria from Abbvie, Eli Lilly, Celgene, Novartis. Travel grants from AbbVie, Pfizer, Celgene and Janssen-Cilag. Board participation from AbbVie, Janssen-Cilag. and Celgene. HS reports consulting fees and honoraria and travel grants from AbbVie, Almirall, Amgen, Janssen-Cilag, Leo Pharma, Eli Lilly, Novartis, Pfizer and UCB. IV reports consulting fees and honoraria from AbbVie, Eli Lilly, Novartis, Janssen-Cilag and Leo-Pharma. Participation in boards from Eli Lilly and Novartis. KWS reports consulting fees and payment for expert testimony from Eli-Lilly and AbbVie. Honoraria from Eli Lilly, Leo Pharma, Janssen-Cilag, AbbVie, Almirall and Novartis. CZ reports participation in boards from Almirall. CJ reports consulting fees, honoraria and board participation from AbbVie, Almirall, Amgen, Boehringer Ingelheim, BMS, Janssen-Cilag, Leo Pharma, Eli Lilly, Kyowa Kirin, Novartis, Pfizer, Recordati Rare Diseases, Sandoz, Takeda and UCB. Travel grants from AbbVie, Almirall, Janssen-Cilag, Eli Lilly, Kyowa Kirin, Takeda. HT has received honoraria from Novartis, AbbVie, Amgen and Leo Pharma, and travel grants from AbbVie, Amgen. NH reports consulting fees and travel grants from AbbVie, Almirall, Amgen, Janssen, Eli Lilly, Neoplas med and Sanofi.

FUNDING SOURCES

PsoRA has been supported by unrestricted research grants or educational grants from the following pharmaceutical

companies: AbbVie, Astropharma, Amgen GmbH, Almirall, Boehringer-Ingelheim, BMS, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Merck Sharp & Dohme, Sandoz, UCB Pharma and Pfizer.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Graier T, Salmhofer W, Jonak C, et al. Evolution of characteristics and biologic treatment effectiveness in patients of the Austrian psoriasis registry from 2004–2022. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2023;21:1513–1523.
https://doi.org/10.1111/ddg.15213