Diploma thesis

Anti-TNF-α induced psoriasis

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Markus Ängsäter

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Statement in Lieu of an Oath

Herewith, I formally declare, that I've written this thesis on my own. Furthermore, I confirm that no other sources have been used other than the ones referred to in this thesis.

Graz, July 2018 *Markus Ängsäter eh*

Abstract

Background: Since their introduction more than a decade ago, tumor necrosis factors alpha (TNF-α) inhibitors have shown to significantly improve the treatment of patients with refractory, severe chronic immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PsA). TNF-α has been shown to have a pivotal role in the immunopathogenesis of these diseases. However, up to 5.3 % of patients treated with TNF-α inhibitors develop anti-TNF-α induced psoriasis.

Objective: The aim of this study was to examine the clinical characteristics and outcomes of patients suffering from anti-TNF-α induced psoriasis.

Methods: A thorough literature review was performed to collect the relevant data for the time period between 1999 and 2016.

Results: In total, 434 cases (281 females, 153 males, mean age 41.1 years) of anti-TNF-α induced psoriasis were analyzed. The compiled data of our literature review revealed that most cases of anti-TNF-α induced psoriasis were attributable to infliximab (n=235/434, 54.1 %), followed by adalimumab (n=116/434, 26.7 %) and etanercept (n=74/434, 17.1 %). Complete resolution was observed in 33.1 % of the patients (n=44/133), who continued anti-TNF-α therapy with the causative agent and in 45.0 % of the patients (n=77/171), who discontinued therapy with the inculpated anti-TNF therapeutic. Interestingly, in 24.0 % (n=12/50) of the patients, who switched to a 2nd TNF-α inhibitor, a complete resolution was achieved.

Conclusion: Concerning the treatment of anti-TNF-α induced psoriasis, there is a significant lack of data, how to treat it most efficiently. Whether the causative TNF-α inhibitor might further be used, when combined with topical medication, or can be switched to another TNF-α inhibitor or a biologic with a different mode of action (e.g. ustekinumab), remains an open question. Therefore, prospective studies addressing this question and the development of guidelines as well as treatment algorithms for anti-TNF-α induced psoriasis are of utmost importance.

Zusammenfassung

Hintergrund: Tumornekrosefaktor-alpha-Blocker haben sich seit ihrer Einführung als eine äußerst effektive Therapieoption für schwere therapierefraktäre Formen chronisch entzündlicher immun-mediierter Erkrankungen wie Rheumatoide Arthritis, Morbus Bechterew, Morbus Chron, Psoriasis Vulgaris und der psoriatrischen Arthritis erwiesen. Dies ist durch die zentrale Rolle von TNF-α in der Pathogenese dieser Erkrankungen zu erklären. Nichtsdestotrotz, entwickelt sich bei bis zu 5,3 %, der mit TNF-α Inhibitoren behandelten PatientInnen, eine paradoxe Nebenwirkung: die TNF-α Blocker induzierte Psoriasis.

Zielsetzung: Ziel dieser Studie war es die klinischen Merkmale von betroffenen PatientInnen sowie das Management und Outcome, der mit den TNF Inhibitoren assoziierten Fälle der Psoriasis, zu analysieren.

Methoden: Eine umfassende Literaturrecherche wurde durchgeführt um relevante Daten im Publikationszeitraum von 1999 bis 2016 zu erhalten.

Ergebnisse: Insgesamt wurden 434 Fälle (281 Frauen, 153 Männer, Durchschnittsalter: 41,1 Jahre) analysiert. Die Datenanalyse ergab, dass die meisten Fälle auf die Applikation von Infliximab zurückzuführen waren (n=235/434; 54,1 %), gefolgt von Adalimumab (n=116/434; 26,7 %) und Etanercept (n=74/434; 17,1 %). Eine vollständige Rückbildung der paradoxen psoriatrischen Hautveränderungen konnte bei 33.1 % (n=44/133) der PatientInnen, die die Therapie mit dem verursachenden Agens fortsetzten, und bei 45 %, welche die Therapie absetzten, beobachtet werden. Bemerkenswert ist, dass bei 24 % derer, bei denen ein Wechsel auf einen zweiten TNF-α Antagonisten erfolgt war, ebenfalls eine Restitutio ad integrum beobachtet werden konnte.

Konklusion: Bezüglich der adäquaten Behandlung der TNF-α Blocker induzierten Psoriasis bleiben viele Fragen mangels derzeitiger Studienlage offen: Wann soll das verursachende Agens abgesetzt werden? Wie lange kann durch Ergänzung von topischen Therapeutika versucht werden, eine Fortsetzung der Anti-TNF-α Therapie zu gewährleisten? Kann der Wechsel auf andere Biologika wie Ustekinumab oder gar auf einen anderen TNF-α Antagonisten sinnvoll sein? Prospektive Studien, die sich dieser Fragen annehmen, sowie die Schaffung von Leitlinien und Therapiealgorithmen zur Behandlung dieser paradoxen Nebenwirkung sind von äußerster Wichtigkeit.

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Abbreviatons

AA	Alopecia areata
ACPA	Anti-citrullinated peptide antibody
ADA	Adalimumab
ADCC	Antibody-dependent cytotoxicity
AP-1	Adaptor protein complex 1
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
AZA	Azathioprine
BMI	Body mass index
BSA	Body surface area
cAMP	cellular cyclic adenosine monophosphate
CARD14	Caspase recruitment domain-containing protein 14
CD	Crohn's disease
CD40L	Cluster of differentiation 40 ligand
CDC	Complement-dependent cytotoxicity
CR	Case report
CRP	C-reactive protein
CS	Case series
CXCR3	Chemokine (C-X-C motif) receptor 3
CZP	Certolizumab pegol
DC	Dendritic cell
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drugs
e.g.	exempli gratia
EMA	European Medicines Agency
ETA	Etanercept
FasL	Fas ligand
Fc-Rn	Neonatal Fc receptor
Fcγ-R	Fc gamma receptor
FDA	United States Food and Drug Administration
GOL	Golimumab
GPP	Von Zumbusch (acute) generalized pustular psoriasis
GWAS	Genome wide association studies
HIV	human immunodeficiency virus
HLA-B27	Human leukocyte antigen B27
HLA-Cw6	Human leukocyte antigen Cw6
HS	Hidradenitis suppurativa
i.e.	id est
i.v.	intravenous
IBD	Inflammatory bowel disease
IFN- γ	Interferon gamma
IFN-α	Interferon alpha
IFN-β	Interferon beta
IRF-1	Interferon regulatory factor-1
IFX	Infliximab
IgG1	Immunoglobin G1
IgG1κ	Immunoglobin G1 kappa
IL-1	Interleukin 1

IL-2	Interleukin 2
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-10	Interleukin 10
IL-12	Interleukin 12
IL-17	Interleukin 17
IL-17R	Interleukin 17 receptor
IL-22	Interleukin 22
IL-23	Interleukin 23
IL-23R	Interleukin 23 receptor
IL-36	Interleukin 36
IL-36RN	Interleukin 36 receptor antagonist
ILAR	International League of Associations for Rheumatology
IMID	Immune mediated inflammatory disease
JIA	Juvenile idiopathic arthritis
kDa	Kilodalton
LEF	Leflunomide
LL37	Cathelicidin
LT	Lymphotoxin
LT-α	Lymphotoxin A
mAb	monoclonal antibody
mDC	myeloid dendritic cells
MTX	Methotrexate
MxA	Myxoprotein A
n/a	non available
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK cells	Natural killer cells
NMSC	Non-melanoma skin cancer
nrAxSpA	non-radiographic axial spondyloarthritis
NSAIDs	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OR	Odds ratio
PAEs	Paradoxical adverse events
PASI	Psoriasis Area and Severity Index
pDCs	plasmacytoid dendritic cells
PPPP	Palmoplantar Pustular Psoriasis
PS	Prospective study
PsA	Psoriatic arthritis
PSORS	Psoriasis susceptibility locus
PUVA	Psoralen and ultraviolet A
RA	Rheumatoid arthritis
RANKL	Receptor activator of NF-κB ligand
RCT	Randomized clinical trial
REL	NF-κB subunit
RF	Rheumatoid factor
RR	Relative risk
RS	Retrospective study
RUNX3	Runt-related transcription factor 3
s.c.	subcutaneous
SADs	Synthetic antimalarial drugs

SAPHO	Synovitis Acne Pustulosis Hyperostosis Osteitis
SNPs	Single nucleotide polymorphisms
SpA	Spondyloarthritis
STAT3	Signal transducer and activator of transcription 3
sTNF	soluble tumor necrosis factor
TACE	TNF-α converting enzyme
TB	Tuberculosis
TLR	Toll-like receptor
tmTNF	transmembrane tumor necrosis factor
TNF-α	Tumor necrosis factor alpha
TNF-β	Tumor necrosis factor beta
TNFR1	TNF receptor 1
TNFR2	TNF receptor 2
TRAIL	TNF-related apoptosis inducing ligand
TRAPS	Tumor necrosis factor receptor associated periodic fever
TYK2	Non-receptor tyrosine-protein kinase 2
UC	Ulcerative colitis
U.S.	United States
UV	Ultraviolet
UVB	Ultraviolet B
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1 Introduction

Since their introduction more than a decade ago, tumor necrosis factors alpha (TNF-α) inhibitors have shown to significantly improve the treatment of patients with refractory severe chronic immune mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PsA).[1–4] Accordingly, TNF-α or the dysregulation thereof has proven to have a pivotal role in the immunopathogenesis of the aforementioned diseases.[5] However, as with every group of therapeutics, side effects may arise. One adverse event in particular has been discussed increasingly in recent publications, due to its paradoxical nature, TNF-α inhibitor induced psoriasis.[6–12] This phenomenon has yet to be fully elucidated and underlines the complexity of the pathophysiology in immune-mediated diseases such as psoriasis.[6–12]

The aim of this study was to examine the clinical characteristics and outcomes of patients with psoriasis associated with TNF-α inhibition. To find out more about this phenomenon is of major importance, as its appearance often leads to the discontinuation of anti-TNF-α treatment and consequently to the cessation of an effective treatment option.

1.1 Tumor Necrosis Factor-α

Despite the fact that TNF-α was initially discovered due to its tumor cytotoxicity about 30 years ago, TNF-α is currently more of interest for its pleiotropic role in immune regulation and its proinflammatory features.[13] Thus, this cytokine became a target in the treatment of inflammatory processes.[14] The significant role of TNF-α in the pathogenesis of distinct IMIDs such as rheumatoid arthritis (RA),[15] inflammatory bowel disease (IBD),[16] psoriasis, psoriatic arthritis (PsA)[17] or ankylosing spondylitis (AS)[18] among others has been validated over the last decade and has been clearly demonstrated by the successful treatment of these disorders with TNF-α inhibitors.[13]

The multifarious range of biological effects of TNF-α is what makes it one of the most researched cytokines.[19] Overall, TNF-α is eventually, owing to its pleiotropy, a cytokine with activities basically found in every biological system, ranging from the presence in immune system physiology to neurobiology and beyond.[19]

As a detailed review of the various properties of TNF-α, such as its role in apoptosis and sophisticated role in neurosciences, is beyond the scope of this thesis, an effort on the following pages will be made, to summarize the most important physiological and

pathophysiological attributes of TNF-α.

In sum, the role of TNF-α concerning health and disease is very complex.[5] However, in simplified terms, TNF-α can be described as a sentinel cytokine of the innate immune system, due to the fact that it is a key player in the initiation and orchestration of inflammation as an initial response to local injury.[5] Low concentrations of TNF-α are considered advantageous, since it leads to the enhancement of host defense mechanisms against infections, whereas overexpression of TNF-α is considered deleterious, as it can lead to abundant inflammation, as illustrated in the course of sepsis, which ultimately may result in septic shock, when released acutely.[5,20] Taken together, inappropriate surplus production of TNF-α may lead to tissue destruction and organ injury, while controlled expression of TNF-α is essential to fight infections and promote tissue repair.[5]

As a result, elevated TNF-α levels can be found in the serum and tissues of patients with inflammatory and infectious conditions, whereas excess amounts of TNF-α are ordinarily not measurable in healthy individuals.[21] Noteworthy, is the positive correlation between serum concentrations of TNF-α and the severity level of infections.[21] Accordingly, surplus amounts of TNF-α have been detected in the sera and in the affected tissues of IMIDs, e.g. in skin samples of psoriasis patients, in synovial fluid punctures of patients with RA, AS or PsA and intestinal tissue samples of IBD patients, respectively.[18,22–25] Besides its own ability to cause pathogenic effects to the affected tissue, TNF-α is generally considered as the origin of an inflammatory cascade within an inflammatory network in immune-mediated inflammatory diseases, as it induces further mediators of inflammation such as IL-1ß, IL-6 and C-reactive protein (CRP).[5] Alternatively, TNF-α can be viewed as an exceptionally important proinflammatory cytokine within a complex inflammatory network.[5]

TNF-α is part of a family of cytokines known as the "TNF superfamily".[20] Apart from TNF-alpha, other cytokines such as lymphotoxin (LT), formerly termed TNF-β, CD 40 ligand (CD40L) or Fas ligand (FasL) are part of this group as well as the TNF-related apoptosis-inducing ligand (TRAIL) and the receptor activator of NF-κB ligand (RANKL).[20] Physiological functions and pathophysiological roles of the various members have shown to be very distinct.[20] Nonetheless, for the most part, TNF family members are involved with the regulation of cell proliferation and apoptosis, albeit TNF-α, LT and FasL also possess proinflammatory properties principally by inducing NFκß (nuclear factor kappa-light-chain-enhancer of activated B cells).[20]

Although the main source of TNF-α are immune cells such as activated monocytes, macrophages, microglia, natural killer cells (NK cells), T cells, B cells, mast cells or dendritic cells, a plethora of non-immune cells including endothelial cells, keratinocytes, neurons and fibroblasts are equally associated with the synthesis of this cytokine.[19,20,26] Cytokines that have been identified to be associated with TNF-α production comprise cytokines such as interleukin 1 (IL-1), interleukin 17 (IL-17), granulocyte macrophage colony-stimulating factor and interferon-γ (IFN- γ).[5] Likewise, bacteria, viruses, immune complexes, complement factors, tumor cells, exposure to irradiation and ischemia, as well as trauma can provoke TNF-α generation.[5] Moreover, there are several feedback loops involved in the regulation and dysregulation of TNF-α production.[5] For instance, a positive feedback loop is mediated by the TNF-α induced cytokines IL-1, IL-2 and IFN-γ, which conversely spur the continuous production of TNF-α.[5] Likewise, negative feedback loops involve mediators such as IL-10, prostaglandins and corticosteroids, which when released suppress additional replication of TNF-α.[5]

TNF-α is initially produced as a precursor homotrimeric transmembrane protein (tmTNF), which can be detected on cell surfaces of the previously listed cells.[19,27] The soluble form of TNF-α, another homotrimer cytokine, which is referred to as sTNF, is the result of proteolytic cleavage of tmTNF by a metalloprotease, termed ADAM-17 or TNF-alpha-converting enzyme (TACE).[19,27] Albeit tmTNF and sTNF are in principle the same molecule, disparities between the two are noticeable, as they seem to differ significantly in biologic function.[28] sTNF is the form of TNF-α that enables the cytokine to exert its endocrinologic function on remote sites, although the biologic and pathologic activity of TNF-α is implemented by both forms.[5,19] tmTNF is suggested to be heavily involved in local inflammation processes, as it exercises its biological function per paracrine and autocrine signal transduction.[29,30] Hence, in contrast to sTNF, tmTNF can either act as a ligand on TNF receptors of target cells or as a receptor on tmTNF-carrying cells,[27] which enables the linked cells to reversely send signals back to tmTNF-bearing cells (outside-to-inside).[29,31] So-called “reverse signaling” of tmTNF has yet to be fully understood, as still very little is known compared to the features of sTNF as a ligand.[29,31]

Apart from the preceding information about their disparities in general, the two TNF-α forms appear to further differentiate regarding their binding predilection.[5] To carry out their function, both the soluble and precursor form of TNF-α can bind to two distinct receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2).[5] TNFR1 can basically be found on every cell type except erythrocytes and carries a death domain-motif.[14] TNF

receptor 2 is mostly inducible and limited to specific cells, as TNFR 2 is preferably expressed on endothelial cells and immune cells.[5,14] Notably, TNFR2 does not bear a death domain and lacks the ability of TNFR1 to induce apoptosis.[14] Interestingly, tmTNF seems to have a much higher affinity for TNFR2 than for TNFR1.[19] Thus, supposedly biologic functions of tmTNF are chiefly mediated through TNFR2.[27] Moreover, recent rodent studies, as Fischer et al.[32] state in their review, point to distinct functions of the two TNF receptors.[32] While tissue degeneration and inflammation is primarily attributed to a TNFR1 mediated pathway, TNFR 2 is suggested to mediate homeostatic effects, as it is involved with tissue regeneration and immune modulation.[32] Therefore, development of new TNF inhibitors has focused on selective blocking of the sTNF-TNFR1 pathway, attempting to leave the tmTNF-TNFR2 pathway intact.[33]

1.2 TNF-α inhibitors

Since the first approval of infliximab (IFX) for IBD in August 1998 by the United States Food and Drug Administration (FDA), TNF-α inhibitors have shown remarkable efficacy in the treatment and management of IMID patients.[34] Biologics in general have the advantage of being more specific than previous treatment options (e.g. steroids, azathioprine, etc.), as they target key mediators involved in the pathogenesis of IMIDs.[35] Inhibition of TNF-α in particular has been established to hinder pathological mechanisms in IMIDs on numerous levels by intervening with the recruitment of inflammatory cells (inflammatory response), engendering apoptosis in inflammatory cells and inducing a decrease of cytokine production in various cell types.[36] Ideally, this implicates the blockage of the inflammatory processes and leads to a rehabilitation of affected tissues.[36] The therapeutic approach for chronic inflammatory diseases usually commences with the induction phase, in which the primary goal is to accomplish a state of remission.[34] Subsequently, the ambition is to retain remission and preclude the recurrence of disease flares.[34] Therefore the induction phase is ensued by the maintenance phase.[34]
At present, five licensed TNF-α antagonists are available on the European and the United States (U.S.) market, namely infliximab (IFX), etanercept (ETA), adalimumab (ADA), golimumab (GOL) and certolizumab pegol (CZP).[13] The currently approved indications, their trade names, the route of administration, administration frequency and various properties of the commercially available TNF-α inhibitors are summarized in Table 1.

Table 1. List of currently available TNF inhibitors and their approved indications[37–47]

Drug name & structure	Trade name (first approval dates)	Route/Frequency/Half-life/Ligand[5]	FDA approved indications	EMA approved indications
Etanercept Recombinant fusion protein: Human TNFR2:IgG1-Fc	Enbrel® (FDA: 11/1998; EMA: 02/2000)	s.c. injection/ weekly (for psoriasis patients only following loading dose 2x a week for 3 months)/ 4 days/ sTNF + mTNF + LT	• RA • JIA • Psoriatic arthritis • AS • Plaque psoriasis • Pediatric plaque psoriasis	• RA • JIA • Psoriatic arthritis • AS • nr-axSpA • Plaque psoriasis
Infliximab Humanized (chimeric) IgG1κ mAb	Remicade® (FDA 08/1998; EMA 08/1999)	i.v. infusion/ every 8 weeks, following loading at 0, 2, 6 weeks/ 8-10 days/ sTNF + mTNF	• IBD (CD + UC) • Pediatric IBD (CD + UC) • RA[a] • AS • Psoriatic arthritis • Plaque psoriasis	• IBD (CD + UC) • Pediatric IBD (CD + UC) • RA[a] • AS • Psoriatic arthritis • Plaque psoriasis
Adalimumab Human IgG1κ mAb	Humira® (FDA:12/2002; EMA: 09/2003)	s.c. injection/ every 2 weeks/ 10-20 days/ sTNF + mTNF	• RA • JIA • AS • Psoriatic arthritis • Plaque psoriasis • IBD (CD + UC) • Pediatric CD • Hidradenitis suppurativa • Uveitis (non-infectious)	• RA • JIA • AS • nr-axSpA • Psoriatic arthritis • Plaque psoriasis • Pediatric plaque psoriasis • IBD (CD + UC) • Pediatric CD • Hidradenitis suppurativa • Uveitis
Golimumab IgG1κ mAb	Simponi® (FDA 04/2009; EMA 10/2009) Simponi aria® (FDA 07/2013; EMA no approval)	s.c. injection/ every 4 weeks/ 7-20 days/ sTNF + mTNF i.v. infusion/ every 8 weeks following loading at 0 and 4 weeks/ approximately 14 days	• RA[a] • AS • Psoriatic arthritis • UC	• RA[a] • AS • nr-axSpA • Psoriatic arthritis • UC • JIA[a]
Certolizumab Pegol Pegylated-Fab' fragment of humanized IgG1κ mAb	Cimzia® (FDA 04/2008; EMA 10/2009)	s.c. injection/ every 2 weeks/ approximately 14 days/ sTNF + mTNF	• RA • AS • Psoriatic arthritis • CD	• RA • AS • nr-axSpA • Psoriatic arthritis

[a] only approved in combination with MTX

Abbreviations: EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; i.v., intravenous; mAb: monoclonal antibody; nrAxSpA, non-radiographic axial spondyloarthritis; s.c., subcutaneous;

All anti-TNF-α agents share the ultimate goal of neutralization of abundant TNF-α by competitively preventing TNF-α from binding to its respective receptors.[19] By impeding TNF-TNFR-interaction the proposed inflammatory cascade along with all downstream proinflammatory mediators such as interleukin-6 is interrupted.[19]
Nonetheless, there are notable disparities between the various agents regarding structure, pharmacodynamics, pharmacokinetics and antigenicity,[5] which will be discussed in the following section.

1.2.1 Structure and binding properties for TNF-α inhibitors

First and foremost, all TNF-α inhibitors apart from etanercept, which is a fusion protein, are so-called monoclonal antibodies (mAbs), which resemble human immunoglobulin G1 (IgG1), or as for certolizumab pegol presents remnants thereof.[5,31] Generally, IgG antibodies comprise two antigen-binding Fab domains that are connected by a pliable hinge region to a glycosylated Fc domain.[5,31] As a result, infliximab, golimumab and adalimumab, as they are whole IgG1 monoclonal antibodies, have the ability to connect to TNF-α bivalently.[48] Furthermore, the development of multimeric antigen-antibody complexes is seen with monoclonal anti-TNF-α therapeutics.[48] Conversely, due to their respective structure, certolizumab pegol and etanercept can solely bind one homotrimeric TNF-α molecule.[5] Anti-TNF-α therapeutics with Fc domains can additionally bind to particular receptors, termed Fc-Rn and Fcγ-R, whose effector functions will be described in the pharmacodynamics section.[48]
The isotype of the immunoglobulin is defined by the Fc portion, which is determined by the heavy chain (α, γ, δ, μ, ε) and the light chain (κ, λ).[34] Every TNF-α antagonist can bind sTNF and tmTNF, yet etanercept is the only agent, which additionally binds lymphotoxin.[5] Numerous studies have been carried out to examine, if discrepancies of the various TNF-α blockers can be explained by disparities in binding affinity and avidity for sTNF and tmTNF.[49,50] The general consensus seems to indicate that all TNF-α antagonists exhibit high affinity for sTNF.[49,50] However, while some authors stated that infliximab, etanercept, adalimumab and certolizumab pegol showed comparable data regarding tmTNF avidity,[49,51] others reported significantly diminished affinity data for etanercept.[50] Interestingly, the affinity of all TNF-α inhibitors is higher for soluble TNF-α than for tmTNF.[49] Additionally, differences in dissociation rates have been proposed.[52] Etanercept, in comparison to the other anti-TNF-α agents, has a relative high dissociation rate,

suggesting that the complexes formed with etanercept are rather unstable.[52] This is of importance, since the ability to form complexes as well as the existence or non-existence of a Fc region is determinant for the variability of TNF-α antagonists in efficacy and pharmacokinetic attributes.[31,48] Whereas etanercept solely generates one on one complexes with TNF-α trimers, infliximab forms more stable complexes, due to its ability to bind two TNF-α molecules and vice versa maximal three infliximab molecules can be bound to each TNF-α homotrimer.[31]

1.2.2 Pharmacodynamics

In sum, anti-TNF-α treatment comprise three main effects: First of all, TNF-α inhibitors neutralize surplus amounts of sTNF and in the case of etanercept additionally LT-α.[19] Furthermore, TNF-α antagonists link to tmTNF, which either leads to the obstruction of cell-to-cell contact signaling of tmTNF or to enhancement of reverse signaling.[19] Lastly, the Fc-bearing anti-TNF-α agents can bind to the aforementioned Fcγ-receptor, which is expressed on various cells and determines the ability of the compound to induce Fc-mediated effects such as complement-dependent cytotoxicity (CDC) and antibody-dependent cell cytoxicity (ADCC).[19,48] The divergent features of the different anti-TNF-α agents to provoke CDC and ADCC might also illustrate the variations in clinical efficacies among this group of drugs.[48]

Regarding the neutralization capability of TNF-α inhibitors, there are two ways to antagonize effects of excess TNF-α.[53] First, there are monoclonal antibodies (infliximab, adalimumab and golimumab) and certolizumab pegol that are competitive antagonists, which prevent the soluble and membrane form of TNF-α from binding to their receptors, thus from implementing their function.[53] To be more accurate, anti-TNF mAbs deactivate TNF-α by identifying the antigenic epitopes on the membrane protein of TNF-α about the area of the receptor-binding region.[53] Accordingly, this leads to a steric blockage of the TNF-TNFR linkage.[53] Second, etanercept, as an alternate therapeutic option, likewise suppresses the TNF-mediated inflammatory cascade,[53] by tying to the receptor-binding region of TNF-α.[5]

As indicated above, the capability to form complexes has implications on efficacy and pharmacodynamics of various TNF-α inhibitors.[48] The bigger, more stable complexes that are generated by the mAbs agents are accompanied by a gradual dissociation rate.[48] This means, it is less likely for sTNF to detach from the antibody binding and in further

consequence return in its free active form to the bloodstream and resume its proinflammatory properties.[48] Conversely, when sTNF links with etanercept and certolizumab, they form less stable complexes with higher dissociation rates.[48] Thus, the likelihood, that sTNF recovers its proinflammatory function is higher.[48] Furthermore, complex formations of etanercept or certolizumab pegol with tmTNF show less to no competence of engendering anti-inflammatory processes via reverse signaling, whereas infliximab, adalimumab and golimumab seem to have that ability.[48]

1.2.3 Pharmacokinetics

The most important pharmacokinetic properties and dosage regimens are shown in table 1. All TNF-α inhibitors have in common that they are extremely large protein molecules, which makes a parenteral administration of these drugs obligatory, as gastrointestinal absorption would be insufficient, when administered per os.[35]

The length of plasma half-lives of the TNF-α inhibitors seems to depend on the ability of their Fc regions to bind to neonatal Fc receptors (Fc-Rn) of endothelial cells.[31] Furthermore, etanercept has a lower affinity for Fc-Rn than its monoclonal counterparts, seemingly leading to a short plasma half-life.[48]

1.2.4 Infliximab

Infliximab is a chimeric monoclonal antibody with specificity for human TNF-α, whereof the variable region is murine and the constant region human.[5,19] As with all TNF-α inhibitors, infliximab binds to both sTNF and mTNF, consequently detaining the binding of either to TNFR1 and TNFR2.[5,19] As a result, the TNF-TNFR signaling pathway is blocked.[5,19] Since the very first trials were undertaken in the late Nineties, infliximab has shown great efficacy in the treatment of inflammatory conditions associated with excess production of TNF-α.[19] Contrary to other TNF-α blockers, which are administered subcutaneously, infliximab is given intravenously.[54] However, in contrast to the European Medicines Agency (EMA) the United States the U.S. Food and Drug Administration (FDA) approved an intravenous form of golimumab in 2013.[37] It is of interest that in RA and in psoriasis patients, it is recommended to combine infliximab with methotrexate.[39,43,54,55] On the one hand to limit the generation of anti-drug antibodies, on the other to elevate trough levels of infliximab.[39,43,54,55]

1.2.5 Adalimumab

Adalimumab is a recombinant, TNF-α neutralizing, monoclonal IgG1 antibody, which is fully human.[19] It was initially involved in clinical trials in 2002, with hopes that immunogenicity would decrease compared to the murine infliximab.[19] As depicted in table 1, adalimumab has the widest range of approved indications of all TNF-α inhibitors including two very recent approvals, acne inversa and uveitis.[42,47] As with infliximab the combination of adalimumab with MTX is endorsed in the treatment of psoriasis vulgaris in order to decrease the formation of anti-drug antibodies and heighten the trough levels of adalimumab.[55]

1.2.6 Etanercept

In 1998, etanercept was the first recombinant receptor-immunoglobulin fusion protein to receive the FDA's approval for the treatment of RA.[19] Etanercept is a genetically engineered fusion protein, composed of a dimer of the extracellular portions of human TNFR2 fused to the Fc portion of human IgG1.[5] Owing to the absence of a hinge region, etanercept is not as pliable as its monoclonal antibody counterparts.[31] As mentioned above, this fusion protein illustrates an alternate way in the neutralization of TNF's cytotoxicity and inflammatory capacity by imitating natural soluble TNFR 2 receptors.[19] Extraordinary for etanercept is the exclusive monovalent binding of the natural trimeric form of TNF-α, additionally to the aforementioned LT-α.[53] This is different from infliximab, adalimumab and golimumab, which bind TNF-α in a bivalent fashion. This disparity can most likely be explained by the lesser pliability of etanercept in the hinge region.[48] The characteristic of etanercept to equally bind to lymphotoxin, could explain the differing efficacy in various treatment indications and outcomes compared to the other TNF-α inhibitors.[49] In contrast to the other TNF-α inhibitors, etanercept has proven not to be a treatment option for IBD patients, as studies have shown that it is not efficacious in this particular group of IMIDs.[52] One explanation could be that etanercept is not as effective as the other agents in restraining the pro-inflammatory cascade implemented by reverse signaling.[52] Furthermore, etanercept seems to be less efficacious than anti-TNF-α mAbs in treating other granulomatous conditions such as uveitis or sarcoidosis.[56] The co-administration of etanercept and MTX has been proven to be more advantageous than etanercept alone in the treatment of plaque psoriasis and is therefore recommended in the European Psoriasis Guidelines.[55]

1.2.7 Golimumab

Golimumab is a fully humanized IgG1 monoclonal antibody directed against TNF-α (transmembrane and soluble).[5] As a complete human monoclonal antibody, the similarity to adalimumab is undisputable.[31] Nevertheless, dissimilar from adalimumab, amino acid sequences of the Fc domain are equivalent to infliximab.[31] As with infliximab, the concomitant administration of MTX in the treatment of RA is obligatory.[37,38,44]

1.2.8 Certolizumab pegol

Certolizumab pegol is the smallest molecule of the TNF-α antagonists with a molecular weight of 91 kilodalton (kDa).[34] In comparison, the other TNF-α inhibitors weigh about 150 kDa, which implies that certolizumab pegol is structurally divergent from them.[34] Certolizumab pegol is a humanized monovalent antibody Fab fragment with specificity for TNF-α.[50,52] The covalent bond to polyethylene glycol, an inactive hydrophilic polymer, expands the plasma half-life and augments the solubility of this TNF inhibitor, as the pharmacokinetics for Fab alone would be unsatisfactory.[31,52] Dissimilar to infliximab, adalimumab and golimumab, the Fc domain in certolizumab pegol is non-existent.[52] Consequently, certolizumab binds to TNF-α in a monovalent manner.[48] Furthermore, neither the activation of the complement system nor the initiation of complement dependent cell lysis or the antibody dependent cell cytotoxicity (ADCC) is implicated by certolizumab pegol.[31] Furthermore, the structural diversity of certolizumab pegol (lack of Fc domain) appears to have a positive effect on the applicability in pregnancy, since it has been demonstrated that the transplacental transfer of certolizumab pegol has been limited to barely detectable concentrations.[57] Therefore, when TNF-α therapy is indicated, certolizumab pegol might most likely be the safest TNF-α inhibitor throughout pregnancy, although data concerning long-term effects of maternal certolizumab administration on infants is lacking.[57]

1.2.9 Biosimilars

In 2015 two of the most prescribed TNF-α inhibitors, infliximab and etanercept, lost their patent protection in the European Union, allowing the first market entrance of TNF-α antagonizing biosimilars.[34,58]

By definition, biosimilars have to show profound similarity to the original drug, despite possible disparities, which can occur because the original clone and manufacturing process are still protected by the patent law, in order to ensure safety, efficacy and quality.[58] The World Health Organization (WHO) defines similarity as "the absence of a relevant difference in the parameter of interest".[59]

As of today, several biosimilars of infliximab, adalimumab and etanercept are approved by the EMA and FDA.[60–75] Table 2 gives an overview of the currently commercially available biosimilars.

Table 2. List of currently approved biosimilars of TNF inhibitors[60–75]

TNF inhibitor	Biosimilar trade name	Approval date
Etanercept	Benepali®	EMA: 01/2016
	Erelzi™	FDA: 08/2016; EMA: 06/2017
	Lifmior®	EMA: 02/2017
Infliximab	Remsima®	EMA: 09/2013
	Inflectra®	FDA: 05/2016; EMA: 09/2013
	Flixabi®	EMA: 05/2016
	Ixifi™	FDA: 12/2017
	Renflexis™	FDA: 04/2017
Adalimumab	Amjevita™/Amgevita™	FDA: 09/2016; EMA: 03/2017
	Cyltezo®	FDA: 08/2017; EMA: 11/2017
	Solymbic®	EMA: 03/2017
	Imraldi®	EMA: 08/2017

1.2.10 Immunogenicity

A critical issue with the prescription and use of protein-based drugs is its capability to engender antidrug antibodies.[5] Anti-TNF-α agents are no exception.[5] Possible implications that might come with the formation of antibodies directed against TNF-α blockers are a reduction of its efficacy and an increase of adverse events.[5] Whereas this phenomenon has been reported with all five anti-TNF-α agents, incidence rates among the agents vary, suggesting a discrepancy in immunogenic propensity.[76]

Infliximab, a chimeric agent, is considered to be the most immunogenic TNF inhibitor to date with anti-drug antibodies in up to 40% of RA patients.[54] Etanercept appears to be the least immunogenic of the five agents with a reported anti-drug antibody formation of 1-18%.[54] Therefore, it has been speculated that the longer drug survival rate in patients treated with etanercept compared to infliximab, might be due to the lower levels of anti-drug antibodies.[54] As mentioned above, immunogenicity of all agents can effectively be decreased by the concomitant use of MTX.[77]

1.2.11 Off-label usage of TNF-α inhibitors

Although official treatment indications are limited to those approved by the FDA or EMA, respectively, TNF-α inhibitors have been widely used off-label, with varying degrees of success, in the treatment of a plethora of different indications.[78–86] However, in order to justify anti-TNF-α treatment, the off-label indications are for the most part limited to very recalcitrant chronic conditions of immune-mediated diseases or mucocutaneous diseases, in which previous treatment strategies (conventional therapy) have failed.[80] Anti-TNF-α therapeutics have proven to be efficacious in several of these diseases, albeit evidence is weak for the most part, due to the paucity of randomized control trials (RCT's).[80,87] Published data are mostly based on case reports and case series.[80,87] In Table 3. an overview of common dermatological off-label indications and their respective evidence is given.[78–87]

Table 3. Selected dermatological off-label indications of TNF-α inhibitors[78–87]

Off-label indication	IFX	ADA	ETA	CZP	GOL
Sarcoidosis	RCT, CS, CR	RS	CR	-	RCT
Granuloma annulare	CR	CR	CR	n/a	n/a
Necrobiosis lipodica diabeticorum	CR	CR	CR	n/a	n/a
Pyoderma gangrenosum	CR, CS	RS, CS, CR	RS, CR	CR	n/a
Sweet's syndrome	RS	RS	RS, CR	n/a	n/a
Subcorneal pustular dermatosis	CR	-	CS	n/a	n/a
Vasculitis	RCT, CS, CR	-	CS	n/a	n/a
Systemic lupus erythematous	RCT, PS	-	-	n/a	n/a
Dermatomyositis	CS	-	CS, CR	n/a	n/a
Behcet's disease	CR	CR	CR	n/a	n/a
Graft versus host disease	RS	-	RCT, CS, CR	n/a	n/a
Pityriasis rubra pilaris	CS, CR	CR	CS, CR	n/a	n/a
SAPHO syndrome	CS	CS	CS	CR	-
Hailey-Hailey disease	-	-	CR	n/a	n/a
Erythema annulare centrifugum	-	-	CR	n/a	n/a
Multicentric reticulohistiocytosis	CR	CR	CR	n/a	n/a
Acne conglubata	RS	RS	RS	RS	RS
Complex aphthosis	RS	RS	RS	-	RS
Chronic urticaria	-	RS	RS	n/a	n/a
Hidradenitis suppurativa[88,89]	RCT	approved	CS	n/a	n/a

Abbreviations: ADA, adalimumab; CR, case report; CS, case series; CZP, certolizumab pegol; ETA, etanercept; GOL, golimumab; IFX, infliximab; n/a, no paper could be found in the literature; PS, prospective study; RCT, randomized clinical trial; RS, retrospective study; -, no treatment option for the particular indication

1.3 Underlying diseases

1.3.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most common chronic progressive immune-mediated inflammatory diseases with a prevalence of approximately 0.5 - 1 % in the industrialized countries.[90–92] In addition to elderly people being overly represented in RA patient cohorts, women have a noticeably higher prevalence rate than men.[90] Besides posing a socioeconomic challenge to the society, as limited work capacity and high medical costs are implications of the functional restrictions of the disease, the burden of the affected individual is as challenging.[15]

RA is defined by a systemic inflammation, which primarily affects the synovial tissues, characterized by the phenotypical "swelling" of multiple joints caused by hyperplasia of the synovia.[15,90] The perpetual joint inflammation ultimately results in destruction of articular cartilage and damage of adjacent bone tissues.[15,90] As a result, patients with RA are afflicted with functional impairment and disability, leading to severe deterioration of quality of life.[93] The clinical course is further dependent on the presence of autoantibodies, since seropositivity implies a more severe course of disease with aggravated symptoms and a more rapid progression of joint damage.[15] Of major importance are the rheumatoid factor (RF) and the anti-citrullinated peptide antibody (ACPA), which can be detected in about 50 to 70 % of RA patients at time of diagnosis.[15,90,94,95] Development of immune aggregates, consisting of ACPAs, citrulline-containing antigens and RFs, is believed to lead to redundant complement activation.[15,90,94,95]

The exact pathogenesis of RA is as with many IMIDs to a larger part not known, but in fact very complex, as a triangle of contributing factors, including genetic, environmental and immunological seem to determine the etiopathogenesis of RA.[23,91] Genetic predisposition is approximated to be found in 45 to 65 % of seropositive RA patients, compared to only 20 % in seronegative disease.[15] GWAS (Genome wide association studies) utilizing single nucleotide polymorphisms (SNPs) have identified more than 100 loci linked to an increased RA risk, the majority involved in immune mechanisms.[15] The main environmental factor associated with a higher risk of RA is smoking, although this appears to be limited to ACPA positive RA patients.[90,96] As of late, periodontitis and microbiomes have been discussed as potential risk factors for the development of RA.[15,23] Nonetheless, the role of abundant TNF-α production in the pathogenesis is definite, at the latest when TNF-α inhibitors proved to be a success in the treatment of RA, ensuring

disease remission and alleviation of this chronic condition.[1] RA is a heterogeneous disease, in which different subdivisions of the disorder encompass various inflammatory cascades of proinflammatory cytokines.[23] However, all eventually will lead to the clinical presentation of RA or boost disease driving mechanisms.[23] Thus, TNF-α is best described as one of those proinflammatory cytokines, which are released by immune cells involved in the pathogenesis, embedded within an intricate network of various synovial cytokines and chemokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), granulocyte-macrophage colony-stimulating factor and many others.[23]

Moreover, systemic features of RA encompass the cardiovascular, pulmonary and the skeletal system.[90] Patients with RA have a higher risk (48 %) of developing cardiovascular disease than the general public,[97] which implicates an increased risk of early mortality.[15] TNF-α inhibitors and rituximab have shown to reduce mortality rates in RA patients, more so than disease-modifying anti-rheumatic drugs (DMARDs) such as MTX or leflunomide, substantiating the benefit of early disease detection and early introduction of biologics.[98] Additionally, as in other IMIDs the incidence of infection is increased compared to the general population.[90,98] Furthermore, the incidence of lymphomas and pulmonary cancer in RA patients is increased compared to the general population.[91,99]

Extraarticular manifestations of RA encompass cutaneous conditions such as rheumatoid nodules, which are the most common manifestation, affecting roughly 20 % of the RA population, palmar erythema, rheumatoid vasculitis and granulomatous dermatitis.[100]

All TNF-α inhibitors have proven to be efficacious in the treatment of RA.[1] However, as a recent systemic review indicates, the combination of TNF-α inhibitors with MTX seems to be significantly more efficient in the long run than anti-TNF-α- or MTX- monotherapy.[1] This is likely due to the reduced development of anti-drug antibodies with concomitant MTX administration.[1]

1.3.2 Inflammatory bowel disease

Inflammatory bowel disease (IBD) is one of the most common and relevant diseases of the gastrointestinal tract and includes two chronic recurring inflammatory disorders, ulcerative colitis (UC) and Crohn's disease (CD).[22] The approximated European prevalence of IBD is about 0.3 %.[101] Noteworthy, is the significant geographic variation in Europe (North/West to South/East gradient), with high prevalence rates in northern countries (i.e. Sweden: 213 cases per 100,000 persons) and low CD prevalence rates in the southern hemisphere (i.e.

Romania: 1.5 per 100,000 persons).[101] Overall, for yet unknown reasons the worldwide incidence and prevalence rates of IBD seem to have increased over the last few decades.[102] In general, incidence rates for IBD indicate two peaks, one in the second and one in the fourth decade of life.[103] Study results regarding sex differences were inconsistent.[101–103] Some authors suggested that IBD occurred equally among both sexes,[101,102] while others noted a marginal male predominance in UC and a slight female preponderance in CD.[103] Extraintestinal manifestations have been detectable in up to 40 % of CD patients and 20 % in patients with UC in a European population.[101] Erythema nodosum, and pyoderma gangrenosum are considered as the most common cutaneous manifestations of IBD.[104] Moreover, concurrent psoriasis manifestation appears to emerge in 7-11 % of IBD patients, which is a substantially higher prevalence rate than in the general population.[105]

Despite some common features, UC and CD can be distinguished by certain disparities, especially owing to clinical, endoscopic and histological characteristics.[22] Although CD can potentially affect any segment of the entire gastrointestinal system (from the mouth to the anus), the terminal ileum and the proximal colon are predilection sites.[22] Specific features of CD involve the presence of so-called “skip lesions” and the transmural involvement.[22] In comparison, UC is mainly located in the rectum and extends from there continuously to the proximal segments, whereas CD spreads in a discontinuous manner.[22] Furthermore, the inflammation process in UC distinguishes oneself by its limitation to the mucosa.[22] Typical symptoms of UC might include diarrhea with blood and pus impurities.[106]

As with other IMIDs, little is known about the etiology and pathophysiology of either one of the diseases.[22] However, it is believed, that IBD development is based on a continuous dysregulated mucosal immune response to commensal gut flora (microbes) in genetically predisposed individuals.[22,103] TNF-α signaling is likely to play an integral part in the pathophysiology of IBD, as increased levels of TNF-α have been found in the mucosa, serum and stool samples of patients with active stages of IBD.[52] Apart from increased concentrations of TNF-α, the cytokine pattern demonstrates enhanced levels of other proinflammatory mediators such as IL-6, IL-8, IL-12, IL-23 and IL-17.[22,103,107] Genome wide association GWAS have identified about 20 susceptibility loci involved in the immunopathogenetics of both CD and UC, e.g. loci encoding for IBD implicated cytokines such as IL-23 and IL-10.[106]

Since their introduction in the early 2000’s, TNF-α inhibitors (infliximab, adalimumab and certolizumab pegol) have shown their efficacy in the treatment of CD and UC.[108]

Furthermore, golimumab is a proven therapeutic for UC.[109] Despite the success of monoclonal TNF-α antibodies in the treatment of IBD, clinical trials concerning etanercept failed to show any significant efficacy in CD treatment.[110]

1.3.3 Ankylosing spondylitis

Ankylosing spondylitis (AS) is one out of six chronic inflammatory rheumatic diseases, which are referred to as spondylarthropathies or spondyloarthritides.[111–113] Besides AS, this includes psoriatic spondyloarthritis, arthritis associated with inflammatory bowel disease (enteropathic spondyloarthritis), reactive arthritis, enthesitis-related juvenile arthritis and undifferentiated spondyloarthritis.[111–113] Moreover, as per the Assessment of Spondyloarthritis International Society (ASAS) defined criteria for axial spondyloarthritis, there are two medical outcomes, the classic AS with radiographic alterations of sacroiliitis and the non-radiographic axial spondyloarthritis (nr-axSpA),[111] which is listed by the EMA as a separately approved treatment indication for TNF-α antagonists except for infliximab.[39,44–47] Hence, the term nr-axSpA relates to a proposed pre-radiographic clinical form of AS with patients presenting typical symptoms of early AS manifestation, despite x-ray based evidence of sacroiliitis is lacking.[114] However, it is debatable, whether AS and nr-axSpA are one entity,[111] as the majority (74 %) of nr-axSpA-patients within a span of 15 years do not progress to radiographic AS.[115] Furthermore, demographic disparities between the two conditions have been noted such as the suggested preponderance of females and the lower prevalence rates of HLA-B27 (Human leukocyte antigen B27) in the nr-axSpA population.[111]

The global prevalence of AS is believed to range from 0.1 % to 1.4 %.[116] Interestingly, the prevalence of AS seems to be increased in populations with a high prevalence of HLA-B27 positivity.[117] Therefore, the genetic association to the HLA-B27 gene can be detected in up to 89 % of AS patients.[111] In the literature the ratio of male to female AS cases was inconsistent depending on the population being studied.[116] The mean European male to female ratio is suggested to be 3.8:1.[116]

As AS primarily affects the axial skeleton, the main clinical feature is inflammatory back pain, which chiefly is attributed to sacroiliitis.[18,111,113] However, other sites in the axial skeleton might also be affected.[18,111,113] Hence, common complaints of AS patients often refer to the vertebral column, such as spinal stiffness and impaired mobility of the backbone.[18,111,113] These symptoms derive from chronic spinal inflammation and/or structural damage.[18,111,113] However, the inflammatory process is not confined to the axial

skeleton, meaning that AS regularly also involves peripheral arthritis, enthesitis and extraarticular manifestations such as anterior uveitis, for instance.[18,111,113] Along with other IMIDs such as psoriasis or RA, AS is associated with a higher occurrence of cardiovascular diseases.[117]

The etiology and pathogenesis of AS has yet to be fully elucidated.[111] However, the significant association of AS with HLA-B27 underlines that genetic factors apart from environmental factors are seemingly determining parts in pathophysiology.[111] Except for HLA-B27, GWAS have detected over 30 non-major histocompatibility complex related genetic regions as probable susceptibility genes.[111] Involvement of the IL-23-Th17 pathway in the pathogenesis of AS has been proposed, as alterations in several genes encoding IL-23 and IL-17 have been discovered.[111]

All TNF-α inhibitors have proven to be highly effective treatment options for AS patients and nr-axSpA patients, reducing disease activity and improving physical function, as a recent meta-analysis by Callhoff et al. indicates.[118]

1.3.4 Hidradenitis suppurativa

Hidradenitis suppurativa (HS), also known as acne inversa, is a skin condition, which is considered a debilitating, chronic, relapsing, inflammatory disorder of hair follicles, primarily affecting apocrine gland-bearing intertriginous body regions such as the axillaries, the groins and the anogenital area.[119] The inflammatory process appears to originate from the hair follicles with a secondary involvement of the apocrine and eccrine glands.[120] Interestingly, there seems to be a gender discrepancy in sites affected, as women tend to have predominantly submammary, axillary and inguinal lesions, whereas the gluteal, perianal and perineal area are the sites seen more often in males.[121] Furthermore, it is suggested that men often are afflicted by a more severe form of HS.[121] Typically, HS affects young individuals, with a peak in their early 20's, and shows a tendency towards overrepresentation of women.[120] Despite the general notion that HS is a rather rare skin disorder, two European studies suggest otherwise, with a European prevalence ranging from 1 to 4 %.[122,123]

HS is initially characterized by painful subcutaneous nodules and boils, which subsequently often progress to abscesses, sinus tracts, fistulas and cicatrisation.[120]

Due to its debilitating and defacing nature, it has a severe impact on patients' quality of life.[124]

The pathogenesis is up to date not fully understood.[125] However, similar to the already introduced IMIDs, a multifactorial genesis is suggested, with TNF-α playing a pivotal role and the interleukin-12-interleukin-23 pathway being involved.[125] There are environmental factors that are associated with a higher prevalence of HS and therefore appear to be heavily involved in the pathogenesis of the disease.[125] Smoking is a known risk factor, with up to 90 % of the patients being active or former smokers.[121,126] On top of that, advanced stages of HS are more likely to be found in active smokers.[127] Non-smokers display considerably, lower disease severity scores.[127] Moreover, multiple studies have identified obesity as an independent risk factor for acne inversa development, as over half of the HS patients exhibit increased body mass index (BMI) levels.[120] Roughly 33 % of the HS patients display a positive family history, underlining the entanglement of genetic factors in the etiopathogenesis of HS.[125] Comorbidities of HS comprise IBD and spondylarthropathies amongst others.[128]

As depicted in table 1, the FDA and EMA have just recently approved adalimumab for the treatment of HS.[42,47,62,129] Infliximab and adalimumab have both proven to be efficacious in treating HS with a significant amelioration in quality of life.[129,130] However, as of yet infliximab has not been approved by neither the FDA nor the EMA for the treatment of HS.[39,43]

1.3.5 Juvenile idiopathic arthritis

This chronic disease is the most seen rheumatic disease among children with a prevalence of 16 to 150 cases per 100,000 in the industrialized countries.[131] The diagnosis “Juvenile idiopathic arthritis” (JIA) is not solely one disease per se, but implies a wider definition of arthritis occurring in patients younger than 16 years.[131,132] JIA is referred to a heterogeneous group of juvenile arthritides of unknown origin.[131,132] In addition, per definition symptoms must have lasted for over 6 weeks with no reasonable explanation.[131,132] As defined by the International League of Associations for Rheumatology (ILAR) the diagnosis of JIA encompasses seven subtypes, systemic arthritis (Morbus Still), oligoarthritis, rheumatoid-factor-positive polyarthritis, rheumatoid-factor-negative polyarthritis, psoriatic arthritis, enthesitis-related arthritis and undifferentiated arthritis.[131] The pathogenesis of JIA still remains unclear.[131] However, as with other IMIDs the involvement of genetics along with environmental factors seems to play a substantial role in the etiopathogenesis of JIA.[131] Similar to other IMIDs, the diagnosis of JIA is accompanied by significant morbidity.[131] Conventional therapy including DMARDs (such

as MTX), regularly showed unsatisfactory treatment outcomes in roughly 30-40 % of the JIA population.[133] The advent of TNF-α inhibitors has contributed to an overall advance in treatment and management results in this patient cohort.[134,135] Currently, as listed in table 1., adalimumab and etanercept are licensed for the treatment of JIA.[41,42,46,47] Adalimumab is licensed for treatment of polyarticular JIA and enthesitis-related arthritis in patients (6 years of age at least).[47] Etanercept is approved by the EMA for the treatment of children and adolescents (aged two to seventeen years) affected with the polyarthritis subtypes (both rheumatoid factor positive and negative) or oligoarthritis.[46,60]

1.3.6 Non-infectious uveitis

Uveitis is an infrequent heterogeneous group of relapsing ocular inflammatory conditions affecting the uvea and eventually the neighboring anatomical structures such as the sclera, cornea, corpus vitreum, retina and the optic disc.[136] The approximated incidence of noninfectious uveitis has a range from 17 to 52 cases per 100,000 person-years.[137] Furthermore, younger individuals seem to be preferably affected, as the initial manifestation typically occurs before the age of forty.[136] Uveitis is one of the leading causes for blindness and seems to account for 10 to 15 % of the total number of sightlessness in the Western hemisphere.[136,138] Loss of sight is the ultimate result of the gradual advancing decline in visual acuity referable to uveitis-related complications such as cystoid macular edema, floaters or retinal scars among others.[139] Non-infectious uveitis can occur solely, restricted to the eye or as a co-manifestation within a systemic disease, mainly other IMIDs such as JIA.[139] Depending on which anatomical structures are afflicted, uveitis may be divided, into panuveitis, anterior, intermediate, and posterior uveitis.[139] Treatment of choice for noninfectious uveitis is glucocorticoids.[137,140] However, the duration of treatment is limited, due to severe systemic and local side effects that emerge after long-dated administration.[137,140]

TNF-α is believed to be a key mediator of ocular inflammation and a contributing cytokine in the pathogenesis of uveitis, as elevated levels have been detected in the serum and intraocular fluid of uveitis patients.[141]

As depicted in table 1., adalimumab has recently been approved by both the FDA and EMA for the treatment of intermediate uveitis, posterior uveitis or panuveitis of non-infectious origin.[42,47]

1.3.7 Psoriasis and psoriatic arthritis

1.3.7.1 Epidemiology

Psoriasis is a chronic inflammatory skin disease affecting roughly 2-4 % of the general population in the so-called industrialized countries.[142,143] However, prevalence rates vary considerably, depending on which geographic region or population is studied.[142] For instance, countries of higher latitude and Caucasians have been related to elevated prevalence rates.[142,144] Within Europe the prevalence varies from 0.6 to 6.5 %.[144] Women and men are believed to suffer from psoriasis equally, although men seem to be overrepresented in patient cohorts with more severe disease.[145] In comparison, the prevalence of psoriasis in children in Europe is considerably lower with approximately 0.71-1 %.[142] Regarding the age of initial manifestation two notable peaks emerge, the first one between the ages of 16 and 25, the second one in the 6th decade of life.[146] Based on this bimodal age at onset, Henseler et al.[147] proposed two types of psoriasis, type I and type II.[147] In type I commencement of the disease is noted before the age of forty years, whereas type II sets in after the age of forty years.[147] Moreover, Henseler et al.[147] noticed that type I, which is responsible for over 75 % of total cases, seemingly were related to a more severe form of psoriasis and had a stronger genetic background than patients with late-onset psoriasis.[147]

Children often present with guttate psoriasis.[148] About 33 % of the patients, who experienced an outbreak of guttate psoriasis in childhood, proceed to develop plaque psoriasis as adults.[148]

Psoriasis in adolescents or children is not uncommon, as a German study revealed a prevalence of 0,71 %.[149] Similar to the adult population the occurrence of psoriasis increases in a linear matter with age.[150] Genetic predisposition seems to play a bigger role in early-onset psoriasis compared with adult psoriasis, as roughly 70 % of the affected adolescents have a positive family history.[150] Typical for early-onset psoriasis are for psoriasis vulgaris uncommon skin site locations such as the face and the genito-anal area.[148]

1.3.7.2 Genetics

In sum, genetics of psoriasis as with other IMIDs is intricate, as the genetic susceptibility for psoriasis development seemingly depends on alterations of various alleles.[151,152] Accordingly, psoriasis is considered a polygenic disease.[151] Since the early 70's researchers have emphasized the genetical involvement in the etiopathogenesis of psoriasis.[153,154] Population based studies detected significantly higher incidence rates of psoriasis between first-degree relatives and second-degree relatives than in the general population.[153,154] In particular, twin studies underpin the relevance of the genetic predisposition in psoriasis with a concordance rate of roughly 70 % in monozygotic twins and about 20 % in dizygotic twins.[155] According to data extrapolated from epidemiological trials, the heritability of psoriasis is suggested to be between 60-90 %.[151] However, Mahil et al.[151] state that no more than 25 % of the psoriasis heredity has been identified by genetic studies so far.[151] A large portion of the pending information of psoriasis heritability is believed to be found in epigenetics.[151] Nonetheless, a myriad of gene loci has been implicated with an elevated susceptibility for psoriasis.[156] Originally, researchers termed these regions of chromosomes that hosted psoriasis susceptibility genes as PSORS.[156] As yet, classic genome-wide linkage analysis of families with numerous individuals affected by psoriasis has identified about 12 different PSORS loci.[156] However, to date, the majority of genes at the PSORS loci are non-identified.[152] So far, solely PSORS1, PSORS2 and PSORS4 have been identified as evident susceptibility loci.[151]

PSORS 1 at chromosome 6p21 has been established as one of the primary loci involved in psoriasis predisposition.[152] HLA-Cw6 is suggested to be a causal psoriasis susceptibility allele and can be detected in up to 50 % of psoriasis vulgaris patients, compared to 4-16 % in healthy individuals.[151,152] The encoded product of HLA-Cw6 is major histocompatibility complex I and is pivotal for antigen presentation to CD8+ T cells.[152,156] According to Asumalahti et al.,[157] HLA-Cw*0602 positive psoriasis patients differentiate from HLA-Cw6-negative patients with psoriasis in terms of younger manifestation age, higher degree of severity and activeness of disease as well as higher frequency of a positive family history of psoriasis (type I psoriasis).[157] Thus, genetic predisposition seems to play a bigger role in type I psoriasis than type II psoriasis (late-onset psoriasis), as roughly 70 % of affected adolescents and children have a positive family history.[147,150] However, in comparison to patients with plaque psoriasis and guttate psoriasis, patients affected by PPPP, erythrodermic psoriasis or psoriatic arthritis are less likely to be HLA-Cw6 positive, corroborating the genetic heterogeneity of the clinical variants of psoriasis.[157] On the

contrary, generalized pustular psoriasis and palmoplantar pustular psoriasis have been associated with mutations in the CARD 14 gene, although CARD 14 mutations have been implicated with psoriasis vulgaris as well.[158] CARD 14 has been suggested as the causative gene at PSORS2.[151] Mutations of the CARD 14 gene entail aberrant activation of NF-κB.[159]

These substantial disparities in the immunogenetic profiles of the different psoriasis variants have led to, that some authors have proposed a classification and nomenclature based on the genetic background rather than the current disease classification based on clinical and macroscopic aspects.[151,152] Furthermore, the varying immunogenetic profiles of the different psoriasis subtypes have implications for their respective treatment selection.[151]

Lately, GWAS have helped to shed more light on the poorly elucidated etiopathogenesis of psoriasis concerning heredity.[152] Grand cohorts of psoriasis cases and matched controls were categorized for so-called single nucleotide polymorphisms (SNPs) and were checked for any statistically significant elevation of SNPs alleles in the psoriasis case cohort compared to the control group.[152] Thus far, more than fifty susceptibility loci for psoriasis have been identified through GWAS, some loci harboring more than one susceptibility gene.[152,160] Genetic linkage and ensuing GWAS have to a large extent detected associations with multiple SNPs within genes mainly involved in immune regulation, barrier function and epidermal microbial defense.[161] The aforementioned HLA-Cw6 is an example for putative causative genes interfering with antigen presentation, which is a central immunological mechanism in the pathophysiology of psoriasis.[160,161] Furthermore, alterations of IL-23 signaling within psoriasis is an illustration of how immune regulation is mutated by genetic variations of IL-23A, IL12B or IL-23R. Moreover, an abundant number of polymorphisms in NF-κB-related genes (REL, TNIP, TRAF31P2, TNFAIP3, KFKBIA, FBX19 and CARD14) appear to affect NF-κB signaling, which is implicated in the perpetuation of chronic inflammation.[160,161] Additionally, gene alterations are found in genes (late cornified envelope, LCE) encoding for proteins of the horny layer, which are important to maintain epidermis integrity.[151] Ultimately, a psoriasis susceptibility locus has been identified to be essential for the epidermal microbial defense, namely the region encoding for β-defensin (DEFB4).[162]

Alterations in the IL36RN gene have been linked to pustular psoriasis.[152,156] The gene product of IL36N is an anti-inflammatory peptide IL-36Ra, which antagonizes IL-1F9, a NF-κB regulated proinflammatory mediator.[152,156] However, mutations in IL36RN lead to

malfunctioning of the encoded interleukin, which in further consequence leads to an unchecked proinflammatory cascade with NF-κB at the head.[152,156] Additionally, a gene termed AP1S3 appears to be implicated in GPP, PPPP and acrodermatitis continua of Hallopeau.[159] The gene product of AP1S3 is a subunit of adaptor protein complex 1 (AP-1), which is involved in the promoting of vesicular trafficking between the trans-Golgi network and the endosomes.[159]

The evident immunogenetic involvement of interleukin 23 (IL-23) in the pathogenesis of psoriasis is strong.[152] Accordingly, SNPs in loci, harboring genes for IL12Bp40 and IL23Ap19, whose gene products form the heterodimeric IL-23, have been identified.[152] Besides the two subunits, SNPs encoding for the IL-23 receptor (IL23R) have been detected.[152]

Another group of psoriasis associated single nucleotide polymorphisms was detected in genes that encode transcription factors REL, TYK2, STAT3 or RUNX3, respectively. REL is part of the NF-κB-family and is a contributing factor in the regulation of various inflammatory mediators and is additionally involved in the regulation of keratinocyte proliferation. TYK2, a janus kinase, is entangled in the signal transduction of interferons and cytokines such as IL-12 and IL-23. STAT3 seems to be of particular interest for researchers, as this transcription factor seems to play a pivotal part in the differentiation process of Th17 cells besides being involved in the regulation of IL23R. Furthermore, the activation of STAT3 is suggested to promote the proliferation of keratinocytes. At last, RUNX3 is another transcription factor, which seems to be involved in the promotion or differentiation of CD+8 T-cells, Th1 cells and Th17 cells.[152,163]

1.3.7.3 Immunopathogenesis

The pathophysiology of psoriasis is very complex and has yet to be fully elucidated.[153] Psoriasis is suggested to be a multifactorial disease, as genetic susceptibility, environmental factors, aberrant function of the keratinocytes and a dysregulated immune system (innate and acquired) all seem to be involved.[153] Thanks to the success of biologics including TNF-α inhibitors, respectively, in the treatment of psoriasis, the pivotal role of an aberrant immune system with all its components within the pathophysiology of psoriasis is definite.[148,153] As GWAS have detected so-called susceptibility loci for psoriasis, the majority of the identified genes and loci are encoding for components of the adaptive or innate immune system.[148] This discovery supports the relevance of the interaction between genetics and the immune system in the pathogenesis of psoriasis.[148]

Nonetheless, the onset of disease is hypothesized, to be elicited by predisposing factors or so-called trigger factors, which will be introduced in a following section, resulting in stressed keratinocytes in genetically predisposed individuals.[153] Albeit, the initiation of the pathophysiological chain of events in psoriasis largely remains elusive, the keratinocyte-produced antimicrobial peptide LL37 (cathelicidin) seems to play a crucial part.[153,156,163,164] It is believed that this autoantigen, which shows sequence homologies to streptococcal m-proteins,[163] is released by stressed keratinocytes following injury to the skin.[153,164] LL37 tends to form complexes with host DNA from stressed or decaying keratinocytes and then bind to the toll-like receptor (TLR) 9 of plasmacytoid dendritic cells (pDCs), which in further consequence leads to the production of interferon-alpha (IFN-α) and interferon-beta (IFN-β).[156,164] Accordingly, pDCs have been detected in an elevated manner in skin samples of psoriasis patients, in particular in early psoriatic lesions, indicating the role of pDCs along with IFN-α as inducers of psoriasis.[153,164] Additionally, LL37 might also link to self-RNA and lead to the activation of myeloid DCs through toll-like receptors 7 and 8, entailing the production of TNF-α and IL-6.[164] Moreover, keratinocyte-derived antimicrobial peptides such as LL37, S-100 and β-defensin are ascribed chemotactic features.[153,164]

Apart from playing an active role in the onset of psoriasis, keratinocytes seemingly generate proinflammatory cytokines such as TNF-α, IL-1 or IL-6 and chemokines upon stimulation of proinflammatory cytokines (TNF-α, nitric oxide, IL-23, IL-22, IL-17) released by DCs and T-cells.[153] Basic characteristic hallmarks of psoriatic histopathology give an idea of central pathophysiological processes concerning the keratinocytes.[164] First and foremost, acanthosis, which is the thickening of the epidermis, demonstrates the hyperproliferative nature of altered keratinocytes involved in psoriasis.[164] Parakeratosis, which is defined by the persistence of keratinocyte nuclei in the horny layer of the epidermis, showcases the alteration in keratinocyte differentiation emphasizing the relevance of these cells in the pathophysiology of psoriasis.[164] The stimulus for the redundant proliferation is proposed to be mediated by IL-17 and IL-22 (secreted from Th17 cells) and IFN-γ (mainly released by Th1 cells).[160]

As illustrated above, DC's (myeloid and plasmacytoid) and T-cells (mainly CD4+-T-helping-cells and cytotoxic CD8+-t-cells) dominate the inflammatory infiltrate and have pivotal roles in the pathogenesis of psoriasis, as they are major sources of proinflammatory cytokines and chemokines.[163]

Dendritic cells, which are antigen-presenting cells, can initiate a T-cell mediated immune response and promote auto-proliferation of T-cells.[160,164] Further proof of, that antigen presentation is essential to the pathogenesis, was found in genetic studies, where the most probable etiological allele within PSORS1 was identified as HLA-Cw6, a gene encoding for class I major histocompatibility complex, which is expressed by DCs among others.[160,164] Activation and differentiation of T cell subdivisions are mediated by IL-12 and IL-23, which seem to be generated primarily by myeloid DCs.[156] However, the differentiation of CD-4+-T-helping cells into Th1- and Th17-cells are believed to be influenced by specialized DCs, termed TIP-cells, which furthermore have the ability to generate TNF-α and nitric oxide.[152,163] Additionally, IL-23, among other cytokines such as TNF-α, IL-1 and IL-6, appears to be the essential cytokine for Th17 cell differentiation.[163] T-cells detected in psoriatic skin lesions are primarily Th1 and Th17 cells.[152] Th1 cells generate IFN-γ and are essential to fight viral infections.[152,160,165,166] Th17 cells are supposedly very important phenotypes of T-cells, as they are suggested to be considerable contributors in the in epithelial immune surveillance.[152,160,165,166] Furthermore, Th17 cells are implicated in psoriasis as they produce IL-17 and IL-22, cytokines that have been shown significantly involved in the psoriatic chronic inflammatory circuit.[152,160,165,166] This is attested by the positive treatment outcomes of psoriasis patients treated with agents antagonizing this cytokine (e.g. secukinumab) or the receptor, IL-17R (e.g. brodalumab).[152,160,165,166] Th17-derived cytokines are believed to spur keratinocyte proliferation, which in turn stimulate the further generation of IL-17, indicating a positive feedback loop for Th17 cells.[163] However, it should be noted, that recent study outcomes indicate that IL-17 production might not be limited to Th17 cells, but also involve cells of the innate immune system such as mast cells and neutrophils, underlining further the great variety of immune cells contributing to the intricate pathogenesis of psoriasis.[163] Elevated numbers of cells present in the inflammatory infiltrate of psoriatic lesions include monocytes, and other innate immune cells such as natural killer cells and endothelial cells.[156] Macrophages, in particular have been detected to be a main source of TNF-α, IL-23 and nitric oxide.[163]

Succinctly, psoriasis emerges per chronic interplay of resident skin cell types with activated invading immune cells and components of the innate and acquired immune system.[148,152] This is perfectly illustrated by the IL-23/Th-17 axis, as IL-23 mainly derives

from ‘innate’ DCs and macrophages, whereas IL17 derives from Th 17 cells of the ‘adaptive’ immune system.[163]

As emphasized previously, due to the success of TNF-α inhibitors in the treatment of psoriasis and psoriatic arthritis, TNF-alpha can be considered to be one of the key cytokines in the pathophysiology of psoriasis.[4,17] Hence, the role of TNF-α was only partly depicted above.[153,156,164] Therefore, an effort will be made to summarize TNF-alpha’s role in the immunopathogenesis of psoriasis. However, it should be noted that the multifarious properties of this mediator within the psoriasis pathogenesis have still not been fully expounded.[17] TNF-α is generated and secreted by several cells involved in the pathophysiology of psoriasis including keratinocytes, DCs, natural killer (NK) cells, Th1, Th17 and Th22 cells.[156,163,164,167] Accordingly, elevated levels of TNF-α, TNFRI and TNFR2 have been detected in early as well as in chronic psoriatic lesions.[167] As a result, TNF-α is involved at onset and in the maintenance phase of this chronic skin condition.[167] Nonetheless, it appears as if TNF-α singularly does not have a meaningful effect on keratinocytes, but rather occupies an augmenting role, developing synergies with primarily IL-17-A, consequently boosting the hyperproliferative effect of IL-17 by upregulating multiple psoriasis-related proinflammatory genes.[17] Moreover, TNF-α upon release from pDCs appears to promote the production of IL-23 by specialized mDCs, the aforementioned TIP-DCs.[164,168] Thus, the efficacy of TNF-α inhibition in psoriasis is most likely explained by the repression of the IL-23/Th17 axis, as one of the main effects of TNF-α is its regulation of IL-23.[164,168] Moreover, TNF-α has been accounted for involvement in multiple other underlying pathophysiological mechanisms of psoriasis.[169] Firstly, TNF-α spurs the maturation of Langerhans cells and DCs, with skewing of lymphocyte differentiation; secondly, TNF-α has a supporting role in DC migration from the dermis to the lymph nodes; thirdly, TNF-α acts as an inductor of adhesion molecules on capillary endothelial cells, keratinocytes and fibroblasts in the dermis and thereby can promote the accumulation of leukocytes in the dermal inflammation site.[169] Besides, stimulation of TNF receptors on sensory nerve endings has been attributed with being a key mechanism in the pathophysiology of itching occurring in psoriasis.[169] Apart from the boosting effect of TNF-α on the IL-23/Th17 axis, TNF-α is a key cytokine involved in the induction of multiple other pro-inflammatory cytokines involved in the pathogenesis of psoriasis.[30] TNF-α along with IL-1 is responsible for the increased expression and

production of cytokeratin 6, with TNF-α specifically upregulating the transcription of this hyperproliferative cytokeratin.[30] Furthermore, TNF-α augments the keratinocyte proliferation mediated through IL-1 and IL-6 by elevating levels of NF-κB and thereby preventing keratinocyte apoptosis.[30] Additionally, TNF-α is one of the key mediators involved in the increased vascular proliferation, which is seen in psoriasis lesions, through the induction of angiogenic factors such as the vascular endothelial growth factor (VEGF).[30,169]

The cross regulation of TNF-α with type I IFNs (IFN-alpha and IFN-beta) and vice versa is very intricate and appears to be determined by the microenvironment.[167] Via the IFN regulatory factor-1 (IRF-1) TNF-α can stimulate the generation of type I IFNs in macrophages.[167] However, TNF-α can equally operate as a negative regulator of IFN-α production through TNFR1 on pDCs.[167] Successively, type I IFNs may act as a mediator of inflammatory processes provoked by TNF-α.[167] Furthermore, type I IFNs have the ability to augment the generation of TNF-α by pDCs, hence repressing their own production indirectly.[167] Consequently, TNF-α antagonism may lead to abundant production of IFN-α and IFN-β.[167]

Th1 cells are regarded as the main origin of IFN-γ present in psoriasis.[164] However, this type II interferon is equally released by DCs and NK cells.[164] IFN-γ is considered to promote antigen presenting cells and in further consequence the secretion of IL-1 and IL-23 from DCs, which then again provokes Th17 and Th22 cell differentiation and activation.[164]

1.3.7.4 Triggers / Predisposing factors in psoriasis

There have been plenty of so-called trigger factors, predisposing factors or risk factors associated with the provocation of new-onset or exacerbation of pre-existing psoriatic conditions.[148] First and foremost, drugs such as ß-blockers and lithium, smoking and physical trauma (Koebner phenomenon) are established trigger factors.[148,153] The more recognized precipitating factors will be presented in the following section of this thesis.

1.3.7.4.1 Psychological stress

Stress in general or psychological distress has broadly been considered a product of the daily challenges that are brought along with the diagnosis of psoriasis.[170,171] However, there is emerging evidence that psychological stress can in fact trigger the exacerbation of

psoriasis.[170,171] A Swedish study even suggests that the most important precipitating factor in the onset of psoriasis vulgaris may be recently experienced negative life events, as 46 % of their plaque psoriasis patients, involved in their study, reported recently experienced negative life events.[171] Hunter et al.[172] provide a review article discussing the possible pathophysiological explanations regarding this topic.[172]

1.3.7.4.2 Elevated body mass index (BMI)

The evidence concerning elevated BMI and increased waist perimeter as independent risk factors for the development of psoriasis is quite strong.[173–177] This association has been documented by cohort studies and case control studies in a regular manner.[173–177] In a prospective study with over 8,000 participants, Danielsen et al.[177] demonstrated a considerably augmented risk of developing psoriasis, when a threshold BMI of 27 kg/m^2 was reached.[177] In fact, patients with BMI levels beyond the threshold of 27-28 kg/m^2 showed an elevated risk of psoriasis greater than 40 percent (compared to patients < 28 kg/m^2), whereas BMI levels at 30 kg/m^2 and beyond were associated with a 71 % increased risk of psoriasis in non-smokers.[177] It seems conclusive that overweight can precipitate the emergence of psoriasis in genetically predisposed individuals, as the adipose tissue is a recognized endocrine organ with the ability to produce adipokines and proinflammatory cytokines, knowingly involved in the pathogenesis of psoriasis such as IL-1, IL-6 and TNF-α.[178]

1.3.7.4.3 Physical stress or trauma

Non-specific trigger factors such as mild trauma (piercings, tattoos, injections or scratches), ultraviolet (UV) radiation and chemical irritants have been shown to be capable of provoking the eruption of psoriatic lesions.[148] This is best illustrated by the Koebner response, a phenomenon first reported by Heinrich Koebner in the 19th century, where trauma induced the emergence of new isomorphic psoriatic skin lesions in previously unaffected skin of psoriasis patients.[179] It seems that mechanical trauma and high dose UV radiation might implicate the release of proinflammatory cytokines involved in the pathophysiology of psoriasis and conceivably lead to the unmasking of auto antigens.[155] Thus, phototherapy has the potential to elicit psoriasis, when used too aggressively.[155]

1.3.7.4.4 Smoking

Albeit smoking is considered a causative factor for development of palmoplantar pustular psoriasis (PPPP),[180] the role of smoking in the etiopathogenesis of plaque psoriasis has been discussed more extensively in recent years.[181] In fact, De Waal et al.[180] suggest a strong association between PPPP and smoking, as approximately 95 % of PPPP patients are current or former smokers at disease outbreak.[180] Several epidemiological studies have suggested that tobacco consumption is strongly associated with increased occurrence of psoriasis.[173,182] Moreover, the increased risk of psoriasis eruption has further been reported within individuals that were exposed to passive smoke during childhood.[183] Nonetheless, epidemiological studies do not prove a causative role of smoking in the genesis of psoriasis.[173,182] However, as a recent meta-analysis indicates, former and active smokers are in fact overrepresented in a psoriasis-cohort.[182] Furthermore, the authors postulate that the amount of cigarettes smoked per day and high numbers of pack years impact the risk of developing psoriasis negatively.[182] Similarly to the pathogenesis in atherosclerosis, the systemic deleterious effects of cigarette smoking, which implicates endothelial dysfunction owing to oxidative damage, are believed to be an equally essential underlying pathological mechanism in the precipitating effect of smoking on increased psoriasis eruption.[182] In other words, smoking induces oxidative stress and seems to down-regulate the gene expression of antioxidants.[181] This results in a preponderance of reactive oxygen species (O_2^- and H_2O_2) over antioxidants (i.e. vitamin C), which eventually besides other systemic effects can have a triggering effect on psoriasis development.[181]

Moreover, nicotine enhances inflammatory mechanisms including cells and cytokines involved in the pathogenesis.[181] The stimulation of keratinocytes, dendritic cells and macrophages leads to the release of proinflammatory cytokines such as TNF-α, which in further consequence elicits a T-lymphocyte response.[181] Thus, a chronic inflammatory state is maintained. Ultimately, tobacco consumption has the ability to influence the genetic predisposition for psoriasis in a negative manner.[181] Increased expression of established susceptibility genes such as HLA-Cw6 have been detected in smokers.[181]

Furthermore, smoking is considered to cause enhancement of psoriasis severity, which can be measured by higher PASI scores compared to nonsmokers.[184,185]

Another reason to quit smoking or should discourage people from smoking, is the fact that psoriasis therapeutics, in particular TNF inhibitors, seem to be less effective in smokers.[186]

1.3.7.4.5 Alcohol

The disputed association of alcohol consumption respecting psoriasis may be partially confounded by smoking.[187] So, there is no definite evidence for this correlation, thus far.[188] However, a prospective cohort study by Qureshi et al.[189] was carried out, to assess whether association of psoriasis development and alcohol consumption depended on which alcoholic beverages were consumed.[189] Interestingly, non-light beer was related to an elevated risk of psoriasis occurrence, while light beer, wine and other liquors showed no increased risk.[189] As for the role of alcohol in psoriasis patients, most data seem to indicate that the level of alcohol consumption among psoriasis patients is larger than in the general public.[188]

1.3.7.4.6 Microorganisms & infections

It is well established that, β-hemolytic streptococci infections are often seen prior to the initial onset of guttate psoriasis.[171] However, the triggering role of streptococcal infection is not just restricted to guttate psoriasis but includes plaque psoriasis as well.[190] A prospective study was carried out by Gudjonsson et al.[191] to investigate in this matter, which asked both a psoriasis group and a control group to report, whenever they experienced sore throat so that they could be checked for streptococcal infection.[191] The psoriasis group was significantly more affected by streptococcal colonization than the control group (10 % vs. 1 %).[191] This implicates that streptococcal throat infection can lead to the exacerbation or worsening of psoriasis.[191] In further consequence, this implies that psoriasis patients affected by sore throat, may prevent exacerbation of their psoriasis by receiving adequate antibiotic treatment.[191]

Additionally, patients with chronic HIV infection have higher odds to develop psoriasis with a relative risk (RR) of 3.5.[192]

1.3.7.4.7 Drugs

Besides anti-TNF-α agents, there are several drugs that have been implicated with the eruption of psoriatic lesions.[193] The intake of ß-blockers or lithium can either induce de novo psoriasis or lead to an exacerbation of psoriatic lesions.[193] In comparison, antimalarial drugs are only considered to aggravate preexisting psoriasis.[193] Furthermore, the discontinuation of corticosteroid therapy has been associated with the eruption of pustular psoriasis.[193] Moreover, it has been discussed latterly, whether or not nonsteroidal anti-inflammatory drugs (NSAIDs) can elicit or exacerbate psoriasis.[193] However, the

correlation of cumulative de-novo appearances of psoriatic lesions or worsening of pre-diagnosed psoriasis conditions following NSAID therapy is quite contentious, as evidence is rather weak.[193] Still, a recent prospective cohort study carried out by Wu et al.[194] implied that discrepancies between NSAIDs are likely, as their results suggested an increased psoriasis risk for regular acetaminophen intake, whereas acetylsalicylic acid did not show any indication of triggering psoriasis.[194]

The role of antibiotics respecting psoriasis is conflicting, as some authors have accredited erythromycin, penicillin and rifampin in particular with advantageous effects in the treatment of psoriasis,[195–197] whereas case reports have described doxycycline, penicillin, amoxicillin and ampicillin as precipitating as well as aggravating factors.[193,198,199] If, however, there is a causative correlation is debatable, since infections themselves can provoke the development of psoriasis.[193]

ß-blockers were one of the first drug groups identified, to be associated with drug-induced psoriasis.[200] Both non-selective ß-blockers such as propanolol and cardio-selective such as metoprolol have been implicated with psoriasiform eruptions.[200] The exact mechanism how ß-blockers induce psoriasis is uncertain.[193] However, there are several hypotheses trying to explain the correlation between ß-blockers and psoriasis.[193] One assumption is that inhibition of epidermal ß-receptors leads to decreased levels of cellular cyclic adenosine monophosphate (cAMP) and subsequently to an increment of epidermal cell turnover.[193] Physiologically, cAMP as a secondary messenger mediates, per its encoding proteins, the differentiation of keratinocytes and regulates the proliferation thereof.[193] Decline of cAMP entails the reduction of intracellular calcium and subsequently leads to abundant proliferation of keratinocytes and to insufficiently differentiated keratinocytes as found in psoriatic lesions.[193] Albeit the prevailing assertion that ß-blockers are triggers of de-novo psoriasis, a large case-control analysis carried out by Brauchli et al. could not corroborate this allegation.[201]

The most frequently seen cutaneous adverse event within lithium-therapy is most likely psoriasis.[202] Several cases of lithium-induced psoriasiform lesions have been reported over the years including pustular psoriasis, nail psoriasis and erythrodermic psoriasis.[202] Lithium carbonate and lithium citrate are primarily used to treat psychological disorders.[202] Nonetheless, lithium has been administered as an uricolytic drug without any correlation to psoriasis whatsoever.[202] The exact mechanism of how lithium treatment can exacerbate psoriasis or entail de novo psoriasis is still under debate.[202] However, lithium seems to have the ability to augment the pathophysiological pathways of psoriasis on a molecular

and cellular basis.[202] The incidence of lithium-induced or -exacerbated psoriasis has a range of 3.4 to 45 % according to Basavaraj et al.[193]

The intake of synthetic antimalarial drugs (SADs) such as chloroquine and hydroxychloroquine is generally recognized to elevate the risk of exacerbation of preexisting psoriasis.[193] Since they do not induce psoriasis de novo, it is believed that their triggering mechanism is based on pharmacological induction or repression of key enzymes involved in the proliferation process of keratinocytes.[193] It is suggested that approximately 18 % of psoriasis patients experience a deterioration of their psoriasis ensuing therapy with SADs.[203]

1.3.7.5 The psychological burden and quality of life in patients with psoriasis

Psoriasis is quite a debilitating disease, not just physically, but also psychologically.[148,204] Physically, patients might find it cumbersome, to cope with symptoms such as pruritus and burning sensations.[204] Psychologically, the major challenge to afflicted patients is to deal with the evident disfiguration, which can lead to social stigmatization.[204] Thus, psoriasis often goes along with a decreased quality of life due to the psychological distress and social isolation it may cause.[204] In fact, the psychological deterioration appears to be worse than other chronic diseases such as cancer, myocardial infarction and congestive heart failure.[204] Solely, chronic lung disease and depression seem to be psychologically more challenging than psoriasis.[204]

The measurement tool of choice to assess the quality of life in patients with dermatological disorders is the Dermatology Life Quality Index (DLQI) score, which is notably high in psoriasis patients, whereby higher scores illustrate worse quality of life.[205,206] The DLQI ranges from 0 (no decline of life quality) to 30 total points (maximum impairment of life quality).[205,207] DLQI is based on a questionnaire regarding current factors (latest symptoms, sentiments, activities of daily living, free time, work situation/school situation, status of personal relationships, treatment) contributing to the quality of life.[205,207] Notably, the DLQI is also dependent on the severity of the disease and the body areas being involved .[208] Nail psoriasis involvement, for instance, is associated with higher severity of skin lesions.[209] Apart from that, due to the public display of the fingers, it commonly causes restrictions on daily working life, which again impairs the total quality of life.[209] However, health-related quality of life may also be substantially impaired in patients with objectively mild psoriasis.[210]

1.3.7.6 Measurements tools to quantify disease severity

Initially, the Psoriasis Area and Severity Index (PASI) was generated by Fredriksson et al. in 1978 to evaluate the outcome of retinoid treatment in psoriasis vulgaris.[211] However, the PASI score is insufficient for the assessment of other clinical subtypes of psoriasis.[205] Nowadays, it is the most established parameter to measure the severity and extent of plaque psoriasis in the evaluation of all treatment regimens and documentation of the general clinical course of the respective patients.[205,212] Basically, the PASI score is an effort to quantify the intensity and extent (BSA) of the psoriatic plaques throughout the body on a numerical scale, whereby four distinct areas of the human body (scalp, trunk, upper and lower extremities) are calculated individually.[205,212] Hence, the percentage of these distinct anatomical regions in relation to the entire integument is calculated.[205,212] The proportion of involvement of the aforementioned sites is admeasured a numerical value of 0-6 with 0 indicating no involvement, 1= 1-9%, 2 = 10-29 %, 3 = 30-49 %, 4 = 50-69 %, 5 = 70-89 % and 6 = 90-100 % BSA involvement.[205,212] Additionally, the PASI score entails the assessment of intensity of erythema, desquamation and induration is based on a 5-point scale.[205,212] Zero equals no involvement, 1 stands for slight, 2 for moderate, 3 for severe and 4 for very severe characteristics.[205,212] The PASI score ranges from 0 to 72.[205,212]

PASI 75 equals a 75 % decline in PASI at primary endpoint compared to the PASI score calculated at baseline.[212] As per the European S3 guidelines, achievement of PASI 75 is considered a clinically significant enhancement.[212] Thus, PASI 75 is used as the main evidence-based efficacy parameter.[212]

Whereas, it appears as if there was a universal accordance concerning the state of severity of certain clinical manifestations such as psoriatic arthritis, pustular psoriasis, erythrodermic psoriasis and inverse psoriasis, it seems like there was some discord regarding the definition of severity chronic plaque psoriasis.[205] As a result, Schmitt et al.[205] proposed a PASI-based definition of severity:[205]

PASI >12: severe chronic plaque psoriasis

PASI 7-12: as moderate chronic plaque-psoriasis

PASI <7: mild chronic plaque-type psoriasis

1.3.7.7 Clinical features of psoriasis

Clinically, psoriasis presents itself as a heterogeneous disease.[148,213] There are following subtypes or variants of psoriasis, which differ clinically, morphologically and in various other features (such as genetics), psoriasis vulgaris, guttate psoriasis, pustular psoriasis and erythrodermic psoriasis.[213] Furthermore, psoriasis might affect special sites such as the scalp, the nails and the inverse/flexural/intertriginous or the genital area.[213] Additionally, psoriasis may be accompanied by arthritis affecting a great variety of different joints.[148,213] Thus, psoriasis is a systemic disease, which is not limited to the skin.[148,213] Psoriasis is defined by its chronic relapsing clinical course, which visually can be observed, as psoriatic lesions wax and wane during the course of disease.[213] Onset of psoriasis often differs among the psoriasis types, as a sudden onset is typically seen in guttate psoriasis, whereas plaque psoriasis develops in a more gradual progressive way.[213] Diagnosis is usually made based on a clinical basis and does normally not require further histological examination.[148]

1.3.7.7.1 Psoriasis vulgaris

Chronic plaque psoriasis, alternatively termed psoriasis vulgaris, is the most common type of psoriasis comprising 85-90% of all psoriasis cases.[148,213] The characteristic morphologic picture encompasses the occurrence of silvery-white scaling erythematous plaques, typically of circular form, that are well demarcated.[153] Shapes and sizes of lesions can vary from millimeters to several centimeters big, as they sometimes merge to bigger lesions.[153] When the onset of psoriasis eruption is sudden and advancing rapidly, lesions might appear as annular.[214] Technically, these lesions can be found at any skin site, anywhere on the body.[148] However, psoriasis plaques are usually located on the so-called predilection sites, which include the extensor surfaces of lower arms and shanks, the perianal, the periumbilical and the retro-auricular area, as well as the scalp.[148] The distribution of psoriatic lesions may appear symmetrically.[148] Whenever the psoriatic lesions clear, hypopigmented patches (psoriatic leukoderma) can be found.[213]

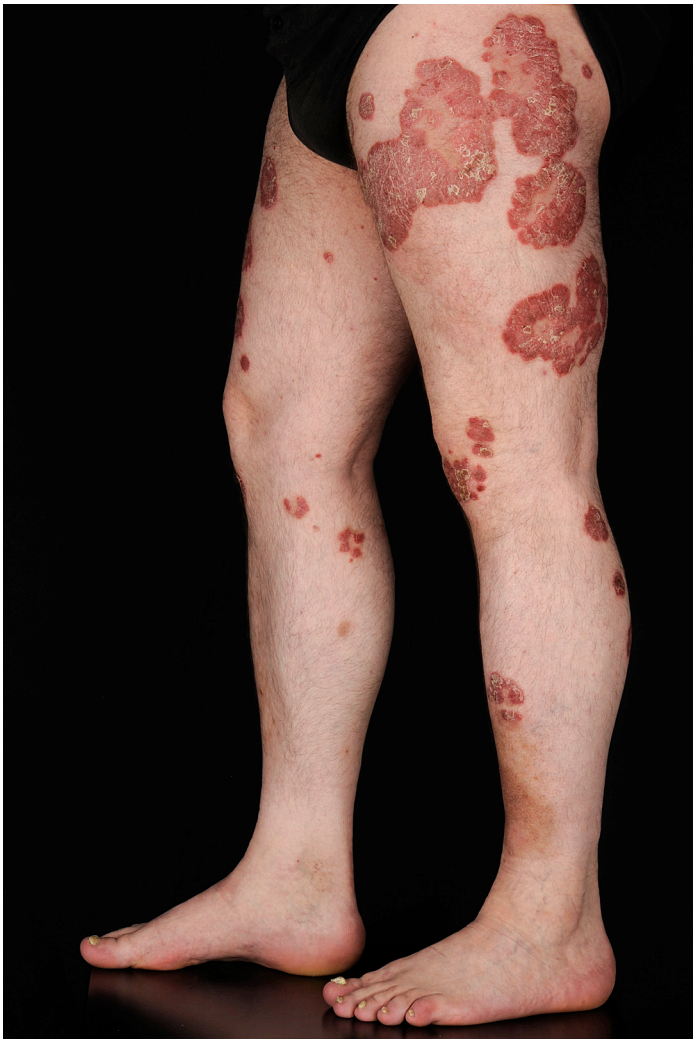

Figure 1. Chronic plaque psoriasis of the lower limbs

1.3.7.7.2 Guttate psoriasis

Guttate psoriasis is a distinctive form of psoriasis that usually affects young patients (younger than 30 years), often following a ß-streptococcal upper respiratory infection.[148] It accounts for about 2 % of total psoriasis cases.[215] Guttate psoriasis characteristically occurs in a rather acute manner, persist for approximately one month, before waning in the third month.[214] This psoriasis form can either occur as a single event with full recovery or appear with guttate flares in relapsing manner, including in plaque psoriasis patients, of which about 10 % state to have a history of guttate flares according to Naldi et al.[213] However, for about one third of the patients with guttate psoriasis, it is the initial manifestation of psoriasis and progresses to a chronic psoriasis vulgaris.[213,216] Typical findings comprise of droplet-like scattered lesions (1-10 millimeters small pink papules and plaques with scarce scaling) on the patient's trunk.[155] Moreover, lesions may also be found on the limbs and the face.[214]

1.3.7.7.3 Erythrodermic psoriasis

Coalescent psoriasis lesions affecting more than 90 % of the skin is regarded as erythroderma.[214] Erythrodermic psoriasis is a very scarce but severe psoriasis variant, which represents a potentially life-threatening condition.[217,218] This type of psoriasis either emerges de novo or is the result of a gradual or acute aggravation of a preexisting expanded active psoriasis condition of any type.[217,218] This severe condition may be triggered by the discontinuation of glucocorticosteroid therapy, infections or the sudden withdrawal of methotrexate.[217] This generalized erythema of the whole body can vary in desquamation degree, sometimes leading to the extreme clinical picture of exfoliative psoriasis.[217] As the skin barrier is severely impaired, patients are more prone to infections.[218] Furthermore, other physiological features of the skin like the thermoregulatory function and the ability to retain fluids and nutrients is lost.[218] Accompanying signs of systemic inflammation such as fever and malaise are frequent.[219] As a result, the erythrodermic condition might lead to sepsis and therefore an increased mortality rate is implicated for this psoriasis subtype.[219]

1.3.7.7.4 Pustular psoriasis

Pustular psoriasis is a number of inflammatory skin conditions, which are defined by large amounts of invading neutrophil granulocytes in the epidermis, reaching such high level of epidermal neutrophil infiltration that sterile pustules appear macroscopically.[159]
In general, a distinction must be made between localized and generalized pustular psoriasis.[220] Pustular psoriasis, has been discussed recently to represent an own entity, distinct from psoriasis, as notable differences exist, in particular on a genetic level.[159,180] Furthermore, pustular psoriasis and psoriasis vulgaris seem to respond variously to different treatments.[159] However, as of now, due to the clinical co-incidence pustular psoriasis is still grouped together with psoriasis vulgaris.[159]
Psoriasis pustulosa is categorized in various subtypes depending on the clinical course and location of the pustular lesions.[220] In table 4. the different clinical variants of pustular psoriasis will be presented.

Table 4. Pustular psoriasis

Generalized pustular psoriasis	
Von Zumbusch GPP	Generalized pustular psoriasis (GPP), also termed Von Zumbusch psoriasis, is a very rare form of psoriasis with a prevalence of 1-9 cases per million.[220] Nonetheless, this psoriasis variant is of clinical relevance, due to the potential life-threatening condition it may pose.[220] In about 30 % of GPP patients a positive family history for psoriasis can be detected.[220] Characteristically, GPP comprises a sudden onset and eruption of sterile pustules, which are scattered on large portions of erythematous dolorous skin.[220,221] Collections of pustules tend to merge to larger figures of pustular blisters, which, after they split open, can show desquamation.[220,221] Constitutional symptoms (fever, malaise and leukocytosis) are frequently seen within GPP patients.[220,221] GPP presents a potentially life-threatening condition as complications, which are observed within GPP encompass, the progression to erythrodermic psoriasis, infection or electrolyte imbalance.[221] However, the disease course can vary significantly, as GPP can equally present itself in a less severe chronic relapsing way.[222]
Annular	Distinguishing for this subtype of pustular psoriasis is the annular, gyrate configuration of psoriatic plaque lesions with or without pustules on erythematosquamous background bundled on the edges.[221] Pustules often emerge quickly with followed exfoliation.[221] This subtype preferably appears in juvenile patients with a notably lesser systemic involvement compared to GPP.[221]
Impetigo herpetiformis	This variant is a very scarce, but a severe acute pustular dermatosis, typically emerging in the final trimester of pregnancy.[223] Macroscopically and clinically it is akin to GPP, often recurring in following pregnancies.[223] Prognosis depends on early detection and adequate treatment.[223]
Localized pustular psoriasis	
PPPP	Chronic recurring localized pustular psoriasis, which is limited to the palms and soles.[221] The prevalence of PPPP is suggested to range from 0.01 to 0.05 percent and is the most common form of pustular psoriasis.[159,220] Primarily, women are affected (82-92 %) with peak incidences in the 6th and 7th decade of life.[180,224] Associations to smoking and thyroid dysfunction have been proven by multiple studies.[221,224] Roughly one out of four PPPP patients displays a positive family history of psoriasis.[225] Percentage of accompanying psoriasis vulgaris in PPPP varies considerably in the literature with a broad range from 4 to 73.2 %.[221,225] Macroscopically, multiple sterile recalcitrant pustular lesions emerging on an erythematosquamous background can be observed.[221]
Acrodermatitis continua of Hallopeau	Scarce disfiguring type of localized pustular psoriasis, which is very refractory.[221] Typical clinical hallmarks encompass peri- and subungual sterile pustules on red scaly skin that often coalesce to 'lakes' of pus.[221] Eventual complications of this chronic relapsing disease include onychodystrophy, permanent onychia and osteolysis, leading to deformation and destruction of the respective distal phalanges.[221] It may appear with concomitant plaque psoriasis lesions or without.[159]

There has been some inconsistency in the literature regarding the definition and classification of palmoplantar pustular psoriasis and pustulosis palmoplantaris.[220] Nonetheless, 'palmoplantar pustulosis' and 'palmoplantar pustular psoriasis' are regularly used synonymously in the literature and refers to the same chronic relapsing form.[220,224] Moreover, psoriasis vulgaris may equally affect palms and soles in about 12 % without any pustular eruptions present or with some concomitant pustules.[224,225] Plaque psoriasis lesions with pustules within or at the border of psoriasis plaques are termed "psoriasis cum pustulatione" and is not viewed as pustular psoriasis.[159]

1.3.7.7.5 Special locations

Inverse psoriasis (flexural psoriasis)

Inverse psoriasis (flexural psoriasis) is regarded as a variant of plaque psoriasis, which is defined by the involvement of special sites, the inverse/intertriginous/flexural body areas.[226] This variant of psoriasis has a prevalence ranging from 12 to 36 % among European psoriatic patients.[226] This broad prevalence range can partially be explained by the discrepancy in the literature, whether or not to include genital involvement of psoriasis to the definition of inverse psoriasis,[226] as some authors view psoriasis of the genitalia as a distinct variant of psoriasis.[227] Nonetheless, both inverse psoriasis, as well as genital psoriasis are believed to be underreported.[226,227] This might be a reflection of the psychological burden, shame and social stigmatization, which is implied with these psoriasis subtypes.[226,227]

According to Weisenseel et al.,[228] there are two subtypes of inverse psoriasis.[228] The term 'flexural' psoriasis is used to describe the manifestation of inverse psoriasis, where mainly flexural regions of above the joints (knee, cubita) are affected.[228] Secondly, patients with inverse psoriasis, where for the most part the intertriginous areas such as the groins, axillae or the submammary region are affected, are referred to as 'intertriginous' psoriasis.[228] Depending on how inverse psoriasis is defined, the affected sites might encompass the axillae, groin, genital area, umbilical area, postauricular area, the intergluteal cleft, inframammary folds, antecubital fossae as well as the popliteal fossae.[226] Seemingly, the most frequently involved site is the groin.[226] The prototypical appearance of inverse psoriatic lesions can be described as strictly confined, reddish, shiny to glazy, humid, thin plaques without scaling often combined with secondary fissuring and maceration.[226] Thus, the clinical presentation of flexural psoriasis distinguishes considerably from the typical lesions of psoriasis vulgaris.[226] The moist, warm condition at the intertriginous sites, which

are defined by a cluster of diverse follicles in addition to sebaceous glands, plus various apocrine and eccrine glands, are the reason that scales cannot develop.[226]
Distinctions to plaque psoriasis are not only noted macroscopically but microscopically with a lesser degree of epidermal hyperplasia and increased spongiosis in samples of flexural psoriasis.[226] Notably, inverse psoriasis is apparently more frequently associated with nail involvement in comparison to psoriasis vulgaris.[226]

Nails

Nail psoriasis can be detected in roughly half of the diagnosed plaque psoriasis patients.[229] However, a questionnaire-based survey undertaken by Klaassen et al.[230] recently indicated that prevalence rates of nail involvement are likely to be higher, as they found a prevalence of 66 % in their study, suggesting that nail psoriasis has previously been underreported.[230] Additionally, the lifetime incidence of nail involvement in psoriasis patients is suggested to be around 80 to 90 %.[229] Furthermore, patients with PsA have shown a heightened prevalence rate for nail psoriasis with up to 87 %.[231] Moreover, nail psoriasis can be the only psoriasis manifestation.[232] Thus, it is believed that approximately 5 % of psoriasis patients have solely a nail psoriasis manifestation without involvement of the skin.[231] Interestingly, fingernails seem to be more frequently implicated than toenails.[146] More common observed nail psoriasis manifestations might vary in clinical appearance, depending on the structures affected within the nail apparatus.[232] Table 5 gives an overview of the various psoriasis-associated alterations affecting the nail matrix and/or nail bed.

Table 5. Signs of nail psoriasis[232]

Nail matrix alterations	Nail bed alterations
Pitting	Oil-drop spots
Leukonychia	Subungual hyperkeratosis
Red dots of the lunula	Onycholysis
Transverse grooves (Beau's lines)	Splinter hemorrhages
Crumbling of the nail plate	

Additionally, nail psoriasis can encompass periungual inflammation.[232] While these clinical features are not psoriasis specific, experienced dermatologists diagnose nail psoriasis clinically by pattern recognition.[232]
Notably, psoriatic nail involvement is considered an indicator for a more severe condition of psoriasis and is related to a protracted duration of psoriatic lesions.[233]

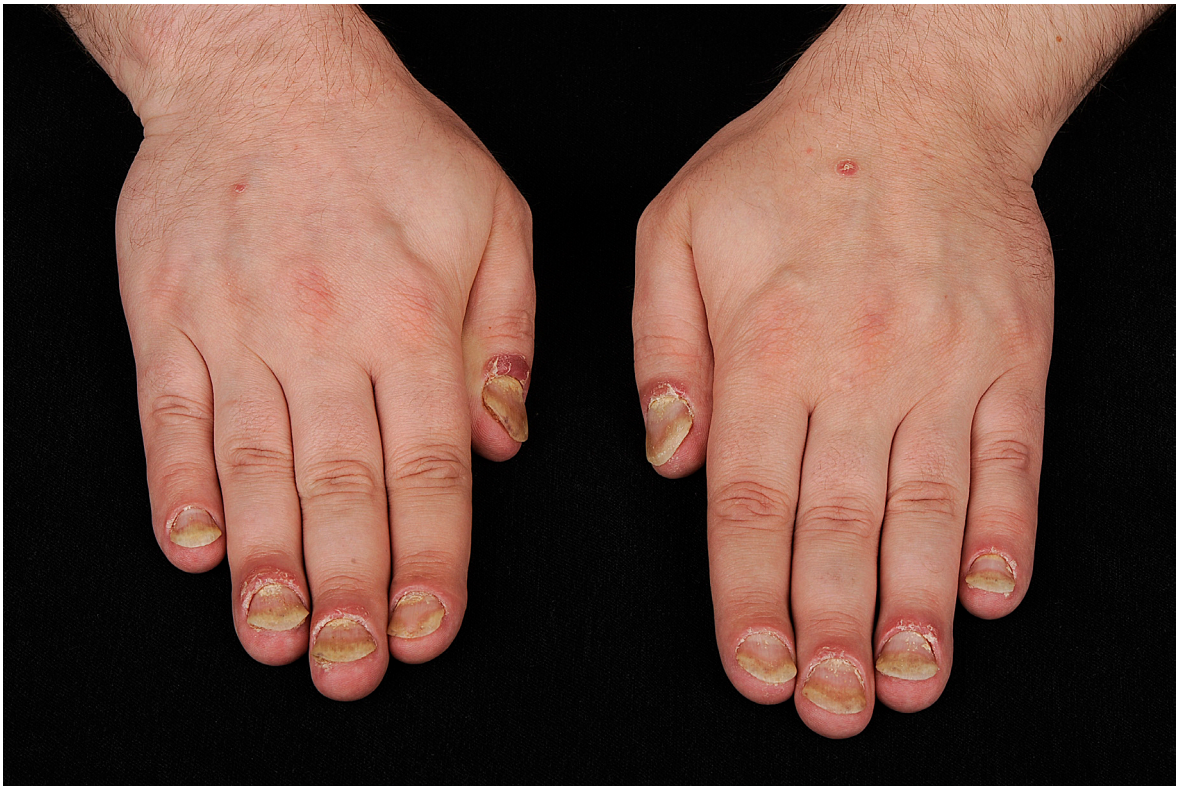

Figure 2. Psoriasis of the nails

Scalp

The scalp is regarded as a predilection site of plaque psoriasis, in particular the retroauricular and occipital area.[214] According to multiple authors, the scalp is the anatomical site, which is most frequently involved in both juvenile and adult psoriasis.[214,234] Scalp involvement occurs in about 80 % of the psoriasis patients.[235] Furthermore, it is often the initial location of new-onset plaque psoriasis.[214,235] The prevalence of scalp psoriasis is approximated to be around 2 % of the European population.[236] The degree of involvement varies from single small plaques to the extreme variant of plaques covering the total scalp.[214] Typical psoriatic lesions of the scalp are described as well-confined erythematous plaques with more and lesser adherent white silvery scales.[214,234] These lesions tend to extend beyond the hairline in the neck and on the

forehead and occasionally expand to the retroauricular area.[214,234] However, the lesions seem to seldom extend more than two centimeters beyond the hairline.[214,234] Pruritus is reported by up to 70 % of the affected patients.[234] Compared to other sites of plaque psoriasis, the lesions do not typically show a symmetrical distribution pattern.[214] This is often attributable to the Koebner phenomenon, as the aforementioned itchiness causes the patients to scratch, pick and scrub in a more frequent manner.[237] Most of the patients with psoriatic scalp involvement do not develop alopecia.[234] However, in severe forms of scalp psoriasis and long-lasting untreated conditions, alopecia lesions secondary to psoriasis may develop, usually the non-scarring type, in rare cases the cicatricial type.[234] As with nail psoriasis, some studies have indicated that scalp psoriasis is a prognostic marker for a subsequent development of PsA.[238] However, this association could not be verified by a study undertaken more recently.[239]

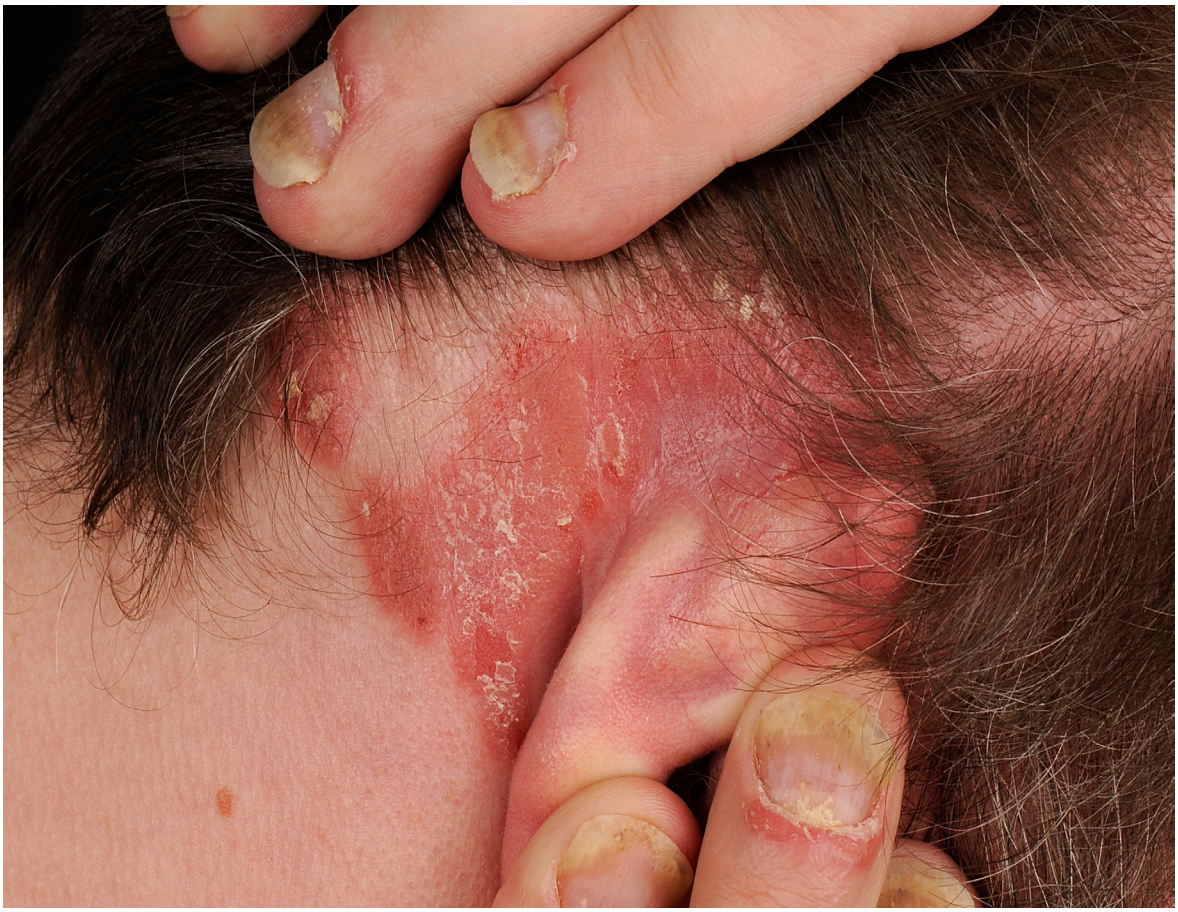

Figure 3. Scalp psoriasis

1.3.7.8 Psoriatic arthritis

PsA is defined as a seronegative chronic inflammatory condition with a close relation to psoriasis and nail psoriasis.[240,241] Prevalence in the general population ranges from 0.02 % to 0.4 %.[242] In the literature great variations in prevalence rates within a psoriasis cohort are noted, depending on the population being investigated.[242] According to Gerdes et al.,[243] prevalence numbers found in medical textbooks tend to be falsely low with prevalence rates under 10 %, pointing to more recent studies undertaken in Germany, where the percentage of joint involvement among psoriasis patients were about 20 %.[243,244] Contrary to psoriasis vulgaris, the genetic linkage to HLA antigens is less distinct.[242] However, independently from psoriasis, SNPs in the IL-13 gene have been detected to go along with increased manifestation risk of psoriatic articular involvement.[242]

Interestingly, according to recent research, some psoriasis subtypes are at a higher risk of having articular involvement than plaque psoriasis.[245] Inverse psoriasis, in particular genital involvement, is considered to have a twice as high risk of developing PsA than plaque psoriasis.[245] Moreover, nail psoriasis is associated with a 3-fold risk and psoriasis of the scalp has a 4-fold risk compared to psoriasis vulgaris sparing the scalp.[245] Therefore, patients with these particular psoriasis phenotypes should be screened thoroughly for articular involvement.[245] Roughly 75 % of the PsA patients develop psoriatic skin lesions precedent to the inflammation of the joints.[242] However, in approximately 15 % of the PsA patients, arthritis will develop prior to psoriatic skin lesions.[242]

Typically, PsA involves the peripheral joints, the axial skeleton, sacroiliac joints and entheses. [240,241] Characteristically, patients develop swelling, pain and stiffness of articulations as well as in ligaments and tendons.[242] Dactylitis, is a prototypical clinical manifestation of PsA, where the chronic inflammatory process involves the tendons and ligaments of one finger or toe, resulting in a “sausage-digit-like” appearance.[242]

1.3.7.9 Histological hallmark features of psoriasis

Histopathologically, psoriasis displays numerous alterations compared to the normal skin.[148,153,155,214] Epidermal acanthosis (thickening of viable layers), hyperkeratosis (thickening of the corneal layer), parakeratosis (cell nuclei present in the cornified layer, which they are normally not) epidermal rete ridges (thickening that expand down between dermal papillae) are decidedly elongated.[148,153,155,214] In the dermis, dilated and contorted blood vessels reach into the tips of the dermal papillae.[148,153,155,214] As a result, the psoriatic

lesions appear reddish macroscopically, through a conspicuously rarefied.[148,153,155,214] An inflammatory infiltrate containing T-lymphocytes, mainly CD4+ and CD8+ T-cells, is noticeably in the dermis and epidermis, in addition to increased numbers of neutrophilic granulocytes, macrophages and mast cells.[148] This gathering of cells is described as Munro micro abscesses or pustules of Kogoj.[148] Basal keratinocytes in mitosis can be found to a greater extent, indeed about 50 times as many mitotic keratinocytes as in normal skin.[155] Hence, the keratinocyte's journey from the basal layer to the cornified layer, which normally takes approximately 30 days, is markedly abbreviated to 3 to 5 days.[155] As a result, the maturation process of keratinocytes is insufficient, leading to undifferentiated cells, parakeratosis and the lack of a stratum granulosum.[155]

1.3.7.10 Comorbidities

Certain relevant disorders have shown a higher prevalence in psoriasis cohorts than in the general population.[153,214] This is not an unexpected finding, since psoriasis is regarded as a systemic disease, which is not solely confined to the skin.[153,214] Comorbid diseases associated with psoriasis comprise of other IMIDs such as CD or non-infectious uveitis, since it has been shown that patients that develop an IMID are prone to develop another one.[107] Similarly, the co-occurrences of cardiovascular diseases and associated conditions such as diabetes mellitus, hypertension, metabolic syndrome, obesity and hyperlipidemia have been observed in an elevated manner.[178,246] As a result, life expectancy is suggested to be lower in cohorts of patients with severe psoriasis, often due to cardiovascular disease associated events.[148]

Shared pathophysiological pathways (with to a large extent involvement of equal proinflammatory cytokines), common risk factors or similar genetic predisposition of the comorbid diseases, might explain some of the increased co-occurrences.[148]

Table 6. Comorbidities of psoriasis

Obesity	Adiposity (all patients with a BMI over 30) is commonly linked to psoriasis.[246] Additionally, obesity has been reported to go along with more severe forms of psoriasis.[247] As a result, the severity and therapy of psoriasis seems to benefit from weight reduction.[248]
Metabolic syndrome	A meta-analysis carried out by Armstrong et al.[249] demonstrated an increased occurrence of psoriasis in patients with metabolic syndrome.[249] Accordingly, psoriasis has been associated with diabetes, hypertension and dyslipidemia.[250–252] Similarly to adiposity, metabolic syndrome has been positively correlated with the degree of severity of psoriasis.[243]
Cardiovascular disease	Studies have demonstrated that psoriasis is an independent risk factor for increased cardiovascular morbidity.[200]
IBD	IBD has been associated with the increased occurrence of psoriasis and vice versa.[242] In fact, CD patients have a roughly 7-fold higher risk of developing psoriasis, whereas psoriasis patients have a 2.9-increased risk of CD manifestation.[242] Furthermore, CD and psoriasis have been identified to have seven susceptibility loci in common.[242]
Uveitis	Uveitis is roughly detected in 2 percent of patients in a psoriasis cohort.[242,253] However, evidence regarding the association of psoriasis vulgaris without articular manifestation and uveitis is not very strong.[253] Accordingly, only PsA and pustular psoriasis are proposed risk factors for the development of uveitis.[253]
Depression	Psychological impairments such as anxiety and depression have been proven to be elevated with psoriasis patients compared to the general population, whereby psychiatric comorbidities are more prevalent in patients with severe psoriasis or PsA.[254]

1.3.7.11 Efficacy of TNF inhibitors in psoriasis

All TNF inhibitors currently available on the market have shown great efficacy in the treatment of psoriasis or psoriatic arthritis.[255–263] Studies have shown that infliximab, adalimumab, etanercept, certolizumab pegol and golimumab are efficacious treatment options for moderate-to-severe psoriasis conditions, proven by the high numbers of patients achieving persistent PASI 75 amelioration within the first year of treatment.[255,257,259,261,263] As shown in table 1 infliximab, etanercept and adalimumab are approved for the treatment of both psoriasis and PsA, whereas golimumab and certolizumab pegol are solely licensed for the treatment of PsA.[39,44–47] Besides, in the European Union etanercept is licensed to treat adolescents (aged twelve to seventeen years) with psoriatic arthritis and the enthesitis-related arthritis subtype.[46,60]

1.4 Potential general side effects of TNF inhibition

With the broader use of TNF-α blockers, the reports and reviews regarding safety and adverse events have been steadily growing in number and in diversity.[264] Various side effects have been attributed to anti-TNF-α treatment.[264] In the following, the most commonly TNF inhibitor related side effects will be presented.

1.4.1 Infusion site reactions & injection site reactions

The most frequently seen side effects of TNF-α inhibitors or with biologics in general, as they are foreign protein-derived treatments, which are administered intravenously or subcutaneously, are infusion- and injection site reactions.[265] Infliximab is the only anti-TNF-α agent available in Europe, which is administered intravenously.[39] Hence, the occurrence infusion site reaction is limited to infliximab.[265] Correspondingly, injection site reactions are seen with anti-TNF-α agents that are given subcutaneously.[265] Infusion- and injection- site reactions are the only side effects with a definite association to the administration of anti-TNF-α therapeutics, whereas the strength of association of all other adverse events varies.[264]

Infusion site reactions can appear concurrently or subsequently to the infusion.[264,265] In psoriasis patients treated with infliximab, it is believed to emerge in 3-22%.[265] Generally, most of these reactions are mild to moderate and are very manageable, for instance, by decrement of the infusion rate.[265] Approximately 1 % of the patients experience reactions severe enough to stop TNF inhibitory treatment.[264]

Moreover, it is important to differ acute reactions (within the first 24 hours) from delayed reactions, which can arise between 24 hours and 14 days after infusion administration.[264] Additionally, a distinction between mild, moderate and severe acute reaction is necessary.[265,266] Patients with severe acute infusion reactions usually present with anaphylactic like symptoms such as hypotension, chest tightness, dizziness, shortness of breath, laryngeal edema, urticaria and bronchospasm.[265,266] Nausea, headache, fever, erythema and itching are typical symptoms associated with mild forms.[266]

Delayed-type hypersensitivity infusion reactions are believed to occur in roughly 2 % of infliximab-treated patients.[266] Signs of delayed reactions might comprise influenza-like symptoms, arthralgia, myalgia, cephalea, fatigue or the eruption of a rash as well as the outburst of urticaria.[265]

In recent years researchers have tried to unmask predisposing factors of infusion reactions and how to avoid the development thereof.[265,266] Correspondingly, a clear positive correlation between the presence of antibodies directed against infliximab and the incidence of infusion reactions has been demonstrated by several studies.[265,266] However, according to Vermeire et al.[267] concomitant immunosuppressive therapy, including MTX and azathioprine (AZA) can effectively decrease the development of antibodies directed against infliximab.[267] Another interesting factor has been implied to influence autoimmunogenicity, the infusion schedule of infliximab.[268,269] Adherence of an introductory phase with three infusions at weeks 0, 2, and 6 seems to be less immunogenic compared to schedules with only one loading dose.[268,269] Furthermore, it appears that detection of anti-infliximab antibodies and occurrence of infusion reactions is less likely during maintenance treatment, in which infliximab is administered every 8 weeks.[265] Common adverse effects of the subcutaneously administered TNF-α antagonists are local site reactions at the puncture site.[264,270] Signs and symptoms encompass pain, erythema, pruritus, tenderness, bruising and swelling.[264,270] Injection site reactions are usually mild, last for a couple of days and do normally not require an interruption or cessation of anti-TNF-α therapy.[270] Interestingly, these site reactions have a tendency to appear more frequently in the first couple of months of treatment, with a subsequent decline of occurrence in the maintenance phase.[270]

1.4.2 Infections

From the very beginning, when they were introduced to the market, there was some concern expressed, whether TNF-α inhibitors would be implicated with an increased risk for the development of serious infections.[5] Hence, large registries were introduced to monitor the efficacy and safety of the new developed biologics.[5] Nevertheless, study results of multiple meta-analyses regarding the safety profile and assessment of the potential increased risk of serious infections are very conflicting, since they differ in their outcomes.[271–275] However, this could be ascribed to the heterogeneousness of the respective studies, differing in major factors such as the investigated study drugs, drug doses, study designs, study durations, disease durations or the underlying diseases (treatment indications) themselves.[271]

Dommasch et al.[276] performed a systematic review and meta-analysis including data form 20 RCTs of psoriasis patients under anti-TNF-α treatment.[276] They concluded that there

might be a slightly elevated risk for general infection associated with temporary TNF-α inhibition.[276] The odds ratio (OR) for any sort of infection was 1.18.[276] Nonetheless, the majority of recorded infections, 97.6 %, were mild, often concerning the upper respiratory tract, followed by flu syndrome and sinusitis.[276] However, no indication was found that psoriasis patients undergoing treatment with TNF-α inhibitors were at higher peril of being affected by serious infections.[276] On the contrary, a resemblant meta-analysis, carried out by Bongartz et al.,[277] found an increased risk for serious infection (OR 2.0) in a RA population.[277] Leombruno et al., again,[278] proposed a dose-dependent risk for infections, as they noted that elevated numbers of infections were restricted to patients, in which recommended dosing limits were surpassed.[278] A more recent systematic review and meta-analysis, including over 106 trials, found that RA patients treated with anti-TNF-α therapeutics (standard-dose and high-dose biological drugs) were in fact attributed with a higher risk of developing serious infections compared to DMARDs, although low-dose biological drugs were not.[279]

Nevertheless, it should be emphasized that atypical infections such as tuberculosis (TB) have been linked with the administration of TNF-α blockers in a variety of patient populations with IMIDs including psoriasis.[280] In comparison to etanercept, the anti-TNF-α monoclonal antibodies such as infliximab and adalimumab are associated with a higher risk of TB development.[280] Therefore, all patients should be screened for TB before starting anti-TNF-α therapy.[276] Furthermore, a variety of other granulomatous diseases such as candidiasis, cryptococcosis, aspergillosis and non-TB mycobacterial diseases have been associated with the administration of TNF-α inhibitors.[265]

Despite the ongoing debate over the association of anti-TNF-α therapeutics and higher infection susceptibility, the majority of authors seem to agree that the first couple of months are the most critical time, where patients seem to be more vulnerable to infection.[274,275,281]

1.4.3 Malignancies

The perception of a TNF-α-antagonists-related increased occurrence of malignancies is very contentious.[282] Due to the tumor lytic properties of TNF-α, which initially led to its discovery, it is a legitimate question, whether the inhibition of TNF-α comes along with an increased risk of cancer.[282] Thus, there are several studies that suggest a marginally enhanced risk of cancer, particularly non-melanoma skin cancer (NMSC),[265,282–285] but also melanoma and lymphomas.[285,286] On the contrary, a systematic review conducted by

Dommasch et al.[276] couldn't show any statistical significance between anti-TNF-α therapy and increased cancer incidence in a psoriasis population.[276] This could imply that differences in underlying diseases or the conducted population cohort also have their influence on differing outcomes of the respective study.[276] Confounding factors make it difficult to evaluate, whether the antagonism of TNF-α is associated with a higher risk of cancer development, as IMIDs in general are associated with increased incidences of cancer themselves.[287,288] Bongartz et al.[277] suggest that the malignancy risk of adalimumab and infliximab in RA patients is dose-dependent.[277] A recent meta-analysis carried out by Chen et al.,[289] which involved various study populations (RA patients, IBD patients, psoriasis patients), inferred that any sufficient evidence regarding an overall increased malignancy association of TNF inhibitors has yet to published.[289]

1.4.4 Cardiovascular diseases

Despite the fact, that advantageous cardiovascular effects have been attributed to TNF-α inhibition such as the preventive effect on ischemia, myocarditis and hypertension, TNF-α antagonism has been inculpated for some deleterious cardiovascular effects such as the participation in the formation of atherosclerosis, in addition to hypertrophy development of the heart and heart failure.[290,291] Therefore, the New York Heart Association (NYHA) recommends the contraindication of anti-TNF-α treatment in patients with heart failure of NYHA III and IV grades.[291]

The inconclusive role of TNF-α antagonists concerning cardiovascular conditions reflects the equivocal function of TNF-α in the pathophysiology of cardiovascular diseases.[292]

1.4.5 Demyelinating diseases and neuropathies

Reports have indicated an association of demyelinating disorders such as multiple sclerosis and Guillain-Barré syndrome, but also other neurological conditions with anti-TNF-α treatment.[293,294] However, compelling evidence concerning the causal relationship is lacking.[293] Additionally, the total annual amount of reported cases seems not to outweigh the incidence rates of patients untreated with this group of pharmaceuticals.[295,296] However, prior to anti-TNF-α therapy commencement, a thorough neurological examination is recommended, followed by stringent monitoring.[296]

1.4.6 Cutaneous adverse events

Several adverse events involving the skin have been noted during anti-TNF-α therapy, although information about anti-TNF-α associated cutaneous side effects is scarce.[264] Accordingly, most data concerning this matter is referable to case series and case reports.[264]

Table 7 summarizes the cutaneous adverse events regularly linked to anti-TNF-α therapy and their respective strength of association, based on a review carried out by Moustou et al.[264]

Table 7. Commonly TNF inhibitor associated cutaneous side effects[7,264]

Adverse event	Drug	Evidence	Frequency	Strength of association
Infusion site reactions				
Acute	IFX	RCTs	< 5 %	Definite
Delayed	IFX	RCTs	< 1 %	Definite
Injection site reactions	ETA, ADA	RCTs	~10 %	Definite
Psoriasis	All TNF inhibitors	PS, RS, CS, CR	< 1 %	Strong
Eczema	All TNF inhibitors	PS, RS, CS	Unknown	Moderate/strong
Lichenoid eruptions	IFX, ETA, ADA	CR	Unknown	Moderate
Lupus erythematodes	IFX, ETA, ADA	RS, CS, CR	< 0.5 %	Strong
Vasculitis	IFX, ETA, ADA	PS, RS, CS	< 0.5 %	Strong
Granulomatous annulare	IFX, ETA, ADA	RS	< 5 %	Poor/moderate
Cutaneous infections				
Bacterial infections	IFX, ETA, ADA	RCT, PS, RS	< 5 %	Strong
Fungal infections	IFX, ETA, ADA	PS	< 8 %	Strong
Herpes virus infections	IFX, ETA, ADA	RCT, PS	1-2 %	Strong
Cutaneous malignant neoplasms				
Lymphomas	IFX, ETA	PS, CR		Poor
NMSC	IFX, ETA, ADA	RCT, PS, RS, CR		Poor
Melanoma	ETA, ADA	CR		Poor

Abbreviations: ADA, adalimumab; CR, case report; CS, case series; ETA, etanercept; IFX, infliximab; PS, prospective study; RCT, randomized clinical trial; RS, retrospective stud.

1.5 Paradoxical side effects of TNF-α inhibitors

Recently, more and more studies describing so-called paradoxical side effects associated with TNF-α antagonists have emerged.[297–300]

Paradoxical adverse events (PAEs) are determined as side effects that appear unexpectedly during treatment of a certain chronic inflammatory condition with biologics, as the occurring pathological condition is ordinarily responsive to the administered group of drugs.[297,298] Hereof, the inculpated drug must have proven efficacy of the condition to be regarded as a 'true' paradoxical side event, as it is the case with the eruption of psoriatic lesions during anti-TNF treatment.[297] Moreover, exacerbation or worsening of the pre-existing conditions due to the administered drug is equally considered a paradoxical effect for that matter.[297] At the same time, the putative paradoxical side effect, might occasionally be a misinterpretation and in reality be the coincidental initial onset of a comorbidity or a de novo extra-articular, extra-intestinal manifestation of the respective treated IMID.[297] Following criteria are believed to be indicative of anti-TNF-α associated PAEs, the timing of onset of PAEs (temporal association with the treatment introduction), the vanishing after discontinuation of the accused therapeutic and the reoccurrence of the respective conditions after re-administration of the causative biologic agent.[298]

There are, however, several paradoxical side effects that have been described as 'borderline' PAEs under biological agent therapy in the literature.[297] By definition, these are immune-mediated disorders occurring during therapy with biological agents, in which a certain degree of evidence or rationale exists for its administration, albeit no definitive proof of efficaciousness has been presented yet.[297] In most cases these are off-label indications for anti-TNF-α treatment such as vitiligo for instance, in which case series and pilot studies have proven a certain benefit, but randomized clinical trials are lacking.[301]

1.5.1 True PAEs

Besides psoriasis, PsA, HS and IBD are considered as true paradoxical adverse events following anti-TNF-α therapy. However, these other true PAEs seem to not occur as often as anti-TNF-α induced psoriasis.[297,298] In the following, the paradoxical occurrence of hidradenitis suppurativa and psoriasis during anti-TNF-α therapy will be presented.

1.5.1.1 Hidradenitis suppurativa

TNF-α antagonist induced HS is a very rare treatment complication, as merely a few case studies can be identified scanning the literature.[302–306] Likewise, worsening of preexisting HS conditions have been observed.[307] In a case series carried out by Faivre et al.,[303] where 22 cases of anti-TNF-α induced HS were detected, the same demographic attributes were observed as in original (idiopathic) HS, with a notable preponderance of smokers, women and overweight individuals.[303] However, disparities were also noticed, as their cohort of anti-TNF induced HS cases showed a seemingly higher median age than in the common HS patients.[303] Furthermore, a positive family history of HS was reported with lower frequency compared to conventional HS.[303] The occurrence of HS following anti-TNF-α therapy might eventually be fortuitous and rather be connected to the underlying disease, since CD is a recognized comorbidity of HS and vice versa, than an actual implication of anti-TNF treatment initiation.[303] However, RA has no reported association with an increased occurrence with HS.[303] In the case series study by Faivre et al. RA patients were also included, which could possibly be indicative of a relation between the administration of TNF antagonists and HS.[303] Intriguingly, half of the patients involved in this study displayed concomitant onsets of immune-mediated conditions such as psoriasis, CD and alopecia areata, which have equally been associated with anti-TNF-α treatment.[303]
The entire mechanism behind this puzzling side effect has yet to be discovered.[306] However, it is believed that the central mechanism behind anti-TNF-α induced HS might be based on cytokine dysregulation, similarly to the hypothesis postulated for anti-TNF-α-linked psoriasis.[306]

1.5.1.2 Paradoxically induced psoriasis

Despite the great efficacy of TNF inhibitors in the treatment of psoriatic conditions (both psoriasis or PsA), the puzzling eruption of anti-TNF-α associated psoriasis or psoriasiform lesions is a well-documented side effect of TNF antagonists.[6–12] The first reported paradoxical case of anti-TNF-α induced psoriasis dates back to 2004, where Verea et al.[308] described a 46-year-old CD patient, who developed a psoriasiform drug reaction following the second administration of infliximab.[308] Since then the numbers of reported cases of this paradoxical side effects have been steadily growing.[6–12] The majority of cases has been described in the rheumatology and IBD literature.[6–12] It has been suggested that this phenomenon is a class-effect, as cases have been reported with all anti-TNF-α

therapeutics.[6–12] Estimated incidence rates for this controversial side effect have been calculated with data from rheumatology registries (RA patients undergoing anti-TNF-α treatment). Harrison et al. found an incidence rate of 1.04 (95 % CI 0.67-1.54) per 1,000 person years, whereas Perez-Zafrilla et al. detected an approximated incidence rate 3.0 (95 % CI 1.4-6.4) per 1,000 person-years.[9,309]

However, paradoxically induced psoriasis has not been exclusively limited to TNF-α antagonists. Although in a less frequent manner, there have been reports involving several other biological agents associated with paradoxical onsets of psoriasis.[297]
Similar to anti-TNF-α therapeutics, rituximab, despite an established efficacy in the treatment of psoriatic conditions,[310] has been linked to the occurrence of paradoxical psoriasiform and psoriatic lesions.[311,312] Abatacept (an anti-CTLA-4 fusion protein) is another biological agent, which has proven to ameliorate psoriatic lesions when given.[313] Nonetheless, the unexpected appearance of psoriatic lesions has been likewise reported with abatacept.[314,315] Furthermore, tocilizumab, a humanized monoclonal antibody targeting the interleukin 6 receptor, is licensed for the treatment of RA and has been successfully used as a reserve off-label treatment option for recalcitrant anti-TNF-α induced psoriasis cases.[316,317] Still, contradictory cases (although borderline) of psoriasis have been reported with this biologic agent.[318,319] Ultimately, another very effective licensed treatment option for psoriasis,[320] ustekinumab, has been associated with the puzzling contradictory appearance of psoriatic lesions.[321,322]

2 Methods

A comprehensive literature review was conducted utilizing PubMed databases and Google scholar. All pertinent scientific articles (clinical trials, case reports and case series) published in English, German and Spanish from 1999 to 2016 were collected concerning anti-TNF-α induced or associated psoriatic and psoriasiform lesions, regardless of the primary treatment indications. Furthermore, all qualifying subordinate references (displaying the variables of interest) such as poster abstracts and letters to the editor were added to the review.

Searching index terms included “tumor necrosis factor alpha inhibitor“, “TNF-α inhibitor”, “tumor necrosis factor alpha antagonist”, “TNF-alpha antagonist”, “anti-TNF-alpha”, “anti-TNF-α “, “anti-tumor necrosis factor”, “infliximab“, “etanercept“, “adalimumab“, “golimumab“, “certolizumab“ combined with the terms “psoriasis”, “psoriasiform”, “pustular“, “palmoplantar“, “side effect”, “induced,“ and “paradoxical.“

In addition, all reference lists of the found relevant scientific papers were scanned, to identify further published articles undetected by database search tools. Relevant studies were carefully selected for further analysis on grounds of article headings and abstracts (when attainable). Studies, in which individual data of patients regarding de-novo psoriasis or an exacerbation of psoriasis following anti-TNF treatment was available, were included. Theoretical review articles that did not comprise of unpublished new cases of anti-TNF associated psoriasis cases, were excluded. Moreover, an effort was made to exclude those cases, in which established trigger factors such as infections, other triggering drugs or recent trauma seemed more likely to contribute to the exacerbation or new-onset development of psoriasis. Moreover, studies, which lacked specific data concerning individual patients were excluded from analysis. Thus, studies that comprised of data on a collective level were omitted from the literature review. Furthermore, studies, in which the compiled data did not solely refer to psoriatic skin lesions but to other skin eruptions associated with anti-TNF-α treatment were likewise omitted.

The variables of interest included, age at first onset of psoriasis lesions, gender, underlying disease or primary treatment indication, disease duration, smoking status, personal history of psoriasis, family history of psoriasis; type, location and distribution of the psoriatic lesions; anti-TNF-α agent used at onset; duration of TNF-α inhibitory therapy at the time of onset, information about the initial treatment of psoriatic skin lesions, whether TNF-inhibition was discontinued, continued or switched to a different agent and the clinical

outcome after treatment, respectively.

Psoriatic skin lesions were classified into 6 types, plaque psoriasis, palmoplantar pustular psoriasis, generalized pustular psoriasis, guttate psoriasis, inverse psoriasis and erythrodermic psoriasis. When a definite categorization into the aforementioned forms of psoriasis was not justifiable, the respective psoriatic lesion was described as "psoriasiform".

Clinical outcome of the applied treatment were classified in four categories, (1) complete resolution – total clearance of active psoriatic lesions and absence of new lesions; (2) partial resolution – retention of several active lesions and healing of some lesions with decreased extent and severity of lesions; (3) no resolution/worsening – endurance of active psoriatic lesions or impairment of severity and extent of the psoriatic lesions; (4) unknown outcome – clinical outcome is unknown or was not detectable (due to lack of follow-up attendance by the patient, for instance).

Missing data were noted as not available (n/a). As the compiled data do not supply any sufficient evidence, a simple descriptive analysis was performed.

3 Results

Applying the aforementioned inclusion and exclusion criteria, 434 cases of de-novo or exacerbated psoriatic skin lesions following anti-TNF-α treatment were found eligible for analysis, as data was extractable on an individual level.[8–10,308,323–493] As a result, the 882 cases, compiled on a collective level, were excluded from analysis.[6,7,11,12,494–501] In total, 6601 records of anti-TNF-α induced or exacerbated psoriasis were found in the literature. However, in virtue of the lack for detailed data on a an individual basis regarding anti-TNF-α related psoriatic lesions and/or due to the risk for double reporting, these studies did not meet our inclusion criteria.[502–515] Nonetheless, they seemed worth mentioning in this literature review in order to get an estimation of the dimension of reported cases in the literature up to date, as the association of the observed psoriatic skin eruptions with TNF-α antagonism reported in these studies seems legit. The 434 cases strong cohort, eligible for analysis comprised mainly of case reports, case series and retrospective cohort studies. In addition, scientific papers were left out from this literature review, when considerable doubts appeared during initial assessment about the possible causal correlation of TNF-α inhibitors with the occurrence of psoriatic skin lesions. This was particularly the case, when other causative trigger factors (recent infections for instance or established psoriasis provoking drugs such as ß-blockers) could not be ruled out or other explanations for the paradoxical appearance of psoriasis seemed more plausible.[516,517]

3.1 Clinical characteristics

Analyzing the data extracted from the literature, a female preponderance was noted, as 64.7 % (n=281/434 of the cases eligible for assessment were women). As a result, the female to male ratio was roughly 2:1. The female predominance was particularly notable in patients, who had CD and RA (n=80/137, 58.4 % and n=129/153, 84.3 %, respectively), whereas in affected AS patients a male preponderance was observed (n=36/61; 59 %). Mean age at onset of the psoriatic lesions was calculated at 41.1 years (range: 3-83 years). Notably, women showed a higher mean age with 42.8 years at onset (range: 6-83 years) than men with a mean age of 38.9 years (range: 3-78 years), when calculated separately for.

73.5 % (n=319/434) reported a negative history of psoriasis prior to the initiation of anti-TNF-α therapy. In comparison, in solely 12.4 percent of the patients (n=54/434) a positive psoriasis history was evident, while in 14.1 percent (n=61/434) the personal history was

undisclosed. As a result, this indicates that psoriasis as an underlying condition was detected in as many as 54 patients (any precedent experience of a psoriatic condition of any kind). Furthermore, 7.4 % (n=32/434) of the affected patients reported a positive family history of psoriasis, whereas 61.1 % (n=265/434) denied any familial affection of psoriasis. In about one third (n=137/434, 31.6 %) of the cases, no data was available concerning the family history of psoriasis.

Concerning the presented psoriasis morphology of anti-TNF-α induced psoriatic lesions, we decided to analyze the 64 identified children and adolescents (of the eligible 434 cases) separately from the adults (n=370).

In the adult group the most commonly observed clinical variant was palmoplantar pustular psoriasis (n=150/370, 40.5 %), followed by plaque psoriasis (n=139/370, 37.6 %) and ill-defined psoriasiform dermatitis (n=87/370, 23.5 %). A generalized pustular version of psoriasis, which we defined as pustular psoriasis lesions that were not restricted to palms and soles, was seen in 10.3 % (n=38/370). Other clinical forms of psoriasis included guttate psoriasis (n=31/370, 8.4 %) and erythrodermic psoriasis (n=3/370, 0.8 %). However, it should be noted that 20.0 % (n=74/370) presented with more than one morphological variant of psoriasis during the time of treatment with the causative anti-TNF agent. Table 8 gives an overview of the most commonly found combinations.

Table 8. Subtypes of anti-TNF induced psoriasis found concurrently in the adult cohort (n=74/370)

Plaque psoriasis + PPPP	n=29/74, 39.2 %
Plaque psoriasis + generalized pustular psoriasis	n=2/74, 5.9 %
Plaque psoriasis + guttate psoriasis	n=5/74, 6.8 %
Plaque psoriasis + psoriasiform dermatitis	n=1/74, 1.4 %
PPPP + generalized pustular psoriasis	n=18/74, 24.3 %
PPPP + psoriasiform dermatitis	n=9/74, 12.2 %
PPPP + guttate psoriasis	n=5/74, 6.8 %
PPPP + acrodermatitis continua Hallopeau	n=1/74, 1.4 %
Psoriasiform dermatitis + generalized pustular psoriasis	n=2/74, 2.7 %
Plaque psoriasis + guttate psoriasis + pustular psoriasis	n=2/74, 2.7 %

Abbreviations: PPPP, palmoplantar pustular psoriasis

The palms and soles were the most commonly affected areas of the body with 52.2 % (n=193/370). Notably, palmoplantar involvement was not limited to patients with PPPP, but included patients with plaque psoriasis and psoriasiform dermatitis. The extremities were affected in 42.2 % of the patients (n=156/370), whereas the trunk was affected in

28.9 % of the cases (n=107/370). The scalp proved to be involved in 20 % (n=74/370) of the cases, whereby 5.1 % of the adult cohort (n=20/370) developed anti-TNF associated alopecia. Forms of inverse psoriasis, where flexural areas, intertriginous areas, were involved, was seen in 8.1 % (n=30/370). Genital psoriasis accounted for 2.2 % (n=8/370). The nail apparatus was affected in 4.6 % (n=17/370). While facial lesions were seen in 2.4 % of the cases (n=9/370), an involvement of the ears was noted in 0.8 % (n=3/370), respectively. However, in 18.6 % (n=69/370) the location of the presented lesions was inadequately described.

The most predominant form of anti-TNF-α associated psoriasis observed in children and adolescents was plaque psoriasis with 67.2 % (n=43/64). In contrast to the adult cohort, PPPP was only seen in 7.8 % (n=5/64) and generalized pustular psoriasis was noted in 6.3 % (n=4/64). Ill-defined psoriasiform lesions were observed in 17.2 % (n=11/64). In the adolescents/children cohort 6.3 % (n=4/64) were affected by guttate psoriasis, while no cases of erythrodermic psoriasis was observed in this group. In 4 out of 64 patients (6.3 %), more than one morphological type of psoriasis was detected upon TNF-α inhibition. The combination of PPPP with a more generalized form of pustular psoriasis was seen in two patients (n=2/4, 50 %). Furthermore, one patient was affected by plaque psoriasis and PPPP concurrently (n=1/4, 25 %), while another patient, besides having PPPP had ill-defined psoriasiform lesions on the scalp (n=1/4, 25 %).

The scalp was the most implicated location seen in this group (n=30/64, 46.9 %), followed by the trunk (n=26/64, 40.6 %) and the extremities (n=26/64, 40.6 %). Notably, 12.5 % (n=8/64) displayed alopecia following TNF inhibitor therapy. Besides the ears and the retroauricular area (n=21/64, 32.8 %), the face was frequently affected (n=14/64, 21.9 %). Palmoplantar involvement was limited to 11/64 patients (17.2 %). Moreover, a form of inverse psoriasis was seen in 9.4 % (n=6/64) affecting mainly the axillaries and/or groins (n=5/64, 7.8 %) or other intertriginous areas such as the intergluteal cleft (n=2/64, 3.1 %). No cases of nail psoriasis were observed in the children-adolescent cohort.

In a total of 178/434 cases (41 %) the anti-TNF-α linked psoriasiform or psoriasis diagnosis was histologically verified.

3.2 TNF-α inhibitors and underlying diseases

The most noted underlying disease was RA (n=153/434, 35.3 %) followed by CD (n=137/434, 31.6 %) and AS (n=61/434, 14.1 %). Moreover, 11 out of 434 patients had UC, which accounts for 2.5 %. In 1.4 % (n=6/434) the IBD condition was not further specified. In total, there were 39 patients (9 %), which had an underlying psoriatic condition as their primary diagnosis. Besides the 15 patients (3.5 %), who had solely psoriasis, 21 patients (4.8 %) displayed psoriasis in combination with PsA and 3 patients were PsA patients exclusively (0.7 %). Furthermore, 7 cases of anti-TNF-α induced psoriasis were identified in JIA patients (1.6 %) and 8 cases in patients with an undisclosed seronegative spondyloarthritis (1.8 %). The remaining 4.1 % comprised of nondisclosed immune-mediated inflammatory conditions (n=2/434) and a selection of off-label indications such as Behçet's disease (n=6/434), SAPHO syndrome (n=4/434), uveitis (n=1/434), HS (n=1/434), vitiligo (n=1/434), Shulman fasciitis (n=1/434), Kawasaki syndrome (n=1/434) and tumor necrosis factor receptor associated periodic fever or TRAPS (n=1/434). Underlying concomitant conditions of this case report cohort (n=434) revealed the following. In 5.3 % (n=23/434) a concurrent underlying IMID was observed. Psoriasis as an underlying condition was reported in 9 RA patients (2.1 %), 4 CD patients (0.9 %), one AS patient, one SAPHO patient and one patient with an undisclosed spondyloarthropathy. Barring psoriasis, other concurrent combinations of immune-mediated conditions included, the coexistence of CD and AS in five patients, as well as the concurrence of CD with a not further disclosed seronegative SpA in two patients.

The mean time of clinical latency between diagnosis of the underlying disease and the first appearance/onset of anti-TNF-α associated psoriasis lesions was calculated at 10.0 years with a range from 0.1 to 45 years.

All five anti-TNF-α agents were associated with the occurrence of paradoxical psoriatic or "psoriasiform" lesions. Nevertheless, the majority of cases were implicated with infliximab (n=235/434, 54.1 %), followed by adalimumab (n=116/434, 26.7 %) and etanercept (n=74/434, 17.1 %). Moreover, 5 cases were attributable to certolizumab pegol (n=5/434, 1.2 %) and 4 cases to golimumab administration (n=4/434, 0.9 %).

Patients underwent TNF-α inhibitor therapy for an average of 52.0 weeks before the onset of psoriatic skin lesions (range: 1-522 weeks). Of the 434 identified cases, information regarding the onset time was missing in 38 patients (8.8 %). Hence, in 91.2 % of the time (n=396/434) the onset time was reported. Etanercept displayed the longest mean onset time

of all agents with 55.2 weeks (range: 2-312 weeks), followed by infliximab with 53.6 weeks (range: 1-522 weeks) and adalimumab with 48.6 weeks (range: 1-269.7 weeks). The two newest TNF-α antagonists showed the shortest average onset times with 19.1 weeks (range: 1-29 weeks) for certolizumab pegol and 11.9 weeks (range: 1-17.4 weeks) for golimumab. Furthermore, the preferred treatment year of initial psoriasis eruption was calculated, as 71.5 % (n=283/396) experienced the onset of psoriasis in the initial year of treatment, 14.9 % (n=59/396) in the second year and 7.1 % (n=28/396) in the third year of treatment. In 6.5 % (n=26/396) the psoriatic lesions did not appear until the fourth year of treatment or beyond.

Concomitant treatment was given in 22.8 % (n=99/434) of the cases. The most relevant administered concomitant treatment at the time of psoriasis onset comprised of MTX (n=57/434, 13.1 %), AZA (n=21/434, 4.8 %), LEF (n=14/434, 3.2 %) and sulfasalazine (n=5/434, 1.2 %). Moreover, 4.6 % (n=20/434) received concomitant systemic steroids at the time of initial psoriasis eruption.

3.3 Management and treatment modalities

Concerning the literature review, the initial management approach and outcome was evaluated, meaning that following management strategies (i.e. switch to a third TNF inhibitor or to another biological agent) with their respective outcomes were not assessed. Table 9, 10 and 11 detail the compiled data regarding the various primary treatment approaches and the respective results of the applied management strategies. Notably, in 11.3 % of the cases (n=49/434) it was unknown, whether the treatment with the causative anti-TNF-α agent was continued, discontinued or switched. Complete resolution was evident in 33.1 % of the patients (n=44/133), who continued anti-TNF-α therapy with the causative agent and where full outcome was available, in 45.0 % of the patients (n=77/171), who discontinued therapy with the inculpated anti-TNF therapeutic (and attainable outcome) and in 24.0 % patients (n=12/50), who switched to a 2nd TNF-α inhibitor and full treatment response was available. Partial resolution or improvement of the psoriatic lesions (in the patients in which the outcome was known) was seen in 52.6 % of the patients (n=70/133), who continued therapy with the causative anti-TNF agent, in 45.6 % (n=78/171), who stopped anti-TNF-α treatment and in 28.0 % of the patients (n=14/50), who switched to a different anti-TNF-α agent.

The data extracted from the literature indicate that topical treatment, first and foremost topical steroids, but also vitamin d analogs such as calcipotriol, salicylic acid and coal tar among others, is a vital part of the primary treatment approach of anti-TNF-α associated psoriasis. Besides, it was the most established therapy, as in total roughly 65 % of the patients (n=280/434) received topical treatment for their psoriatic eruption at some point during the occurrence of this paradoxical side effect (firstline and/or secondline treatment approach).

Likewise, systemic therapy was administered in numerous patients either in combination or as a lone treatment, as in total 23.3 % of the patients (n=101/434) were treated systemically for their paradoxically anti-TNF-α associated lesions. Methotrexate, cyclosporine A, prednisone and azathioprine were the most common systemically given medications. However, a few patients did also receive antihistamines, antibiotics or etrinate among other therapeutics. Phototherapy (PUVA or 311nm UVB) was added to the treatment in 6 % of the cases (n=26/434).

Table 9. Management and outcome of continuous therapy with causative TNF inhibitor

	Outcome				
	CR	PR	NR	n/a	Total
Total number of patients, n (%)	**44**	**70**	**19**	**14**	**147/434 (33.9)**
Topical therapy only n	33	54	11	9	107
topical steroids	27	42	6	2	77
topical steroids + vitamin d analogs	1	8	2	1	12
topical steroids + coal tar	2	0	0	0	2
topical steroids + salicylic acid	0	3	0	0	3
other topical combinations	2	1	0	0	3
topical treatment not disclosed	1	0	3	6	10
Systemic treatment only n	3	3	0	0	6
MTX	2	0	0	0	2
CsA	0	2	0	0	2
prednisolone	0	1	0	0	1
other systemic treatment options	1	0	0	0	1
No treatment solely continuation n	2	3	4	0	9
Topical therapy + systemic therapy n	3	4	2	0	9
top. steroids +/- vit. d-analogs + MTX	2	1	2	0	5
top. steroids +/- vit. D-analogs + CsA	0	1	0	0	1
other combinations	1	2	0	0	3
UV therapy n	1	3	1	0	5
PUVA + topical treatment	1	1	1	0	3
narrowband UVB +/- top. Treatment	0	2	0	0	2
Treatment not specified n	2	3	1	5	11

Abbreviations: CR, complete resolution; PR, partial resolution; NR, no resolution; n/a, not available

Table 10. Management and outcome of switching to a 2nd TNF inhibitor or ustekinumab

	Outcome				
	CR	PR	NR	n/a	Total
Total number of patients, n (%)	**12**	**14**	**24**	**3**	**53/434 (11.5)**
switch to ADA	5	1	9	1	16
switch to IFX	1	2	1	0	4
switch to ETA	5	8	6	0	19
switch to CZP	1	1	2	1	5
switich to non disclosed anti-TNF agent	0	2	6	1	9
Switch to ustekinumab, n (%)	**0**	**2**	**0**	**0**	**2/434 (0.5)**

Abbreviations: CR, complete resolution; PR, partial resolution; NR, no resolution; n/a, not available

Table 11. Management and outcome of cessation of causative TNF inhibitor

	Outcome				
	CR	PR	NR	n/a	Total
Total number of patients, n (%)	**77**	**78**	**16**	**12**	**183/434 (42.2)**
Topical therapy only n	34	29	2	2	67
topical steroids	29	18	1	2	50
topical steroids + vitamin d analogs	5	6	1	0	12
topical steroids + salicylic acid	0	1	0	0	1
topical treatment not disclosed	0	4	0	0	4
Systemic therapy only n	8	7	3	0	18
MTX	1	3	2	0	6
CsA	2	1	0	0	3
Prednisone	2	2	1	0	5
other systemic treatment options	3	1	0	0	4
No treatment solely discontinuation n	17	19	6	6	48
Topical therapy + systemic therapy n	12	17	4	3	36
top. steroids +/- vit. D-analogs + MTX	3	6	0	2	11
top. steroids + CsA	4	2	0	0	6
top. steroids + prednisone	1	1	2	0	4
top. steroids + AZA	1	2	0	0	3
top. steroids + antihistamines	1	2	0	0	3
top. steroids + antibiotics	1	0	0	1	2
top. steroids + etrinate	0	2	0	0	2
other treatment combinations	1	2	2	0	5
UV-therapy n	6	6	1	1	14
PUVA + topical treatment	0	4	1	0	5
PUVA + top. Tr. + systemic treatment	0	1	0	1	2
PUVA + systemic treatment	2	0	0	0	2
PUVA + 311nm UVB	1	0	0	0	1
311nm + topical treatment	3	1	0	0	4

Abbreviations: CR, complete resolution; PR, partial resolution; NR, no resolution; n/a, not available

4 Discussion

Anti-TNF-α induced psoriasis has become a well-documented and established side effect of TNF inhibitors.[6–12] As mentioned before, the first reported paradoxical case of anti-TNF-α induced psoriasis dates back to the year 2004,[308] and ever since the numbers of reported cases have been steadily increasing, involving all commercially available TNF antagonists.[6–12] Therefore, TNF-α induced psoriasis has been postulated to be a class-effect.[6–12] The prevalence of anti-TNF-α induced psoriasis reported in the literature ranges from 0.6 % to 5.3 %.[6,503,518–521] The exact prevalence of anti-TNF-α induced psoriasis remains yet elusive, since the prevalence may be influenced by multiple factors (the population studied or concomitant immune modulating medications used in the different patient groups).[522] Additionally, no prospective studies studying the prevalence of TNF-α induced psoriasis have been performed up to now investigating this matter, so that the true incidence of this side effect is still not known. Underreporting might further pose a problem in evaluating the prevalence and incidence of this side effect, as mild cases might often go unnoticed, or when diagnosed are treated without being reported to health authorities or registries.[503,523] As noted previously in the introduction, the incidence rate ranges from 1.04-3.0 per 1,000 person-years.[9,309]

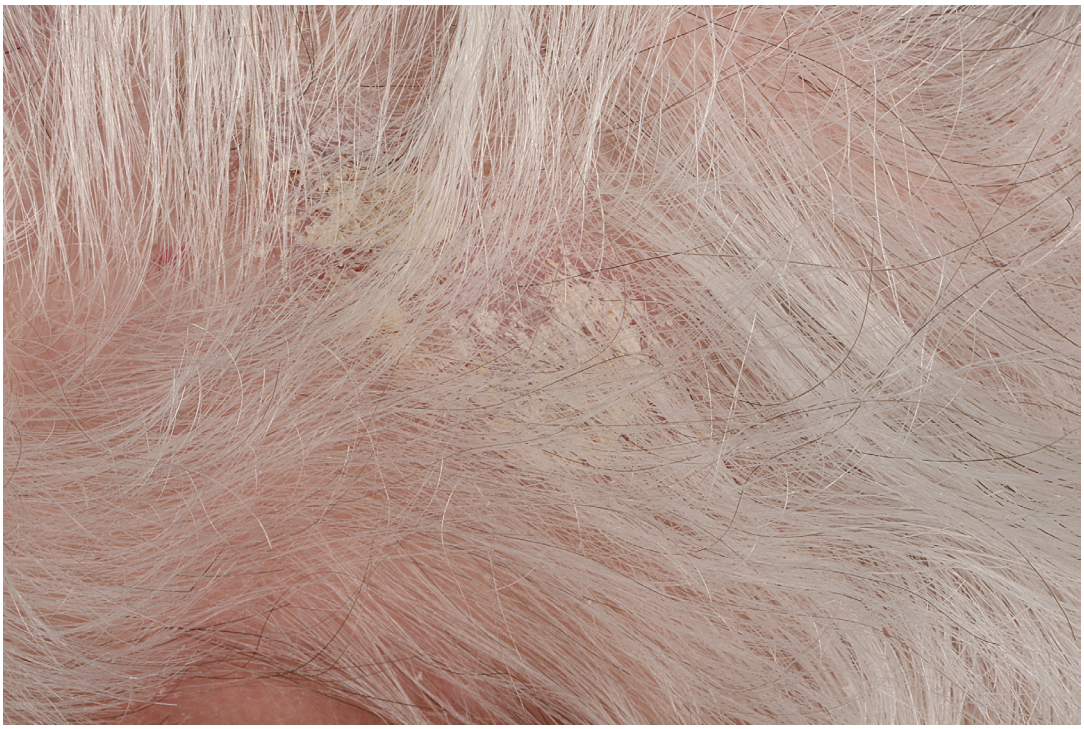

Figure 4. Anti-TNF-α induced scalp psoriasis

4.1 Pathogenesis and predisposing factors of anti-TNF-α induced psoriasis

Since the unexpected advent of this baffling side effect, little is still known about its etiopathogenesis and potential predisposing factors of TNF-alpha induced psoriasis. However, several hypotheses have been proposed, attempting to shed light into this immunopathological conundrum.[524] At the time, when initial reports of this adverse event surfaced, some authors discussed the possibility of this side effect representing a hypersensitivity reaction.[524] However, this hypothesis has been discarded, since anti-TNF-α associated psoriasis normally erupts after the initial two weeks of treatment, whereas a hypersensitivity drug reaction is characterized by a more immediate response within the first two weeks of treatment.[524] Initially, the increased occurrence of psoriatic lesions following TNF inhibition was also attributed by some authors to be, due the possibility that affected patients were suffering from psoriasis/psoriatic arthritis without cutaneous psoriatic or late onset cutaneous psoriatic manifestations and the underlying disease had been simply misdiagnosed.[524] These explanations were rapidly scrapped however, when evermore reports of anti-TNF-α associated skin lesions were published in various populations with diverse underlying diseases undergoing anti-TNF-α therapy.[524] Hence, it was evident, that this anti-TNF-α associated paradoxical side effect occurred in a frequent manner regardless of the underlying condition.[524] Furthermore, the temporal correlation between the beginning of TNF inhibitor administration and the first eruption of psoriasis lesions hints at a causal link.[522]

As the majority of the patients treated with TNF antagonists do not develop anti-TNF-α related psoriasis lesions, authors such as Cullen et al.[11] argue that, genetics might play a *considerable* role in the etiopathogenesis of this paradoxical adverse event.[11] Supporting this assumption, Vedak et al.,[525] based on the general imbrication of susceptibility genes such as IL12B, IL-23R, REL and TYK for IBD and psoriasis, found a stronger genetic susceptibility in patients with anti-TNF-α induced psoriasis compared to patients treated with TNF inhibitors without psoriatic manifestations.[525] Two SNPs, particularly ETS1 and NOS2, have been identified to be significantly associated with the development of anti-TNF-α induced psoriasis.[525] Moreover, Tillack et al. detected that patients affected with severe anti-TNF-α induced psoriasis were homozygous wild type carriers for a rare IL-23R variant.[6] Notably, these patients responded very favorable to ustekinumab.[6] This is in

concordance with a pediatric IBD study, who also noticed a correlation between IL23R polymorphisms and anti-TNF induced psoriasis.[380]

As stated above, the exact pathophysiological mechanism of anti-TNF-α associated psoriasis remains to a large part indeterminate.[522,524] In sum, the interplay of TNF inhibitors with regulatory and inflammatory parts of the cutis is believed to generate an imbalance of the skin homeostasis and is believed to provide the basis for the underlying pathophysiological mechanisms of this perplexing adverse event.[524]

As of today, some pathophysiological mechanisms appear to be significantly implicated in the development of psoriasis following TNF-α inhibition. One of the most established theories involves a disequilibrium between TNF-α and IFN-α.[433] As thoroughly described in the introduction section of this thesis, interferon-α (IFN-α) has a significant role in the pathophysiology of psoriasis. Besides, the connection between IFN-α and psoriasis has been proven, not least because of imiquimod, a potent inducer of IFN-α and consequently psoriasis.[433] IFN-α is believed to play an integral part, especially in the initial phases of the development of psoriasis, as IFN-α promotes the activation and proliferation of Th17 cells, which in turn produce IL-17 and in further consequence leads to hyperkeratosis.[433]

Likewise, plasmacytoid dendritic cells (pDCs), the cells mainly responsible for IFN-α production, are implicated in the pathogenesis of psoriasis.[433] Palucka et al.[526] was first to propose a significant role of pDCs in correlation with anti-TNF-α induced psoriasis, as TNF-α normally acts as an inhibitor of pDC maturation from hematopoietic progenitor cells and consequently reduces the production of IFN-α.[373,433,526] Additionally, TNF-α is also capable of hindering the release of IFN-α by pDCs upon viral infection.[373,433] Hence, inhibition of TNF-α may eventually lead to increased production of IFN-α by pDCs, as there is a lack of alternative antagonistic mechanisms.[373,433] In further accordance with this assumption, Tillack et al.[6] detected increased IFN-α expression in all biopsy samples taken of anti-TNF-α induced psoriasis patients in their study.[6] Likewise, in a Canadian study elevated levels of IFN-α were found in the vasculature of the subcutis and in perivascular, mainly lymphocytic infiltrates of anti-TNF-α induced psoriasis skin samples.[433] Moreover, Seneschal et al.[373] detected elevated amounts of myxoprotein A (MxA), a protein induced by type I interferon, in skin samples of anti-TNF-α associated psoriatic lesions and showed that this IFN-α signature marker is markedly stronger expressed in biopsy samples from anti-TNF-alpha induced psoriasis than in those of genuine psoriasis.[373] Additionally, a

recent study corroborated these findings, as they detected higher concentrations of type I interferons and accumulating pDCs in anti-TNF-α associated psoriasis lesions than in conventional psoriasis biopsies.[527] In fact, Conrad et al.[527] found that TNF inhibitors were able to extend the feature of pDCs to generate type I IFNs in vitro and in vivo.[527] This is due to the blockade of TNF-α and its ability to regulate the generation of type I IFNs by pDCs, as TNF-α also promotes the maturation of pDCs to DCs, which in further consequence forfeit their capability to produce type I interferons.[526,527] As a result, Conrad et al.[527] indicate that both classical psoriasis and anti-TNF-α psoriasis are prompted by pDCs and type I IFN.[527] However, solely conventional psoriasis seems to progress into a T cell dependent immune mediated disease (with an adaptive immune response), while the underlying inflammatory process in anti-TNF-α related psoriasis appears to be based on a self-amplifying pDC-mediated immune response (innate immune response).[527]
Furthermore, IFN-α appears to implicate an up-regulation of chemokine T-cell receptors such as CXCR3, which in further consequence leads to an augmented influx (T-cell homing) of T-cells as well as neutrophils to the skin.[373,426,528] This again, leads to a TH-1-mediated immune response in conjunction with cytotoxic effects to the skin, causing skin damage.[373,426,528] Additionally, T-cells appear to have gained an elevated sensitivity to IFN-α, when found in psoriatic skin compared to invading T-cells of non-psoriasis affected skin lesions.[529] Moreover, it has been suggested that IFN-α, through CXCR3 ligands can extend the recruitment of pDCs into the skin and thus sustaining a self-amplifying loop.[527] Another interferon, which has been demonstrated to have a central role in the pathophysiology of anti-TNF-α associated psoriasis, is IFN-γ.[6,519] In a recent study carried out by Stoffel et al.,[519] elevated levels of IFN-γ were found in anti-TNF-α induced psoriasis lesions compared to genuine psoriasis lesions.[519] The cellular origin of the augmented levels of IFN-γ are Th1-cells, as a heightened number of these IFN-γ-producing cells have been detected.[6,519] This implies further an involvement of the Th1 adaptive immune axis in the inflammatory process in patients affected by anti-TNF associated psoriasis.[519] The intense Th1 response might be spurred by the previously described abundant levels of IFN-α.[519]
Furthermore, as indicated above and similar to the pathophysiology of genuine psoriasis, the IL-23/Th17-axis seems to be significantly involved in the pathophysiology of TNF inhibitor associated psoriasis.[522] Accordingly, Tillack et al.[6] were able to identify elevated levels of Th17 cells (IL-17 and IL-22 releasing cells) in their histological analysis of skin

samples from anti-TNF-α induced psoriasis.[6] Interestingly, the level of IL-17A expression seemed to correlate with the severity of skin lesions, as milder forms of this cutaneous lesion, responsive to topical treatment, tended to show a weaker IL-17A expression.[6] Elevated levels of IL-17A and IL-23 were also detected in CD patients suffering from anti-TNF-α induced psoriasis compared to the control group (healthy participants), further emphasizing the involvement of the IL-23/Th17 axis.[510]

More recently, Friedrich et al.[528] describes a new potentially essential proinflammatory mechanism, in which the IL36γ/IL-17 C axis has a central role.[528] IL-36γ leads to an up-regulation of TNF-α expression in keratinocytes and maintains a positive feedback loop with IL-17C, resulting in abundant generation of IL-36γ and IL-17C along with other proinflammatory cytokines such as TNF-α.[528]

Tillack et al.[6] also named smoking an independent risk factor for the development of anti-TNF-α induced psoriasis.[6] As illustrated in the introduction, numerous detrimental effects of cigarette smoke extract exposure may be involved in the pathophysiology of psoriasis and thereby might also play a role in anti-TNF induced psoriasis.[530] Free radicals are suggested to be involved, as they intervene with important pro-inflammatory mediators and signal pathways implicated in psoriasis such as NF-κB.[531] Moreover, nicotine provokes the heightened expression of several pro-inflammatory cytokines involved in the pathogenesis of psoriasis such as IL-12, TNF-α or IL-2.[531] Torii et al.[532] detected that smokers have elevated levels of circulating Th17 cells compared to nonsmokers and that cigarette smoke extract promotes the production of Th17 cells from central memory T cells and thereby leads to abundant amounts of IL-17 and IL-22, two cytokines heavily involved in the pathogenesis of psoriasis.[532,533]

In sum, anti-TNF-alpha induced psoriasis might rely on a combination of the proposed mechanisms, which might show great individual variability. Moreover, as the pathogenesis of anti-TNF-alpha induced psoriasis is still not fully elucidated, yet undiscovered immune-pathological mechanisms might play a role.[524,534]

As anti-TNF-alpha induced psoriasis poses a great clinical challenge, clinicians were looking to identify risk factors predisposing to development of this cutaneous adverse event.[11,521]

Smoking as an established risk factor of psoriasis is therefore of special interest.[180,182] While Cleynen et al.,[503] found a notable total of patients with anti-TNF-α induced

palmoplantar pustular psoriasis (78 %) to be current or former smokers, they could not observe any disparities in proportions of smokers in the patients, who presented with non-pustular anti-TNF-alpha induced psoriasis.[503] A prospective German study identified smoking as an independent main risk factor for the development of anti-TNF-α induced psoriasis, as 76.2 % of the patients were current or former smokers, while only 42.6 % of the patients that did not experience any psoriatic skin lesions were smokers or had a positive prior smoking history.[6] This is in line with the results of a retrospective Italian cohort study, where Pugliese et al.[502] noted a higher rate of active or former smokers in the patient cohort with anti-TNF-α induced psoriasis than in the patient cohort without this cutaneous side effect (36 % vs. 18 %).[502] Moreover, smoking might influence the efficaciousness of TNF inhibitors in a negative manner, as smokers tend not to respond as well to TNF antagonists as non-smokers.[186,535]

Another suggested predisposing factor linked to TNF antagonist induced psoriasis is an elevated BMI, although the data in the literature are conflicting. Tillack et al.[6] found higher levels of BMI in the patient cohort, which displayed psoriatic lesions (24.9), than in their cohort without psoriatic skin lesions (22.7; OR: 1.13).[6] Consequently, they proposed an augmented BMI as an independent risk factor for developing these cutaneous lesions.[6] Nonetheless, George et al.[499], as well as Pugliese et al.[502] did not find any disparities in the BMI between those patients with and those without anti-TNF-α induced psoriasis in their studies.[499,502]

The inflammatory state of the primary disease, for instance, has been also been under investigation for being a predisposing factor.[522] However, many IBD patients, who experience anti-TNF-α associated psoriasis, are in a clinically quiescent state at the onset of psoriatic lesions.[521] In fact, about 88.1 % are in clinical remission, while displaying this adverse event.[521] In a pediatric IBD population, which was affected by these TNF inhibitor associated cutaneous lesions, decreased levels of calprotectin (an indicator of the intestinal inflammatory conditions) were observed.[508] Whether the inflammatory state of the underlying disease can be considered a predisposing risk factor still remains undetermined.

Furthermore, the implication of the drug level regarding the onset of anti-TNF-α linked dermatologic adverse events has been discussed as a precipitating factor in the literature, as Huang et al.[536] linked higher titers of infliximab to an increased chance of developing infliximab associated cutaneous side effects.[536] However, Protic et al.[494] could not detect

any infliximab level dependent association with the occurrence of anti-TNF-alpha induced psoriasis.[494]

In psoriasis both genders are normally affected equally.[145] However, this seems not to be the case with TNF inhibitor associated psoriasis, where the female sex was found to be the predominant one.[9–11,500,506] However, there has been some dispute in the literature, whether the female sex shall be viewed as a risk factor for developing anti-TNF-α induced cutaneous lesions.[500,534] In fact, Guerra et al.[500] stated that women are in fact more prone to the development of anti-TNF-α associated psoriasis lesions.[500] Despite this, in a comprehensive literature review carried out in 2010, Collamer et al.[534] assert that males and females are evenly affected.[534] However, the female to male ratios might heavily depend on the underlying disease (RA, CD, AS) of patients studied.

As our literature review reveals, in most studies, a personal history or a family history of psoriasis was not observed in the vast majority of the study population. Nonetheless, Darrigade et al.[518] observed a positive personal and/or family history in up to 27.7% (n=23/83) of their patients, although only 13 of them were primarily suffering from psoriasis or psoriatic arthritis.[518] Hence, the majority of anti-TNF induced psoriasis cases identified in the literature are new-onset including patients with known psoriasis or psoriatic arthritis, as they tend to display a change in morphology and/or in distribution pattern of anti-TNF-alpha induced psoriasis lesions compared to their genuine psoriasis lesions.[501]

4.2 Clinical aspects of anti-TNF-α induced psoriasis

As anti-TNF-alpha induced psoriasis is observed in up to 5.3% of patients treated with TNF-alpha inhibitors, the question arises, which of the five TNF-alpha inhibitors is the most common inducer of this adverse event.[520,522] The compiled data of our literature review revealed that most cases of anti-TNF-alpha induced psoriasis were attributable to infliximab (n=235/434, 54.2 %), followed by adalimumab (n=116/434, 26.7 %) and etanercept (n=74/434, 17.1 %). The two more recently licensed agents, golimumab and certolizumab were much less commonly noted as the causative agents. However, this is most likely due to their later introduction and use in the treatment of immune mediated diseases.

Nonetheless, variations between TNF-α antagonists in their respective risk profiles have been proposed in the literature.[9,496,502] Interestingly, the British Society for Rheumatology

Register study indicated a significantly higher risk for new onset psoriasis in patients receiving adalimumab (unadjusted incidence rate 1.84 per 1,000 person-years, compared to infliximab 0.88 and etanercept 0.59).[9] Accordingly, the authors suggested a 4-fold increased risk of adalimumab compared to etanercept and a 3-fold increased risk compared to infliximab.[9] In comparison, Afzali et al.[496] found the highest frequencies of psoriasis among patients treated with certolizumab pegol (6.4 %) and the lowest with infliximab (1.3 %), while 4 % of the patients taking adalimumab developed psoriasis subsequently.[496] Notwithstanding, a retrospective Italian study found no higher association of adalimumab, compared to infliximab, of developing psoriasis.[502] Moreover, etanercept has been more frequently linked to exacerbations of preexisting psoriasis, whereas the monoclonal antibodies (e.g. adalimumab or infliximab) have been mainly associated with new-onset onset of anti-TNF-α induced psoriasis.[537] Adding to the confusion is the observation that a notable number of patients has been observed, in whom the initial onset of psoriasis did not occur until treatment with the second or third anti-TNF-α agent.[11]

The latency period between initiation of treatment with TNF antagonists and the first occurrence of TNF-alpha induced psoriasis does show great variability, ranging from 1 to 522 weeks (mean time of onset 52.0 weeks), in the data extracted from the literature. All data regarding the mean onset time, emphasize that onset of psoriatic lesions may occur at any time during anti-TNF-α treatment. However, when analyzing the data extrapolated from the literature, there seems to be a predilection time for anti-TNF-alpha psoriasis development following initiation of anti-TNF-alpha therapy, as 71.5 % experienced the onset of this side effect during the first year of treatment. Furthermore, the risk of developing anti-TNF-alpha-induced psoriasis appears to decrease with time. Moreover, Eickstaedt et al. noted in their study that TNF inhibitor naïve pediatric patients have a greater mean onset time than those, which have been previously treated with TNF antagonists.[438] Moreover, there are notable disparities in onset time between TNF inhibitors, as the shortest mean onset time in our literature review was observed with adalimumab (48.6 weeks), followed by infliximab (53.3 weeks) and etanercept (55.2 weeks).

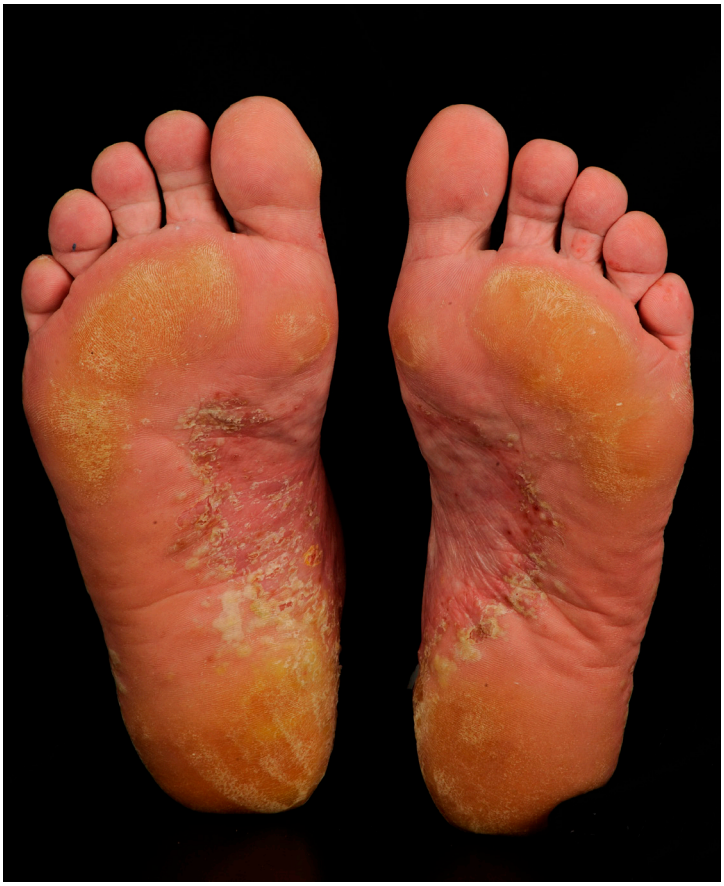

Figure 5. Anti-TNF-α induced plantar pustular psoriasis

4.3 Psoriatic phenotypes of anti-TNF-α induced psoriasis

The evaluation of the adult cases (n=370/434 of eligible cases) extracted from the literature yielded the following results, PPPP and plaque psoriasis were found to be the most predominant types with 40.5 % (n=150/370) and 37.3 % (n=138/370), respectively. Psoriasiform dermatitis was diagnosed in 23.5% of all patients with anti-TNF-alpha induced psoriasis. Intriguingly, 20 % (n=74/370, Table 8) of patients with anti-TNF-alpha induced psoriasis displayed different morphological psoriasis phenotypes at the same time. Whether a certain phenotype of anti-TNF psoriasis can be associated with a certain TNF-α antagonist in a more frequent manner is an intriguing question. Some authors have proposed a pustologenic tendency for certolizumab pegol, as a notable number of new-onset pustular psoriasis[332,476,477] or exacerbations of pustular psoriasis (either GPP or PPPP)[379] have been noted following certolizumab administration.[332,379,476,477] Nonetheless, this observation must be put in perspective, as the reported number of cases is too small[332,379,476,477] to draw any firm conclusions and cases of certolizumab-induced non pustular psoriasis have been reported as well in the literature.[416,447]

It has also been postulated that etanercept might not affect the palmoplantar area as frequently as adalimumab and infliximab (28 % vs. 43 % vs. 52 %, respectively).[520] However, we were not able to discard nor confirm this proposition, as our literature review did not reveal any percentage disparity of palmoplantar involvement by such a wide range (40.5 % vs. 50 % vs. 47.2 %).

Notably, there are differences in the prevalence rates of the diverse morphological clinical subtypes of psoriasis between anti-TNF-α induced psoriasis and psoriasis. First and foremost, the high percentage of palmoplantar pustular psoriasis in TNF inhibitor induced psoriasis differs significantly from psoriasis, in which PPPP patients account solely for about 1.7-4 % of the general psoriasis population.[501,538] Besides, anti-TNF-α induced psoriasis (either pustular or plaque type) appears to more often affect the palms and soles in general (n=193/370, 52.2 %) than genuine psoriasis.[520]

TNF inhibitors induced psoriatic nail alterations seem to be rare and were reported only in 2.4 % of patients.[500] Analyzing the adult case-series cohort extracted from the literature, yielded an equivalently low percentage of nail psoriasis (n=17/370, 4.6 %). This is in contrast to genuine psoriasis, as nail psoriasis is a common feature of psoriasis.[230] Inverse psoriasis was detected in 8.1 % (n=30/370) in our analysis. Data concerning inverse psoriasis in anti-TNF-α induced psoriasis are conflicting, as Shmidt et al.[12] reported a very low percentage (3.6 %) of anti-TNF-α induced inverse psoriasis cases,[12] but Rahier et al.[7] detected a very high rate of inverse psoriasis (44 % of their total anti-TNF-α induced psoriasis cases) in their trial.[7]

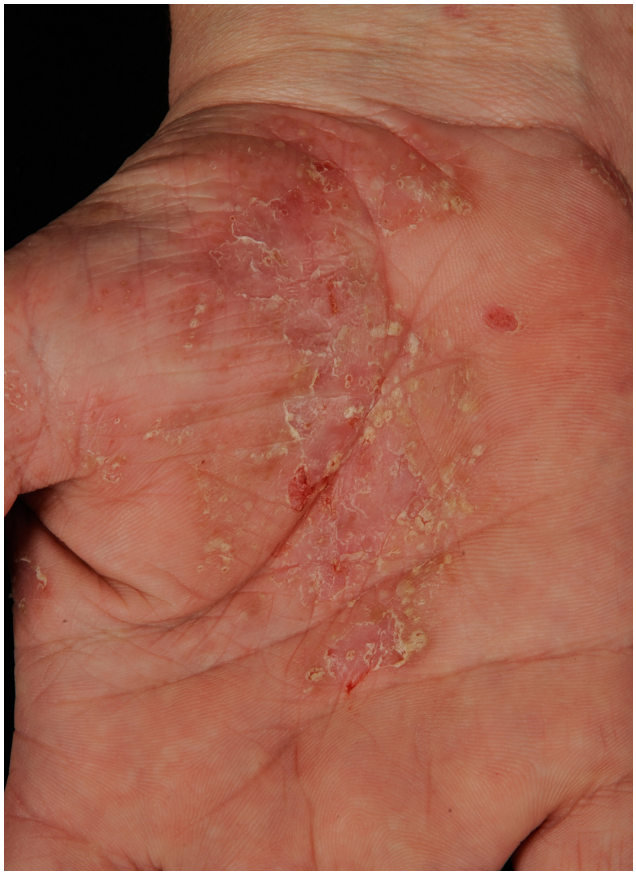

Figure 6. Anti-TNF-α induced palmar pustular psoriasis

Regarding the data extrapolated from the literature, morphology and distribution of psoriatic lesions in adolescents and children markedly deviated from adults. Interestingly, TNF inhibitor associated palmoplantar pustular psoriasis or pustular psoriasis were significantly less seen in the children/adolescent cohort compared to the adult population. Correspondingly, plaque psoriasis was the most common subtype with 67.2 %, which is a significantly higher percentage than in the adult cohort. This is in accordance with the respective prevalence rates of pediatric psoriasis, where the rate for plaque psoriasis ranged from 60.6 to 74 %.[539] However, guttate psoriasis, which is the second most identified psoriasis subtype in pediatric psoriasis (rate ranges from 9.7 to 28.9 %), appears to be not as commonly found in cases of anti-TNF-α induced psoriasis (6.3 %).[539] Furthermore, inverse psoriasis was seen more frequently with children undergoing anti-TNF treatment than in the adult cohort (14.1 % versus 8.1 %). Unlike in the adult group, the scalp was the most commonly affected area in children/adolescents (20% versus 40.6%). Moreover, involvement of the ears and the face was identified in an enhanced manner. This is in line with observations made in pediatric psoriasis, where involvement of the face or the anogenital area are more frequent than in adults.[148]

4.4 Treatment of anti-TNF-α induced psoriasis

Treatment of anti-TNF-alpha induced psoriasis poses a significant clinical challenge, as the clinical picture of anti-TNF-α induced psoriasis is very heterogenous. Moreover, a high share of patients suffer from PPPP, a clinical form of psoriasis, which also often poses a great therapeutical challenge in the general psoriasis population.[159] Apart from the palmoplantar area, the scalp is considered a site of psoriasis, which is more difficult to treat site.[11] Besides, nearly 20 % (n=74/370) of patients with anti-TNF-alpha induced psoriasis displayed different psoriasis phenotypes at the same time. A finding that might further complicate the treatment of anti-TNF-α induced psoriasis.

The question of utmost interest for the majority of clinicians is whether the treatment with the causative or the original anti-TNF-α agent or a different TNF-α inhibitor can be continued. Especially in patients with IBD the occurrence of anti-TNF-α induced psoriasis poses a major problem, as till 2017 the only biologics that had been approved for treatment of CD and psoriasis were adalimumab and infliximab.[39,42,43,47] Since 2017 ustekinumab has also been approved for both indications.[320,540]

Complete resolution was observed in 33.1 % of the patients (n=44/133), who continued anti-TNF-α therapy with the causative agent and in 45.0 % of the patients (n=77/171), who discontinued therapy with the inculpated anti-TNF therapeutic. Interestingly in 24.0 % patients (n=12/50), complete resolution was achieved by switching to a 2nd TNF-α inhibitor.

Partial resolution of the psoriatic lesions (in the patients in which the outcome was known) was seen in 52.6 % of the patients (n=70/133), who continued therapy with the causative anti-TNF agent, in 45.6 % (n=78/171), who stopped anti-TNF-α treatment and in 28.0 % of the patients (n=14/50), who switched to a different anti-TNF-α agent.

However, in 11.3 % of the cases (n=49/434) it was unknown, whether the treatment with the causative anti-TNF-α agent was continued, discontinued or switched.

Although anti-TNF-α associated psoriasis is considered a class effect, the treatment strategy of switching to another anti-TNF-α agent can be successful in some patients, as the data extrapolated from the literature indicates. However, some studies have reported high recurrence rates with poor responses to the substitution of one TNF-α inhibitor with another.[7] Whereas Cullen et al.[11] reported that solely 15 % showed an improvement of their anti-TNF-α induced psoriasis after switching to a different TNF-α antagonist,[11]

Rahier et al.[7] noted a very high recurrence rate (96 %) of anti-TNF-alpha induced psoriasis in their patient cohort, when switching to a second anti-TNF-α agent.[7]
Moreover, the same French multicenter cohort study reported a final cessation rate of 40 %,[7] while Cullen et al. noted a 43 % definite discontinuation rate of TNF-α inhibitory therapy.[11] Interestingly, Afzali et al.[496] found notable differences in cessation rates between adalimumab, infliximab and certolizumab pegol.[496] While 60 % of the adalimumab patients and 50 % of the certolizumab patients discontinued anti-TNF-α treatment, only 17 % of the patients receiving infliximab stopped treatment.[496] However, Cleynen et al.[503] made a solid point in questioning, whether the elevated cessation rates of TNF-α inhibitory therapy in some studies could be explained by a selection bias, as cases seen in tertiary referral centers tend to be more severe, whereas mild or less severe cases often might go unnoticed or are not referred to tertiary referral centers.[503]

Unfortunately, concomitant medication with DMARDs (such as MTX or AZA) have not been shown to successfully prevent the occurrence of anti-TNF-α induced psoriasis.[534] Ustekinumab could be a legit treatment option for anti-TNF-α associated psoriasis, as some authors have indicated an overall good favorable response of patients to ustekinumab.[6,502] Paradoxically, ustekinumab has also been implicated with the onset of psoriasis,[321,322] as noted in the introduction section, which raises further questions. Nonetheless, based on the success of ustekinumab in treating anti-TNF-α associated psoriasis patients with high levels of invading IL-17A$^+$ cells,[6] the inhibition of either IL-23, IL-17 or both should be considered in this particular subset of TNF-α inhibitor induced psoriasis patients.[522]

4.5 Conclusion

Anti-TNF-α induced psoriasis occurs in up to 5.3% of patients treated with TNF-α inhibitors and poses a great challenge in the treatment of patients with immune mediated diseases. The pathogenesis of anti-TNF-α induced psoriasis is still unclear. However, IFN-α and IL-36, as well as genetic predisposition might play a central role in its pathogenesis. According to the literature, the most important predisposing factor for anti-TNF-α induced psoriasis seems to be smoking. The clinical picture of the disease is complex, displaying a much higher percentage of patients suffering from PPPP than seen in the non-anti-TNF-α induced psoriasis population. Concerning the treatment of anti-TNF-α induced psoriasis, there is a significant lack of data, how to treat it most efficiently. Whether the causative TNF-α inhibitor might further be used when combined with topical medication or can be switched to another TNF-α inhibitor or a biologic with a different mode of action (e.g. ustekinumab) remains an open question. Therefore, prospective studies addressing this question and the development of guidelines as well as treatment algorithms for anti-TNF-α induced psoriasis are of utmost importance.

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