Diploma Thesis

CHANGE IN DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS PATIENTS OVER TEN YEARS OF THERAPY

A real-life retrospective observation

submitted by

Markus Wild

in fulfilment of the requirements for the academic degree

Doktor der gesamten Heilkunde

(Dr.med.univ.)

at the

Medical University of Graz

performed at the

Institute of Rheumatology and Immunology

Department of Internal Medicine

University Hospital of Graz

under the supervision of

Univ.-Prof. Dr.med.univ Winfried Graninger

Priv.-Doz. Dr.med.univ Josef Hermann

Graz, 15th May 2016

Statutory Declaration

I declare that I have authored this thesis independently, that I have not used other than the declared sources/resources and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Graz, 15th May 2016 *Markus Wild eh*

Acknowledgements

I would like to thank Professor Graninger, head of the Institute of Rheumatology at the university hospital of Graz, for the initiation of this project and his continuous assistance and dedication to it over the last year. Many thanks as well to Assistant Professor Simonic for his invaluable help at the start of this work. I also gratefully thank Assistant Professor Hermann for helping me out especially with the RCQM computer software. My thanks go out as well to all the doctors, nurses, secretaries and other staff from the Institute of Rheumatology for their help and patience. Last but not least, very special thanks to my parents for their ongoing support throughout my medical studies.

Zusammenfassung

Einleitung. Die Behandlung der chronisch-systemischen rheumatoiden Arthritis (RA) nach den etablierten Leitlinien mit engmaschigen Kontrollen führt in den meisten Fällen zu einem guten Behandlungserfolg. Es war für uns von Interesse anhand unserer eigenen Kohorte zu prüfen, ob die Veränderung und Anpassung des therapeutischen Verhaltens der Ärztinnen und Ärzte der letzten Jahre einen positiven Einfluss auf dieses Behandlungsergebnis zeigte. Auch sollte der Effekt der Einführung neuartiger biologischer Wirkstoffe auf die Krankheitsaktivität der RA untersucht werden.

Methoden. Wir bezogen Daten von 103 RA-PatientInnen, die über mehr als zehn Jahre unter regelmäßiger und stringenter Kontrolle standen, aus dem klinischen Informationssystem RCQM und teilten sie in Gruppen je nach initialem Krankheitsaktivitätswert (DAS) oder Medikation auf. Anschließend führten wir eine retrospektive Regressionsanalyse durch, um die Krankheitsaktivität in der Kohorte über diesen Zeitraum zu betrachten. Zur statistischen Aufarbeitung wählten wir ein linear gemischtes Model aus.

Ergebnisse. PatientInnen mit initial hoher oder moderater Krankheitsaktivität zeigten eine signifikante Reduktion der Aktivität um 2,4 bzw. 1,3 Punkte. Bei der Gruppe mit anfänglich niedriger Aktivität konnte ein anhaltend niedriger DAS-Wert um 3,2 erreicht werden. Wertet man die Gruppen nach Medikation aus, so erzielte die Kombination aus Biologika und synthetischer Wirkstoffe (z.B. MTX) ein um 0,3 DAS-Punkte besseres Ergebnis als eine Monotherapie mit synthetischen Präparaten.

Schlussfolgerung. Die statistisch signifikanten Ergebnisse zur Fragestellung des zeitabhängigen Krankheitsverlaufs lassen uns das Tight control bzw. Treat-to-Target Konzept als förderlich für die Therapieergebnisse erachten. Die Behandlung mit biologischen Wirkstoffen oder einer Kombination mit solchen erschien uns ebenso effektiver. Dieser Effekt zeigte sich zwar nicht statistisch signifikant, der Trend war in der grafischen Aufbereitung jedoch erkennbar.

Schlagwörter. Rheumatoide Arthritis, Therapieergebnisse, Regressionsanalyse, Biologika, klinisches Informationssystem

Abstract

Background. In most cases treatment of the systemic and chronic inflammatory disease rheumatoid arthritis (RA) according to established tight control guidelines leads to a good outcome. It was of interest for us if we could prove that the changes and adaption of the physicians' therapeutic behaviour in recent years had a positive impact on the therapy outcome in our cohort. Additionally, we wanted to evaluate the effect of newly introduced biologic agents on disease activity of RA-patients in comparison to synthetic pharmaceuticals (sDMARDs), such as methotrexate.

Methods. We extracted data of 103 rheumatoid arthritis patients who were under regular and stringent control over ten years from the clinical management software RCQM and divided this patient collective into groups according to their initial disease activity score (DAS) or medication. A retrospective analysis of the data was performed in order to examine the course of disease activity of these patients over the observed time. A linear mixed effects model was chosen for the statistical regression analysis.

Results. Patients with an initially high or moderate disease activity showed a significant decrease of disease activity by 2.4 and 1.3 DAS points, respectively. The low disease activity group presented with a continuously low DAS around the 3.2 mark. When looking at the specific medication of the patients, we could find that a combination therapy of biologic and synthetic agents (sDMARDs) indeed resulted in a better outcome than an sDMARDs-monotherapy and lowered the DAS stronger by 0.3 points.

Conclusion. The statistically significant findings for disease activity over time allow us to support the tight control and Treat-to-Target concepts for RA-therapy. Furthermore, treatment with biologic agents or a combination with them can be seen as more effective. However, these results were not statistically significant, but a trend was visible from the graphical solution.

Keywords. Rheumatoid arthritis, therapy outcome, regression analysis, biologic DMARDs, clinical information system

Table of contents

List of figures

List of tables

1 Introduction

1.1 General Information

1.1.1 Definition of rheumatoid arthritis

Rheumatoid arthritis is an incurable autoimmune disease that is defined as systemic and chronic inflammation of the patient's joints, particularly of the synovial layer. The primary cause for this chronic synovitis, which leads to an ongoing and often symmetrical destruction of multiple joints, is still unknown. The disease can also be accompanied by extra-articular manifestations, such as vasculitis, endocarditis or lung fibrosis. (1)

1.1.2 Historical overview of rheumatoid arthritis

The historical existence of rheumatoid arthritis before the 19th century has long been subject of debate. Definite prove for it is still missing, but recent paleopathological findings as well as many written and pictorial accounts of the disease that date back to pre-Christian Rome and India strongly suggest that RA was already present in those times. In ancient Greece Hippokrates (c. 460 – c. 370 BC) reported on a disease that he found to usually start at the age of 35 and to gradually destruct the patient's joints. Other pre-modern works of art and literature indicate the presence of the disease throughout the Middle Ages and the following centuries as well. This led various researchers to the conclusion that rheumatoid arthritis is not an exclusively modern disease. (2,3)

It was the French doctor Augustin Jacob Landré-Beauvais (1772–1840) from the Salpêtrière Hospital in Paris who postulated the first widely accepted characterisation of rheumatoid arthritis in the year 1800. However, he considered RA to be a subform of gout found predominately in poor and female patients (3). Sir Alfred Baring Garrod (1819–1907) from the United Kingdom later separated gout from arthritic diseases by finding high levels of uric acid in the blood of gout but not of arthritis patients. One of his sons Sir Archibald Edward Garrod (1857–1936), a member of the Royal Medical Society, continued the research on RA. It was him who eventually coined the term "rheumatoid arthritis" in his book "A Treatise on Rheumatism and Rheumatoid Arthritis" in 1890 (4).

The next major step in rheumatoid arthritis research was achieved by researchers Erik Waaler (1903–1997) from Norway and Harry M. Rose (1906–1986) from the United States of America, who independently discovered and described the antibody rheumatoid factor in 1940 and 1948, respectively (5,6). At the same time, both researchers and their teams developed a testing measure for rheumatoid factor, now known as the Waaler-Rose-Test. The test finally made it possible to differentiate rheumatoid arthritis from other arthritic diseases by blood-testing and was later modified and improved (7,8).

Later research included, among others, newly developed genetic methods and focused on the decoding of the disease's etiology and evolvement of treatment options. Today, while the disease and its pathophysiology are still not yet fully deciphered, knowledge about rheumatoid arthritis and its therapy has increased significantly.

1.1.3 Serostatus and variations of rheumatoid arthritis

Rheumatoid arthritis is a variable medical condition with a number of special forms. RA itself is divided in a so called seronegative and a seropositive variant based on whether the antibodies rheumatoid factor (RF) or anti-cyclic citrullinated peptide (ACPA) are present in the patient's blood or not. The latter has a specificity of 95% for rheumatoid arthritis, which is generally higher than that of RF (9). This partition of the disease is important for the prognosis and the disease course, as seropositive patients are believed to usually suffer from a more severe form of RA. Newer studies, however, suggest that the disease might be underestimated in seronegative patients and therefore not treated sufficiently enough in these patients (10). Seroconversion from negative to positive and vice-versa has been described (11).

In this work I will deal with the most common variant of rheumatoid arthritis, which is referred to simply as adult rheumatoid arthritis. Beside this main form, other more rare forms of RA have been characterised based on characteristics, such as age of onset or typically accompanying symptoms. These other variations are (1):

- Juvenile rheumatoid arthritis
- RA with secondary Sjögren's syndrome
- Felty's syndrome

- Adult-onset Still's disease
- Late-onset rheumatoid arthritis
- Caplan's syndrome
- RS_3PE (remitting seronegative symmetric synovitis with pitting edema)

1.1.4 Epidemiology of rheumatoid arthritis

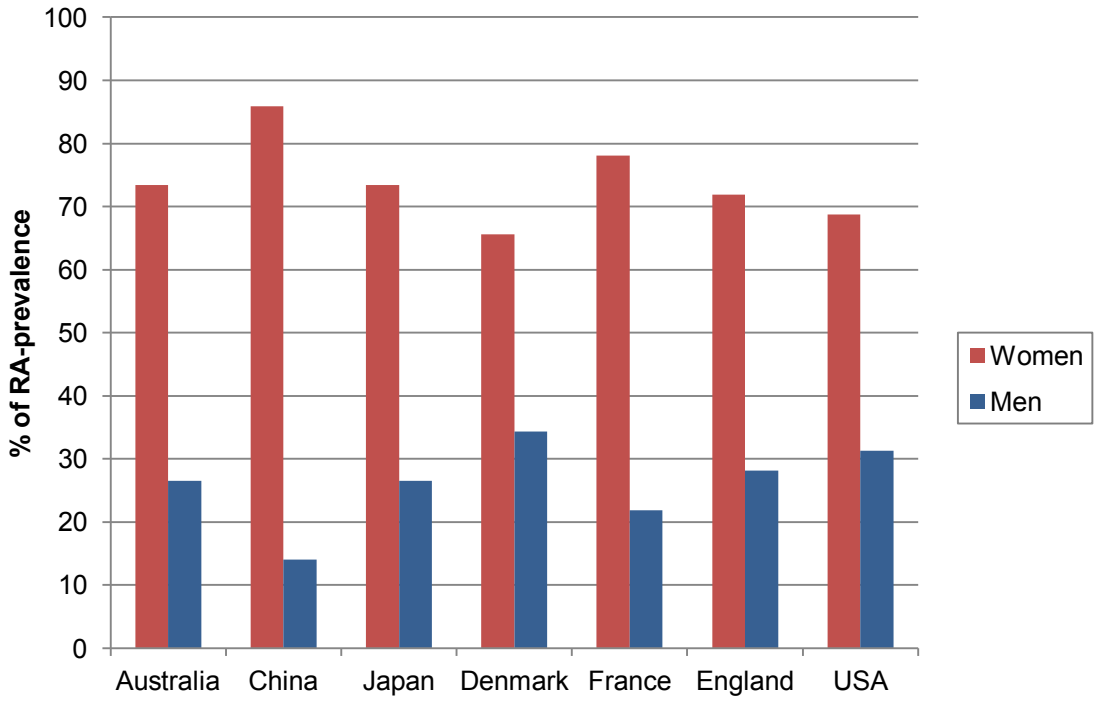
It has been established that rheumatoid arthritis is prevalent in all parts of the world with the average worldwide prevalence of the disease estimated at 0.5 to 1.0% of the population (12,13). Patient numbers can vary within different regions, because socioeconomic factors, such as lifestyle and life expectancy might influence the prevalence of the disease (1). In the Sub-Saharan Africa region and among Caribbean immigrants in the United Kingdom, for example, the prevalence was lower than in other parts and populations of the world. However, the African numbers indicate an increase of RA-cases over the last 20 years (14,15).

A recent meta analysis carried out by Australian researchers showed more exact numbers and concluded that the mean global prevalence of RA for the year 2010 was 0.24% with an estimated 4.8 million adults affected worldwide (16). In the same study RA was ranked 42nd among the 291 most burdening global conditions. Numbers gathered by the German Society of Rheumatology, on the other hand, indicated a prevalence of 0.8% in Germany for the year 2014, which equalled 550,000 adult patients (17). The Centre of Disease Control in the USA gathered numbers that would estimate the prevalence of rheumatoid arthritis among US-citizens at 0.6% with approximately 1.5 million people affected by the disease (18). Generally speaking, these numbers and estimations can be regarded applicable to most Western countries.

The incidence of rheumatoid arthritis is estimated at 25-30 new cases among men and 50-60 among women per 100,000 people per year, respectively. Looking at the entire population, this would result in a mean incidence of 20-40 new patients in 100,000 per year. These numbers are similar in the aforementioned epidemiologic studies. The statistics also highlight another epidemiologic fact of RA that women are up to three times more often affected by the disease than men (19), which is demonstrated in figure 1 based on the table provided by Ngo et al (20). Moreover, adult RA can occur in all age-groups with an onset peak at 30-60

years. Age has shown to be an important factor, with epidemiologic data indicating that patients who are older than 65 years show a prevalence of more than 10% in comparison to the 0.3% among the age-group below 35 years (19). An increased incidence of the disease can also be found in populations where risk factors, such as smoking and obesity, are more prevalent.

Figure 1. International RA-prevalence data divided by gender (20)



1.1.5 Pathogenesis of rheumatoid arthritis

Despite ongoing research and new findings over the last few years, the exact etiology and pathogenesis of rheumatoid arthritis is still not fully discovered. Instead, several hypotheses have been formulated that are being considered and investigated as the primary cause of the disease (21,22). The most accepted hypothesis considers RA to be caused by genetic factors (23,24) that make the affected person more likely to develop RA. This hypothesis is based on the identification of specific genetic markers that were found predominately in RA-patients and linked to a particularly severe course of the disease (25).

These markers include the human leukocyte antigen (HLA) variants DRB1*0401, *0404, *0408 and *0101/2. HLA-DRB1 is a polymorph gene and part of the main histocompatibility complex (MHC). It is responsible for the activation of T-lymphocytes. The mobilisation of these T-cells leads to a stimulation of B-lymphocytes and macrophages, which causes them to distribute rheumatoid

factor, metalloproteinases, prostaglandins and other pro-inflammatory cytokines. T-cells therefore play a crucial role in the complex pathogenesis of the disease (26).

To our current knowledge this marks the pathophysiological onset of the chronic disease (22). Patients who showed to be homozygotic for these HLA-variants were at higher risk of developing RA (27). We further believe that this cascade of HLA-induced and increased cell-activity leading to chronic autoimmune destruction could be caused by a specific environmental trigger. One hypothesis is that the aforementioned genetic factors make patients vulnerable to some form of microbial inflammation, which would then lead to the typical reaction of the immune system (28,29). The exact environmental triggers have not been discovered yet, though.

As mentioned before, many mediators contributing to the pathological cascade of RA have been identified, so far. The best-researched pro-inflammatory cytokines that have an important influence on the pathogenesis of rheumatoid arthritis are tumour necrosis factor alpha (TNFα) as well as interleukins 1 and 6 (30). These factors are responsible for the proliferation of fibroblast-like synoviocytes and the activation of the immune system specifically within the synovial fluid of the patient's joints (22). As a result, the joint destructing pannus is formed, consisting of granulomatous and fibrovascular tissue. Most modern therapies for RA target this process by inhibiting one or more of these cytokines (1).

Another important finding has been the identification of the "receptor activator of NF-κB ligand", or in short RANKL, and its role in the pathogenesis of rheumatoid arthritis. The RANKL is responsible for the stimulation of osteoclasts and hence induces bone-erosion (31,32). Additionally, the counterpart of RANKL was found out to be a mediator called osteoprotegin and it became obvious that the balance between these two agents is deranged in RA. This cascade is now also a target for new pharmacological agents (33,34).

1.1.6 Risk factors for rheumatoid arthritis

Apart from age, gender and genetic factors, several environmental risk factors have been associated with rheumatoid arthritis. Smoking is to be named first. Epidemiologic data indicate a strong interdependence between the onset of

rheumatoid arthritis and smoking. A twin study conducted by Silman et al in 1996 confirmed such interdependence (35). Another study carried out by the Karolinska Institute Stockholm in 2006 also concluded that smoking cigarettes can be directly linked to a higher incidence of the disease in patients who had distinctive HLA-DRB genotypes (36). Smoking is therefore one of the best-examined risk factors for RA and can be regarded as the only such factor that has been verified.

Other risk factors that are thought to negatively influence the onset and course of RA are intercurrent infections, obesity and coffee consumption (27,37). Moreover, hormone replacement therapy (38) and irregular menses (39) are associated with the onset of the disease. Maternal smoking and low socioeconomic status have been found to show an increase of RA-prevalence in children (40). On the other hand, antioxidant nutrition, physical activity, pregnancy, oral contraceptives and breastfeeding are believed to be positive or even protective influences (27,41–45). However, it is important to note that the studies which resulted in these findings could not deliver definite prove or were even partially conflictive. It is therefore not yet possible to precisely determine further environmental risk factors for rheumatoid arthritis.

1.2 Clinical information

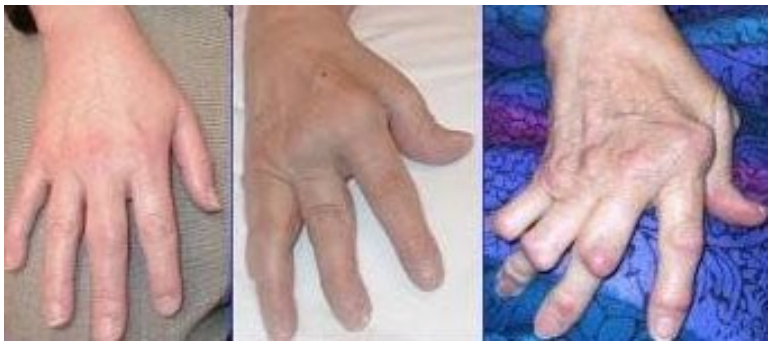
1.2.1 Clinical picture and onset of rheumatoid arthritis

Rheumatoid arthritis is a chronic disease that in most cases progresses steadily over the course of years. However, the beginning of RA can also be marked by a much more unusual form of acute onset. In this case, the first attack of the disease unfolds merely within a few days. Initially, the inflammation in both onset forms is located predominately in the joints of the patient's hands or feet. While mostly these smaller joints show signs of the disease during the early stages of RA, it is also possible that the larger joints, such as the knees or elbows, are affected first. Moreover, RA usually affects more than five different joints during its initial onset, but disease courses where only one or fewer than five joints show signs of inflammation and destruction have also been described, highlighting the variability of rheumatoid arthritis once more. (46,47)

The symptoms that are caused by the underlying autoimmune synovitis of rheumatoid arthritis define most of the disease's clinical picture. RA-patients usually present with joint stiffness for more than one hour and with painful or tender joints that also show a typical form of soft and fluctuating swelling. These major symptoms are strongest in the morning and can be persistent even during the night or time of rest, often leading to deprivation of sleep or insomnia. Approximately 20% of RA-patients show so-called rheumatoid nodules. These are small formations of fibrous and granulomatous tissue, often located alongside the tendons of the extensor muscles of the arms and hands. Rheumatoid nodules can be found almost exclusively in patients who are seropositive for the rheumatoid factor. The severity of the symptoms as well as the time frame of the continuous destruction of the joints varies strongly. (48,49)

Other characteristics of RA are the symmetrical manifestation in the joints and sensitivity towards the application of cold from the outside (50,51). Additionally, the ongoing joint destruction leads to distinctive deformities of the affected joints, when untreated. The most visible and typical deformity for rheumatoid arthritis patients is the ulnar deviation of the fingers, caused by the destruction of the MCP-joints, as shown in figure 2. However, deformities of the feet and larger joints can also occur and require treatment (52,53). In even more severe cases, the fingers and toes themselves can show malpositions, such as the swan neck or cross-over deformity (54).

Figure 2. Ulnar deviation of the fingers throughout the stages of (untreated) RA



Due to the fact that rheumatoid arthritis is a systemic disease, the inflammation not only affects the joints in form of synovitis, but can also occur in numerous other organ systems of the body. Other manifestations often develop in the later and more aggressive stages of RA. They can include vasculitis, pleuritis, conjunctivitis, lung fibrosis, endocarditis, myocarditis or secondary amyloidosis. These advanced

conditions can lead to serious complications, such as ischemic or thromboembolic events, arrhythmia, malnutrition, kidney failure, skin ulcers, neuropathy, paraesthesia or myelopathy, which itself can be caused by an instability in the columna vertebrae or by compression from rheumatoid nodules. The disease also affects the bone marrow, resulting in normochrome anaemia in combination with low serum-iron. Most importantly, almost all patients present with generalised osteoporosis that is caused by the hyperactivity of osteoclast cells and the increased absorption of bone tissue. (55–59)

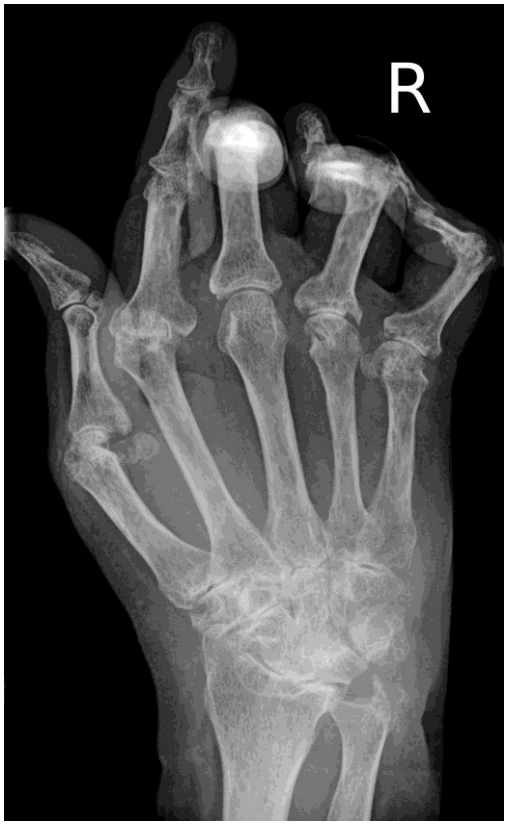
1.2.2 Diagnosis and diagnostics of rheumatoid arthritis

The existence of multiple therapy options has made it obvious that it is important to diagnose rheumatoid arthritis already in its early stages, as new drugs are most effective when applied as soon as possible. However, the clinical variety and non-specific early symptoms of RA, such as malaise, fever or weight loss, complicate the early diagnosis of the disease significantly. Moreover, the lack of secure diagnostic methods for RA in medical routine adds to this challenge. There is no blood test, imaging technique or other method that would allow a 100 per cent correct diagnosis, especially during the first years of disease progress. For the diagnosis of RA it is therefore necessary to gather a range of clinical information and observe the development and changes of symptoms over an extended period of time. These clinical findings should include the medical history, physical examination, blood tests, imaging and in certain cases even invasive methods. (1,60,61)

I have described the most common clinical symptoms of rheumatoid arthritis earlier in this introduction. Additionally to these symptoms, RA can show a typical picture when examined with diagnostic imaging. An x-ray of the affected joints is performed in almost all cases and an example can be seen in figure 3. In the later disease course the x-ray can show signs of destruction (62), such as swelling, ankylosis, demineralisation, slimming of the articular space, bone cysts or even subluxation (63,64). In ultrasound examinations the articular capsule, tendons, ligaments and the possible existence of bone cysts can be evaluated, allowing the conclusion if synovitis is present or not (65–67). A more exact assessment of the joints can be achieved via an MRI-scan (68,69). MRI and to some extent also ultrasound (70) enable the detection of the disease even in earlier stages, contrary

to the conventional x-ray where usually only changes of later stages become apparent (71,72).

Figure 3. Typical radiological picture of advanced RA



In blood tests, on the other hand, various parameter deviations help to suspect systemic inflammation. This includes an increased erythrocyte sedimentation rate, increased levels of C-reactive protein, thrombocytosis, anaemia, low levels of serum-iron or an increase of the alpha-2 globulin fraction. Moreover, blood parameters that are more specific for rheumatic diseases exist, but even those do not allow a secure diagnosis and can only be used as a supporting measure in the diagnostic process. Apart from rheumatoid factor, which can be found in approximately 85% of the patients after two years of disease activity, more specific test parameters include antinuclear antibodies (ANA) or the aforementioned ACPA. (1,73,74)

Eventually, I would also like to briefly mention the rare invasive techniques that can be used in diagnosing rheumatoid arthritis. There are two main methods available, including the so-called micro arthroendoscopy. The joints are hereby examined with an endoscope, which makes it possible to take tissue samples for histological assessment from inside the joint. A more simple technique is the

tapping of the joint with a biopsy needle (arthrocentesis). This allows synovial fluid and tissue to be obtained for microscopic examination. (1)

1.2.3 Classification and differential diagnoses of rheumatoid arthritis

The American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) have agreed on guidelines for the classification of rheumatoid arthritis patients. They defined those who are potentially affected by the disease as patients who present with symptoms of synovitis, such as morning stiffness, pain, etc. in at least one joint and not more feasibly explainable by another disease. For a more accessible approach the two organisations developed the simple scoring system I directly quote and present in table 1, which might help to assess the patients in question. The new system includes four major criteria and works by distributing points for the most common clinical parameters of RA. When the score's cumulative amount of points is higher than five the underlying disease is likely to be rheumatoid arthritis. (75–77)

Table 1. 2010 ACR/EULAR guidelines for classification of rheumatoid arthritis (76)

Category	Points
A. Number of affected joints	
1 large joint	0
2-10 large joints	1
1-3 small joints (independent from involvement of large joints)	2
4-10 small joints (independent from involvement of large joints)	3
> 10 joints (with at least 1 small joint)	5
B. Serology	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase parameters	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms according to patient self-report	
< 6 weeks	0
≥ 6 weeks	1
≥6 points in total means classification as definite rheumatoid arthritis	

This classification system is supposed to simplify the differentiation of rheumatoid arthritis from other rheumatic diseases or articular arthrosis. Generally speaking, there is a wide range of differential diagnoses for RA, including but not limited to degenerative joint disease, fibromyalgia, systemic lupus erythematosus (SLE),

Sjögren syndrome, psoriasis arthritis, sarcoidosis, polychondritis, myelodysplastic syndrome, Lyme disease, osteoarthritis or paraneoplastic syndrome. RA can be distinguished from these other diseases often by a simple look at the medical history and the main symptoms of the patient. Degenerative joint diseases, for example, do not present with morning stiffness, which is therefore a distinctive feature of RA. Moreover, skin rashes, fever, photosensitivity, tophi, etc. are not typical symptoms of rheumatoid arthritis and instead linked to other diseases, such as SLE or gout. (78–80)

1.2.4 Disease activity scores for rheumatoid arthritis

Due to the chronicity of rheumatoid arthritis the disease requires constant observation and regular re-assessment of the patients, which poses an extensive process with frequent clinical examinations. The problem hereby is that, as mentioned before, we do not have a single clinical parameter that would allow us to evaluate the disease activity of RA over time. This led rheumatology researchers to work on practical scores that could be used in substitution. After several years of research on this matter the current gold standard of RA observation scores DAS28, standing simply for “disease activity score”, was formulated (81). Numerous other scores have been developed since then and they all have in common that they are standardised combinations of several parameters, which were validated to best depict the extent and change of disease activity (82). Apart from the DAS, I will also describe and further scrutinise the disease activity index (DAI), which is among the most common scores being used today.

The DAS28 was developed in the late 1980s by a team of EULAR researchers from the Netherlands and eventually adopted as the standard score for measuring RA-activity (81). The number attached to “DAS” indicates the amount of joints evaluated by the physician in the examination and can vary from 3 to 68. It is important to note that the interpretation of the DAS value depends on that number of assessed joints, so the standard amount was set to 28 in order to allow an internationally standardised interpretation of the score (83). The formula for calculating the DAS with the ESR is “$DAS28 = 0.28*\sqrt{sw28} + 0.56*\sqrt{t28} + 0.70*\ln(ESR) + 0.014*VAS$” (81) and is hence rather complicated. It is therefore recommended to use a computer system or spreadsheet for its calculation.

The variables that are assessed for the DAS28 are the number of swollen joints out of the 28 examined (sw28), the number of tender or painful joints (t28), the erythrocyte sedimentation rate (ESR) in mm per hour and the patient self-reported global health assessment on a visual analogue scale (VAS) from 0 (best) to 100 (worst) in mm. There is a variant of the formula consisting of three parts where the VAS is not included, but the four-variable version is the more commonly used one. The 28 evaluated joints include the MCP, PIP and wrist joint as well as the shoulder, elbow and knee on both sides of the patient's body. Additionally, it is possible to replace the ESR with C-reactive protein (CRP), which has the advantage that it is an acute phase parameter, indicating disease activity changes more quickly (84,85). The DAS28 (CRP) does have a slightly different calculation formula though. When counting in all parameters, a value range of 0.00 up to 10.00 can be calculated for the DAS28. A perfect score of 0.00 is unlikely though , because both the ESR and CRP usually cannot amount to 0.

The "disease activity index" (DAI) was developed as a simplified score (86). It is based on the same principle as the DAS and uses similar variables, but its assessment and calculation is easier. Among the DAI there is the differentiation between the simplified (sDAI) und the clinical index (cDAI). The sDAI comprises the parameters of swollen and tender joints like the DAS28, CRP-levels in mg per dl and the VAS, which is this time assessed by the patient and the doctor and ranges on a scale from 0 (best) to 10 (worst) in cm. These variables are simply added up to the eventual score, so there is no complicated formula. The sDAI's value varies from 0.0 to 86.0. The cDAI works the same way, but does not include the CRP-level. It is therefore a purely clinical score that does not require a laboratory parameter and ranges from 0.0 to 76.0 (1). An interpretation scale for these three scores is summarised in table 2.

Table 2. Interpretation table for DAS and DAI (87,88)

Score	Remission	Low	Moderate	High
DAS28 (ESR)	< 2.6	≥ 2.6 - < 3.2	≥ 3.2 - ≤ 5.1	> 5.1
sDAI	≤ 3.3	> 3.3 - ≤ 11.0	> 11.0 - ≤ 26.0	> 26.0
cDAI	≤ 2.8	> 2.8 - ≤ 10.0	> 10.0 - ≤ 22.0	> 22.0
When considering the DAS28 (ESR), a significant improvement is defined as reduction by > 1.2 points at low and moderate and > 0.6 - ≤ 1.2 points at high disease activity.				

1.2.5 Therapy principles for rheumatoid arthritis

Treating rheumatoid arthritis follows the principle goal of detecting the disease as early as possible and bringing the systemic inflammation to a halt (remission). This is to relieve patients from the symptoms of the disease and achieve prevention of future complications, such as further joint destruction or organ damage (89,90). The basic idea is to improve the patient's health, function and well-being. Currently, the approach to reach this goal as quickly as possible is a strike early and strike hard strategy, which is then followed by a long-term treatment plan with the purpose of continuously reducing the disease activity under medical surveillance. The patient is supposed to be involved in all decision-making, highlighting the patient-individual or patient-centred approach in RA-therapy, which has shown to have a positive effect on therapy outcome (91). These principles have been summarised as a tight control concept, which was followed loosely in the past. Eventually, the so-called Treat-to-Target was shaped and established as a basic guideline for RA-therapy (92).

There is a variety of methods for the treatment of RA, the most important of which is the therapy with medication. Other options are mostly supporting measures to this pharmacotherapy, forming a whole concept of RA-treatment. One part of this concept is physical therapy (93–96), including cryotherapy, hydrotherapy, movement therapy, galvanisation and iontophoresis. This is supposed to help reduce pain and improve rehabilitation after surgical interventions. Surgical therapy itself comprises joint replacement, synovectomy, stabilisation of the cervical spine or other reconstructive measures (97–100). However, surgery is considered a last resort option and the numbers of RA-patients who require surgery is declining due to the improvements in non-surgical treatment (101). Moreover, for the completion of the concept occupational therapy can be included (102). This involves appliances that aid patients' independence, such as purpose-built cutlery, hygiene gadgets or fitted splints. Special training on movement techniques that reduce pain and joint destruction is also part of this kind of therapy.

Pharmacotherapy is the main column of rheumatoid arthritis therapy. Its concept and the applied pharmaceuticals have improved significantly over the last decades, which led to a much better prognosis for the patients. However, these

new developments have also raised the complexity of RA-treatment and it is therefore highly recommended to refer RA-patients to specialised rheumatologic departments for further assessment and target-oriented care (1). This complexity becomes apparent when looking at the updated and extensive treatment guidelines from the American College of Rheumatology (103). Basically, the three main drug types of RA-pharmacotherapy are nonsteroidal anti-inflammatory drugs (NSAIDs) for pain-relief and inflammation management, corticosteroids for short-term treatment of high disease activity and disease-modifying antirheumatic drugs (DMARDs), which will be explained more thoroughly in the next chapter, for long-term baseline therapy.

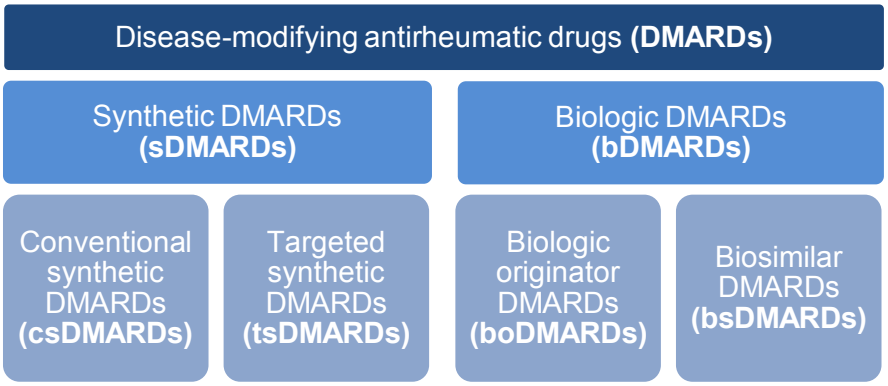
NSAIDs and corticosteroids are among the most commonly prescribed and best-known drugs in medical routine and I will therefore not describe them in more detail concerning their pharmacological information. Their role in rheumatoid arthritis treatment is very important though. NSAIDs function as basic inflammation inhibitors and painkillers, but do not fight the cause of the disease (104). In case of severe and ongoing pain it is also possible to replace NSAIDs with stronger analgesics, as recommended by the World Health Organisation in its analgesic ladder (104). Corticosteroids are applied to either bridge until a DMARD-treatment becomes effective or treat acutely high disease activity (105). It is also possible to prescribe them in low doses for a long-term supporting therapy (106,107), but the side effects of a chronic corticosteroid therapy (e.g. increased risk for osteoporosis) should be considered when doing so (105).

1.2.6 Disease-modifying antirheumatic drugs (DMARDs)

DMARDs are a large group of rheumatic therapeutics comprising a number of drugs and various drug classes. This includes the immune system modulators methotrexate (MTX), leflunomide and sulfasalazine. Moreover, anti-malaria drugs like hydroxychloroquine or antibiotics are considered DMARDs in RA-therapy. In recent years, however, the better understanding of major pathophysiological processes in the disease's onset and course have made it possible to develop new pharmacological agents that directly target and inhibit specific factors of the pathogenesis of rheumatoid arthritis. These drugs are able to modulate the disease activity much more effectively and are usually referred to as biologic response modifiers or "biologics" in short.

An elegant nomenclature and classification for these various categories of DMARDs has been proposed by Smolen et al and is summarised in figure 4. According to this new system, DMARDs are generally divided into synthetic (non-biologic) and biologic agents. Among the synthetic DMARDs (sDMARDs) there is another categorisation into "old" conventional (methotrexate, leflunomide, etc.) and targeted synthetics (e.g. tofacitinib), which are agents that function as modulators in distinctive disease cascades similar to biologics but are produced synthetically. Biologics (bDMARDs) are also divided again into the well-known biologic originators (infliximab, adalimumab, etanercept, etc.) and biosimilars. The latter was proposed in order to categorise future pharmaceutical agents that are engineered from biologic originators with slight modifications, which is a currently ongoing development (108).

Figure 4. Newly developed nomenclature for DMARDs (108)



Biologics are a promising category of pharmaceuticals used in many fields of medicine today, e.g. in the treatment of various forms of cancer (109). These drugs are defined by the way they are manufactured, which is a complex process including recombinant DNA technology and using microorganisms (E. coli, yeast), animal cells (e.g. Chinese hamster ovary cells) or plants as production hosts (110–112). The first developed biologics engineered in this way were human hormone substitutions, such as insulin. In the last decade biologics have become increasingly important in the treatment of rheumatoid arthritis as well. Today, we mostly use monoclonal antibodies in RA-therapy that have the tumour necrosis factor α (TNFα) as their dedicated therapeutic target. Other such bDMARDs include CD or interleukin inhibitors. Table 3 provides an overview of the biologics that are in use at the rheumatology department of the Medical University of Graz and that will be subject to further evaluation in this work.

Table 3. Biologic therapeutics used in rheumatoid arthritis treatment in Graz

Name of agent	Trade name	Target
Abatacept	Orencia®	CD80, CD86
Adalimumab	Humira®	TNFα
Certolizumab	Cimzia®	TNFα
Etanercept	Enbrel®	TNFα
Golimumab	Simponi®	TNFα
Infliximab	Remicade®	TNFα
Rituximab	MabThera®	CD20
Tocilizumab	RoActemra®	Interleukin 6

1.2.7 Tight control and Treat-to-Target concept

Therapy of rheumatoid arthritis patients is complex and poses a continuous process. Over the years a tight control concept for RA-treatment has been established that aimed to reduce disease activity by shifting to a more patient-centred and outpatient care approach, by intensifying the therapy and performing more frequent reassessments on the patient (113,114). This strategy showed good effects on the general course of the disease and was gradually implemented by most rheumatologists. However, the interpretation and application of the concept on each patient was mostly up to the individual physician. It is therefore not surprising that the desire for a standardised and simple-to-follow concept in RA-treatment was very high (92). In the late 2000s this led to the formation of an international and of a EULAR task force that both started to work on simplified guidelines and were able to publish their results in 2010 (115,116).

A new guide for RA-therapy proposed by the international task force is called “Treat-to-Target” (T2T). It is based on and backed by expert opinions and empirical data collected in an extensive literary search (117,118). Work on the outlet and concept of T2T is still ongoing with the latest update having been released in 2014 (92). The basic idea of Treat-to-Target is to carry out the treatment of the patient in order to reach either the main target of disease remission (DAS28 < 2.6) or the alternative target of low disease activity (DAS28 ≥ 2.6 and < 3.2). If the target was lost after initially reaching it or not reached at all, T2T requires the chosen therapy to be adapted. Patient reassessment is set according to the success of the applied treatment plan. Moreover, the concept consists of four main principles (A-D). Quoted directly from the latest T2T-update, these are:

A. *"The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist.*
B. *The primary goal of treating patients with rheumatoid arthritis is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and participation in social and work-related activities.*
C. *Abrogation of inflammation is the most important way to achieve these goals.*
D. *Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis."* (92)

In accordance with these four points the team also gave out a set of ten key advises for the treatment of RA, for example recommendations on how to deal with a patient's co-morbidities, how to assess disease activity with fitting measures or the frequency and form of documentation that is needed for the concept to fully show its effect (92). Additionally, the research team developed a simple algorithm to show the path from active RA to the target including constant and regular reassessments of the disease activity. Every step of the path should be taken only in agreement with the patient and modified to their specific needs. In figures 5 and 6 these algorithms are depicted for the main and the alternative target, respectively, according to the task force's proposal. Treat-to-Target is now widely accepted as an important and well-thought-out guide to the treatment of rheumatoid arthritis and is also subject to a constant process of improvement and evaluation by the influx of new evidence and findings from further research.

Figure 5. Treat-to-Target algorithm for the main target (92)

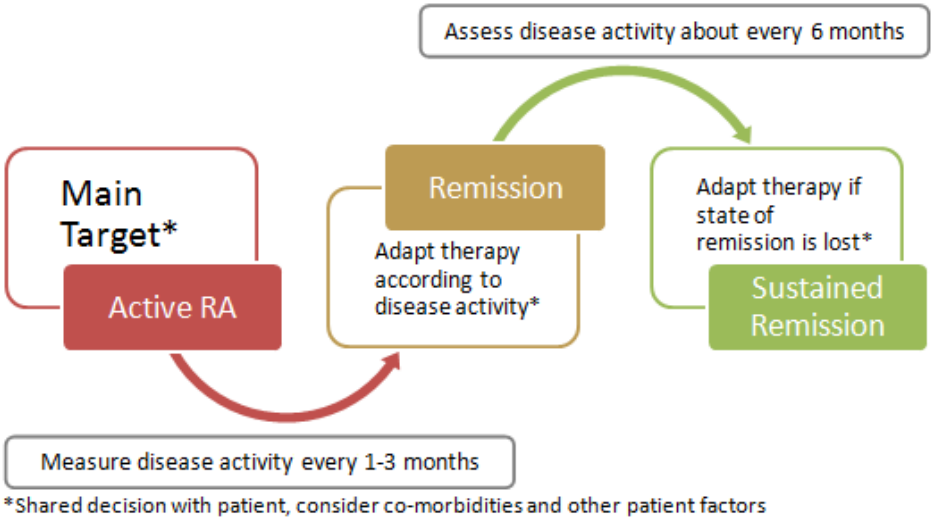
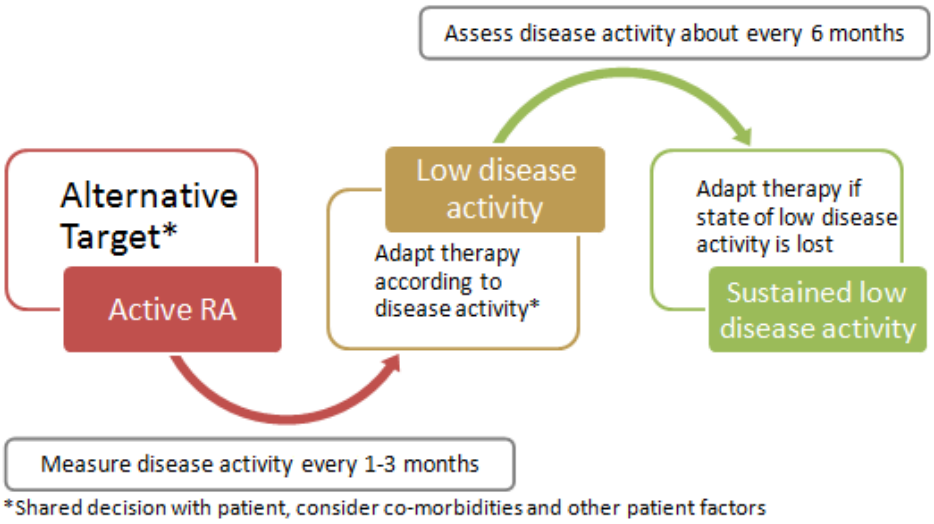


Figure 6. Treat-to-Target algorithm for the alternative target (92)



Alternatively to Treat-to-Target, the EULAR task force developed a concept that is similar to T2T but a little bit more complex. These EULAR guidelines are also under continuous advancement with the latest update having been published in 2013 (119). They include recommendations on the usage of DMARDs and break the therapy plan of RA down to three phases according to what kind of DMARDs should be applied. A comprehensive table of the concept can be found in the respective publication (116). Albeit being more extensive, the EULAR guidelines also comprise a set of key messages with three major statements (A-C). Directly from the 2013 update these are quoted as follows:

A. *"Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist*.
B. *Rheumatologists are the specialists who should primarily care for RA patients*.
C. *RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist."* (119)

1.3 Evaluation of therapy outcome

1.3.1 Study premise

At the rheumatology department of the Medical University of Graz a clinical computer software (RCQM) is utilised for the assessment and follow-up of rheumatoid arthritis and other rheumatology patients. The software has been in place at the institute for over ten years and for this work I was allowed to use its

extensive database, which included clinical patient information on the disease, such as disease activity scores and medication. Together with Professor Graninger, head of the department, I considered that with this data pool of a whole decade it would be interesting to study and evaluate several aspects of therapy outcome of RA-patients where more evidence and observations would be beneficial to the general scientific opinion in the rheumatology field.

1.3.2 Main Objective

For our study we chose one major objective that we wanted to explore in this work. The main question was to study the effects the therapeutic behaviour of the physicians had on the patient's therapy outcome over the observed time, measured both with the DAS and cDAI. This includes evaluating the evolvement of the therapy guidelines in use (tight control, T2T) and the continuous process of their implementation by the physicians over the last ten years, as well as looking at the prescription behaviour of the doctors concerning the use of the various types of DMARDs for baseline therapy. We investigated if the department was able to achieve and maintain continuously low disease activity in RA-patients with the therapy options offered here. The hypothesis in that case was that we expected a significant disease improvement in the patients over the observed time span of ten years. We think that our decade-long observations may reveal interesting findings concerning the long-term effects in such patients.

1.3.3 Side objectives

Having this large database, we also added a few side questions. First, we will look at epidemiologic statistics regarding the overall number of rheumatoid arthritis patients who have visited the outpatient department and their characteristics, such as age, gender, etc. and compare our patient statistics with such data from fitting publications. Moreover, we will discuss the interdependence between the DAS and DAI disease activity measurements and see if our large data pool allows us to prove and therefore confirm the hypothesis that the cDAI correlates well to the DAS28 despite not including an inflammation parameter, which has been raised in previous publications (120).

During the work on the main objective I found a small patient collective that was not only followed up over ten years but also received the same treatment

throughout that time span. I thought it was therefore interesting to assess this group of patients further and see if there were differences in their therapy outcome depending on their medication. In this smaller calculation that is linked to the main objective I will thus compare two groups who received either a synthetic DMARD monotherapy or a combination therapy of such and a biologic. The hypothesis in this case was that the combined therapy of bDMARDs and sDMARDs has a positive influence on the overall therapy success and hence shows a significantly better outcome than an sDMARDs-monotherapy. In the process of answering all of these questions, I will also present the RCQM computer system in use for data management at the department and scrutinise its purpose and the documentation quality of the data.

1.3.4 Adding our observations

In order to work out all of these objectives and eventually be able to present and add the results from the observations to the scientific canon, I chose a retrospective data analysis study design, gathering the necessary data from the department's computer systems and processing it further with fitting statistical measures and graphics. The data for the study includes patient information from the years 2004 up to the end of 2014. Approval by the ethics committee of the Medical University of Graz for the usage of this data was granted on 27th March 2015. In my work I will later cite an unpublished study performed by Professor Simonic from the Institute for Medical Informatics, Statistics and Documentation of the Medical University of Graz in 2007. The unpublished manuscript that will be referenced later was handed to me personally by Professor Simonic.

2 Methods and material

2.1 Rheumatology Clinical Quality Management (RCQM)

2.1.1 About RCQM

I have already described the efforts that are necessary for a successful treatment of rheumatoid arthritis patients. This includes regular short-term medical examinations, tight control of disease activity, constant adaptation of therapy and the handling of a massive amount of information. The selection of suitable therapy for the RA-patient is thus a straining experience for both the physician and of course the patient. From there derived the natural desire to simplify this process. At the rheumatology department of the Medical University of Graz this led to the development and implementation of a comprehensive clinical information system with the intention of making it easier to manage the information flow and provide a standardised guide for patient assessment to the doctors. The new computer system was eventually called “Rheumatology Clinical Quality Management” or in short “RCQM”.

The idea for RCQM was based on the “Swiss Clinical Quality Management” (SCQM) which had been successfully implemented in Switzerland already in the late 1990s. Run by the SCQM Foundation the registry started out exclusively for RA-patients, but has now become a nationwide stable in the management of all major rheumatic diseases in Switzerland (121). Efforts to build and finance a similar collective foundation for rheumatology patient management and research in Austria have been made, but have not yet resulted in the formation of such an institution.

RCQM was introduced at the rheumatology department in 2004 and has been in use ever since. As it was developed with doctors, it offers a large variety of functions tailored precisely to the work of a rheumatologist. Moreover, RCQM can not only manage rheumatoid arthritis patients, but also other diseases, such as systemic lupus erythematosus or sarcoidosis. At the outpatient clinic every patient visit is documented in the system, including all measures that have been performed during that visit. It is important to note though that while RCQM

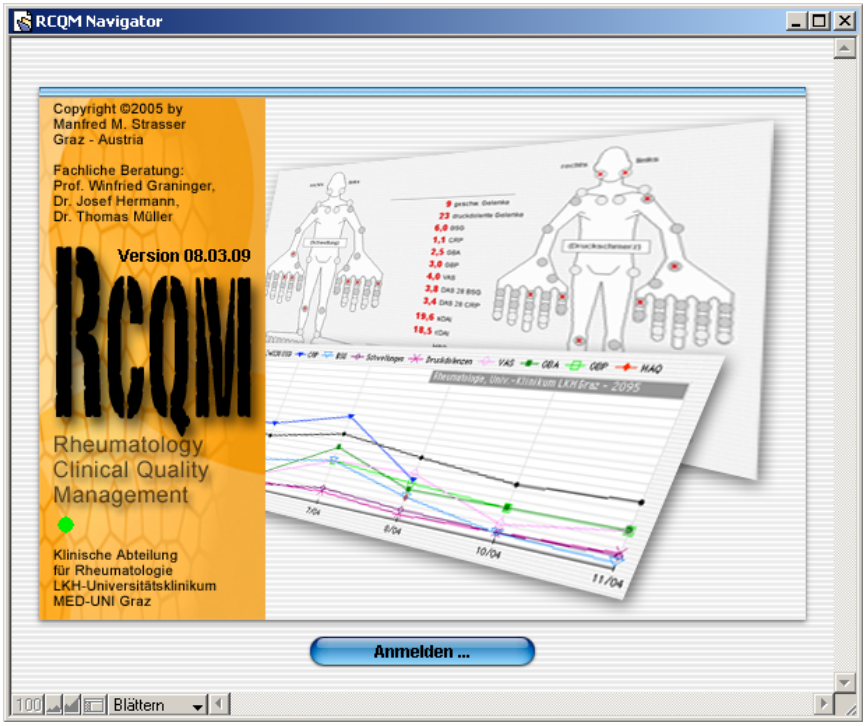
simplifies the assessment and information flow, it does not replace the actual physical examination and evaluation of the patient's health status. It only offers support for the decision-making process, meaning the final and ultimate decision is always made by the physician. (122)

After more than ten years of using the system, it has become a vital part in the daily clinical routine of the department. However, its long time of use also made it necessary to adapt and develop the system further. Therefore, the head of the department, Professor Graninger, decided to have RCQM remodelled and improved according to the large amount of experience gathered throughout the last ten years. This development of the new system is currently undergoing.

2.1.2 Functions and interface of RCQM

RCQM's interface is entirely in German with an English version not yet planned. It was programmed on the FileMaker® Pro platform and is installed on every computer of the rheumatology department at the university hospital of Graz. Access to RCQM is password-protected and each user has individual login data. The system also offers an elaborate rights management where administrators can authorise different users to specific functions and information. I would now like to present the RCQM-features and show some screenshots with patient or doctor-identifying information blurred out.

Figure 7. RCQM front page



One of the basic and most important functions of RCQM is its detailed search engine. It is possible to search individual patients by their personal information or by many of their distinctive characteristics. The system also dedicates an individual ID-code to each patient and numbers the registered visits continuously, which makes it easier to search for older information. Moreover, the engine not only allows scanning individual patients but entire groups of patients based on the features the group has in common, such as diagnoses, age, gender, disease activity, medication, etc. The results from each scan are displayed as either a list of patients or a list of the patient-specific visits when having searched for a single person. I primarily used these search functions to collect the data I needed in this study.

For the clinician the essential features that RCQM offers are the patient management functions. When clicking a patient's profile an information centre is opened that provides an overview of the patient's data. In figure 8 the basic patient table can be seen with information on the main and other diagnoses as well as disease activity at the latest visit, indicated by several different scores, and an extra column where the physician can scroll through and find additional notes taken during the last few visits. In the example screenshot the patient suffered from high disease activity ("hohe Krankheitsaktivität") which is specifically highlighted in red. The notes for low or moderate activity are written in grey. This table also shows whether the activity scores have increased, decreased or stayed at the same level by the addition of little arrows next to the values that point either up or down accordingly. As mentioned before, all of that data was submitted to the system manually by the physicians during each visit. The disease activity scores, however, are calculated automatically by RCQM.

Additionally, it is possible to get a more detailed presentation of the results of the examination that was performed on the patient. This page of the programme that is shown in figure 9 includes an enlarged graphic of the human body, which is used for the joint assessment during the physical examination. The left graphic functions for the marking of swollen joints and the right one is for indexing tender or painful joints. Affected joints are then labelled with a red "x". Joints that are painted in darker grey are the ones that need to be examined for the DAS28. In the example, the patient had very low disease activity and did not show symptoms

in their joints. This is also highlighted by the oversight of activity parameters presented in the middle of the page and summarised by the low disease activity note (“niedrige Krankheitsaktivität”) below the scores

A feature that offers a good overview of the disease development and changes over time is pictured in figure 10. RCQM can analyse all input data and produce an evaluation table that with only a short glimpse gives the physician the opportunity to interpret the long-term trend of the disease and see if there are certain patterns that demand therapy adaptation or other intervention. This feature is also quite flexible, as it allows selecting specific parameters that should be evaluated, eventually making it a helpful tool in decision support. The screenshot shows the same patient as before with continuously low disease activity. Depicted are the curves over time, representing parameters, such as DAS28, cDAI or the health assessment questionnaire (HAQ). Below the line chart there is also a second timeline block where the accompanying baseline (blue) or corticosteroids (orange) medication is outlined, which in this case would be Etanercept 25mg. A clinician can immediately see what kind of treatment the patient received and if there had been changes in disease activity depending on that medication. This is supposed to help the physician planning the next steps of the patient’s therapy.

Figure 8. RCQM clinical patient information centre

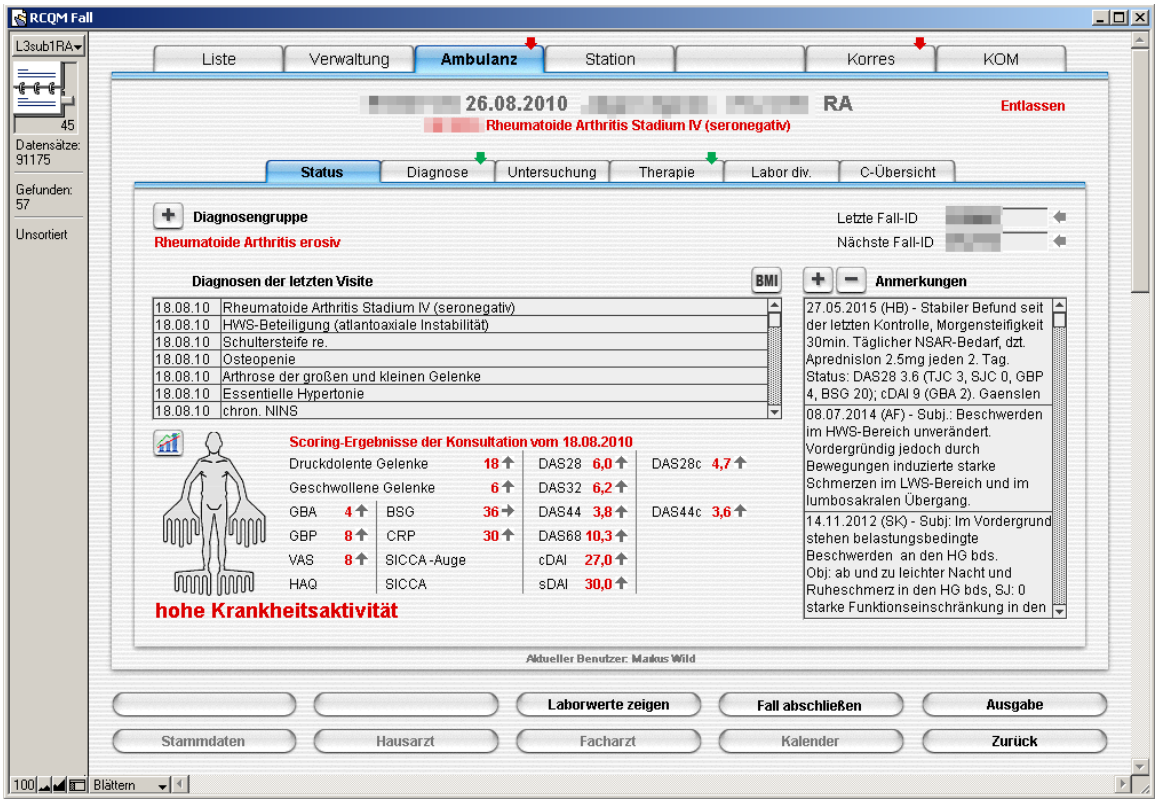


Figure 9. RCQM detailed view of clinical parameters

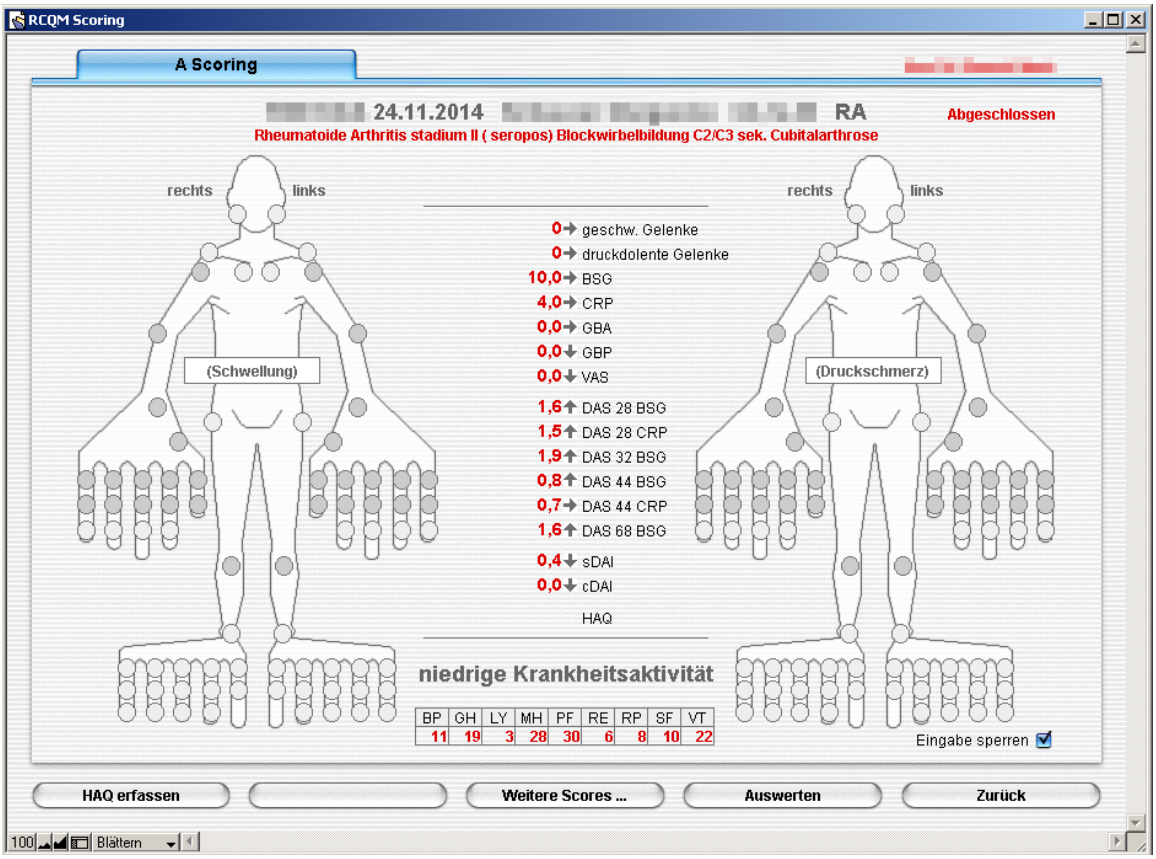
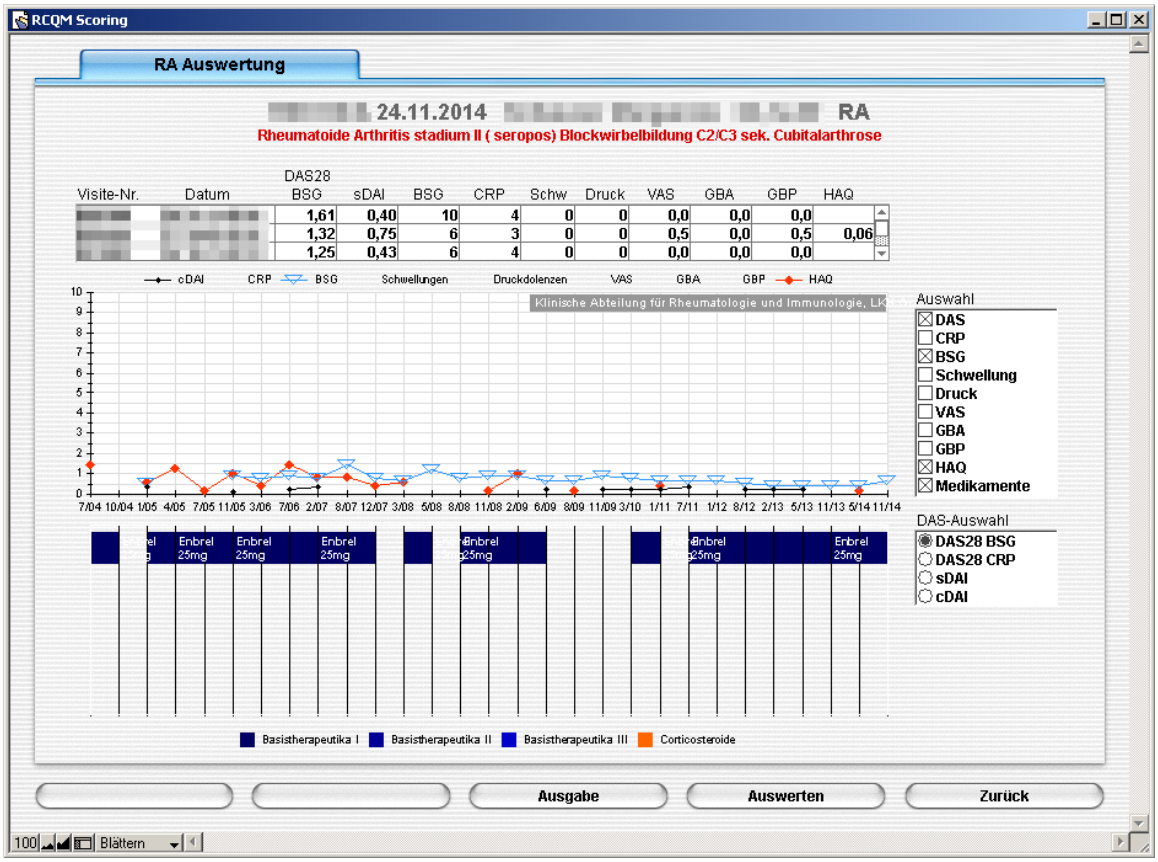


Figure 10. RCQM view of disease course and medication



These are the main features of the system, but it also has a variety of other functions. One of those is the option of writing, editing and reading medical reports and referral letters. RCQM offers a special input mask for such documents that later automatically exports the finished letter. Another tool is the medication database where it is possible to document the current pharmacotherapy divided into DMARDs, corticosteroids or NSAIDs. The medication can then be categorised as baseline therapy (up to three different drugs), pain medication or steroids and is displayed in the patient information centre, as can be seen in figure 10. Apart from the medication database, RCQM also incorporates databases for predefined diagnoses and other clinical information like the interpretation table of the disease activity scores.

2.2 Data material

2.2.1 Collecting the data

I gathered all data that I used in this study exclusively from RCQM. I did not have to consult with the hospital own patient information system MEDOCS, as the data in both systems is synchronised and therefore identical. The gathering and usage of the data for the intended purpose was approved by the ethics committee of the Medical University of Graz in March 2015. I additionally signed a data privacy statement at the department for this specific study.

The first batch of data I collected included all RA-patients that were continuously followed up by the rheumatology department over the last ten years. I will call this group the “observation group”. For this I thankfully received the list of patients who had been part of the retrospective data analysis study by Professor Simonic. This collective of 184 individual rheumatoid arthritis patients had been under regular observation at the outpatient clinic of the rheumatology department at least from 2004/2005 to 2007. In March 2015 I manually extracted the data and checked every single record of this collective for each of its individual.

For the secondary objectives I wanted to retrospectively evaluate the data of all RA-patients who had visited the department at one point in the last decade and were registered in RCQM. For a large search like this RCQM offered the aforementioned search engine, which allowed me to easily display such an

extensive list of patients. I searched the database several times with different variables, such as main diagnosis or diagnosis group, so that I could be sure to include all RA-patients from RCQM. The computer system also provides a practical data saving option that made it possible for me to extract and download these lists as Excel® files. This second data batch was gathered in June 2015.

2.2.2 Screening the data

After having collected all the necessary data material, I pseudonymised it by deleting personal identification of the patients from the list. However, each individual would still be identifiable by their ID in RCQM. The remaining information included IDs, date of birth, gender, disease activity scores, HAQ scores and medication for each visit that was assessed and saved in RCQM.

The next step was merging the files I downloaded for the collective cohort into one comprehensive Excel® spreadsheet. I then searched through that large amount of data and deleted all duplicates that have resulted from the repeated data retrieval. Furthermore, it was necessary for me to thoroughly scan the data for documentation errors and mock patients or test dummies. In this case I had to eliminate six nonsensical or test data sets. Finally, this overall group of rheumatoid arthritis patients who had visited the outpatient clinic at least once from mid-2004 to mid-2015 comprised 1,839 individual patients.

It is important to note that there is a small gap in the graphs I will provide in the results section of this work. This gap covers three months at the beginning of 2010 in which no documentation in RCQM could be performed due to a technical problem. However, this does not have a relevant impact on the study data.

2.2.3 Preparing the data

The data was arranged by RCQM in “long format” meaning that every visit was placed in a separate row with the general parameters arranged as the columns of the table. The visits were organised chronologically from earliest to latest visit date and sorted by the patient IDs from lowest to highest ID number. There was no further rearranging required, as this was the format I needed for the statistical calculations. However, to simplify the epidemiologic data evaluation I created a special table where each ID appeared only once with the accompanying patient-specific epidemiologic information. I eventually added a new column to the tables

including sequential numbers so that I could easily reorder the data to its initial sorting at any point of time.

In order to be able to use the data in this study, I had to additionally categorise it into different groups according to disease activity and baseline medication, which will be explained thoroughly later. I therefore added extra columns for these new categories and operated specific Excel® formulas to automatically assign each individual ID and its associated visits to these predefined subgroups. A major data-modification I had to perform for this to be possible was the renaming of the drugs in the medication columns and the attachment of an extra column for their respective DMARD-types (biologic, methotrexate or other). As RCQM only gives out trade names and accompanies them with the prescribed dosages, I had to manually change each medication to its agent and then add what type it was. For this I created a spreadsheet of all the medication used for rheumatoid arthritis treatment and changed and categorised the medication columns accordingly.

Other data processing included small changes, such as deleting the unnecessary columns for doctor's ID and case ID and adding a column for the specific age of the patients at each visit, because this information was only presented in age groups covering two age decades. Further major processing of the data was not necessary. However, I had to make smaller changes during the course of the evaluations, which will be mentioned when applied.

2.3 Statistical solutions

2.3.1 Assigning groups

As mentioned before, I defined one major group for this study and called it "observation group". It included those rheumatoid arthritis patients who had been regularly observed over the last ten years, which resulted in 103 study individuals. The collective data, consisting of all RA-patients who had visited the outpatient department, served as the base for the evaluation of the secondary objectives and for supporting the findings of the main objective. This group of patients thus included also the subjects of the observation group. It was then reasonable to divide the observation group further into several subgroups according to the two

parameters I wanted to look at in this work, which are disease activity over time and therapy outcome in dependence of the different baseline therapies.

I defined three subgroups that comprised smaller collectives arranged after the disease activity upon their first visit at the department. There is disease activity group 1 ($Group_1$) which included 51 patients who had an initial DAS28 ESR of below 3.2 (low disease activity) at their first visit that was recorded in RCQM. $Group_2$ included 32 patients with a DAS28 of 3.2 up to 5.1 (moderate disease activity) and $Group_3$ was reserved for 20 patients with high disease activity indicated by a DAS28 of more than 5.1. These subgroups were additionally formed and observed with the cDAI-scale instead of the DAS28, in order to compare the two scores. The interpretation scale of the DAS can be found in table 2.

For the smaller evaluation of the baseline therapies I divided the observation group into two subgroups. This time the patients were assigned to the groups according to the their therapies and included a collective who had continuously received a monotherapy of non-biologic DMARDs (sDMARDs) over the last ten years ($Group_{MT}$) and another group of patients with a combination therapy of sDMARDs and biologics ($Group_{CT}$). I also evaluated if there were differences between men and women for the main objective. Other than that I did not divide our cohorts any further. An overview of all subgroups is depicted in figure 11.

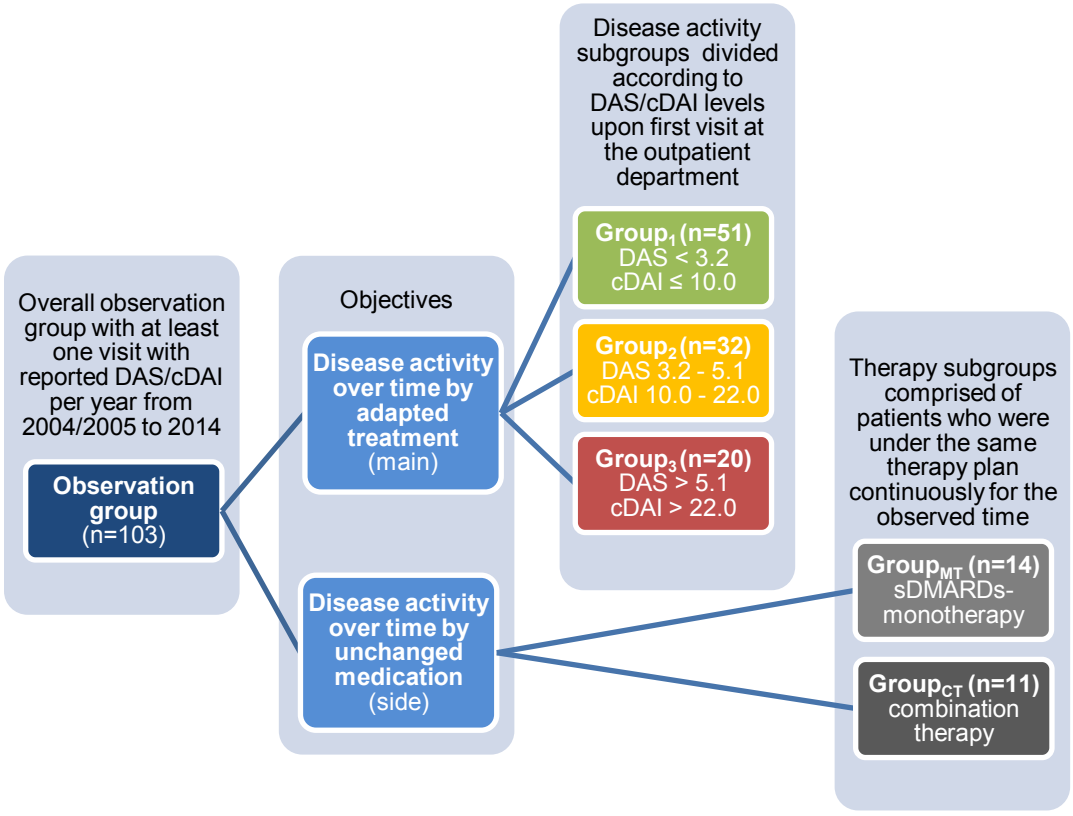
2.3.2 Inclusion criteria and final sample sizes

In this study I tried to keep the inclusion criteria simple. Therefore, I did not set any inclusion or exclusion criteria depending on age, gender or other socioeconomic factors. A recent study conducted by the SCQM Foundation suggests that, for example, the effect of biologic treatment might not be dependent on such factors or the heterogeneity of the patients (123). While I did not restrict the large collective cohort (n=1,839) further for the assessment of the basic epidemiologic and documentation data, I limited this patient group for the other statistical evaluations. The main criterion I chose was that only patients who had visited the department at least twice with an eligible DAS28 ESR reported in those visits, were taken into account for these additional statistics. This was supposed to make sure that the documented diagnosis was correct and that for each included patient a trend of their disease activity could be reproducible. These restrictions left this group with 1,166 individuals (n=1,166).

The observation group was restricted to all patients who had been regularly followed up over ten years from 2004/2005 to 2014 and had at least one visit with a reported DAS28 ESR in each year. However, I decided to include four patients who only missed this criterion very narrowly, because two of their appointment dates were set at the beginning and at the end of one year instead of two separate years during their ten year follow-up. 103 patients (n=103) were eventually eligible for the overall observation group and the disease activity over time evaluation.

For the division by medication I limited the sDMARDs taken into account for the calculation to methotrexate, leflunomide and sulfasalazine. Furthermore, only patients who consistently received the same pharmacotherapy (sDMARD-monotherapy or combination therapy) throughout the entire observation time of ten years were considered for these statistics so that therapy changes could not distort the results. After applying the criteria the two subgroups included 14 patients (n=14) for the sDMARDs-monotherapy and 11 patients (n=11) for the combination therapy group. I considered a group for the biologic-monotherapy, but dismissed it because of the small sample size of only four patients. I summarised all criteria and groups for the observation group in figure 11.

Figure 11. Assigned groups and inclusion criteria for the observation group



2.3.3 Solution for epidemiologic data and documentation

Evaluating the epidemiologic aspects of the data was a relatively simple task, especially after I had prepared the necessary data for this process properly, which in regards to the high amounts of data was a time-consuming effort, nonetheless. The observations and results from this part of the work are basic descriptive statistics, so I used the function of the same name in the statistics software SPSS version 23 by IBM®. This function provides a few ways of processing the data for description. I chose the frequencies category and had the system calculate the various numbers and mean values presented in chapter 3 for the epidemiologic data. The associated graphs were also created in SPSS. All the provided tables were compiled by me.

2.3.4 Solution for the correlation between DAS and DAI

Another secondary aim of the work was to prove the hypothesis that the disease activity index (DAI) and the disease activity score (DAS), albeit calculated with different formulas, were highly correlated. This was achieved again with the help of SPSS. Before I could use the correlation functions offered by the software though, it was necessary to check if the four scores in question (DAS ESR, DAS CRP, cDAI and sDAI) were distributed normally, because this is the requirement for using the Pearson correlation analysis, which is the standard correlation analysis method offered by SPSS. If a normal distribution is not apparent, it would be possible to apply the rank correlation coefficient by Spearman instead (124).

I looked at this by creating simple distribution curves for each variable where the distribution can be seen immediately. While the DAS ESR was normally distributed, the DAI parameters were not, which is most likely due to their linear scale. Also the DAS CRP did not show a correct normal distribution. I therefore used the aforementioned Spearman coefficient as the fitting method to check the hypothesis. It is also important to note that for this entire process I only looked at the data of visits where all four scores were assessed and reported in RCQM, deleting all data sets from the calculation that missed one or more scores. The graphs that I added to the results of this evaluation were created in Excel®. Moreover, I calculated the main objective of this study by using both the DAS ESR and cDAI separately to additionally see whether I could find any differences between the two scores or not.

2.3.5 Solution for the longitudinal data

Dealing with the data for the main objective was a lot more complicated. I worked on this solution mostly with the help of the book “Applied longitudinal analysis” by Garrett M. Fitzmaurice (Wiley, 2011). In medical statistics there is often the differentiation between cross sectional and longitudinal data. The former refers to data that was measured for a cohort at a single point of time leaving out the aspect of development over time. In this work, however, I dealt with data that was assessed for many individuals at repeated point of times, thus including this factor of time for each patient. A data set like this is referred to as longitudinal data. Such observations of changes over time, both prospectively and retrospectively, have become an important base for studies in the medical field. This also led to the creation of new statistical methods, which were able to deal with this kind of longitudinal data better (125).

In health science the problem with data like this is that for various reasons the repeated measures, in this study the patient visits, are often assessed irregularly at different points of time for each study subject. Longitudinal data like this which is incomplete and/or irregular thus requires complicated modelling so that it can be used in a statistical calculation. I would like to try to explain what that means. There are two factors in this calculation that need to be fitted into the model. That is the time dependence of the repeated measures, which in this case is simply the irregular time periods between the visits, and the fact that the disease activity trend was inconsistent during that time. Both of these aspects are interrelated and additionally the repeated measures are correlated within each study subject. The best way to deal with a data situation like this is to use the method of a linear mixed effects model (122,125). This model calculates these fixed effects and adds random effects into the statistical outcome. It can therefore handle the unbalanced nature of a longitudinal data set like the one I used for this study.

The fixed effects in this model included the parameters that the individuals have in common. In this case that was the assigned groups (see chapter 2.3.1) and that the disease activity trend changed with time (time factor). The implementation of the time component for the irregularly assessed visits into the model, however, required additional modelling. It was necessary to express these trend patterns in form of polynomials or functions of time (122,125). That means that the disease

activity was simply multiplied by the observed time period in the model. The random effects are the variables that unbalance the data. I defined those in the model as the random intercepts and slopes. In simple terms, this means that the random effect was the different starting date and different initial DAS of each individual patient in the cohort. For the covariance pattern I chose the default model of variance components (VC), which is supposed to keep the random effects independent from the fixed effects (126). It is a complex model, but luckily the statistics software handles all of these effects and factors automatically.

After having formulated the linear mixed effects model and considered it to be fitting for the data sets, I applied the model to the longitudinal data and used the Statistical Analysis Software (SAS) in its 9.2 version for this calculation. I could not utilise SPSS this time, because it did not offer a function to implement polynomials into the mixed effects model. Therefore, I had to write a suitable syntax code for the PROC MIXED task of SAS, as the software does not provide a user interface like SPSS. In the code I specified the DAS ESR or cDAI, respectively, as the dependable variable. The fixed effects were the dedicated groups and the time periods in form of the visit dates. The random effect was defined as the intercept. For SAS to calculate the individual course of each patient I had to state the subject variable to be the patient IDs. The statistical procedure I chose for the model was the Chi-squared test and for the results I wanted SAS to additionally offer information about the covariance and variance parameters. The final code can be seen in a simplified form in figure 12.

Figure 12. Syntax code for the mixed effects model

```
PROC MIXED DATA=work COVTEST;
 CLASS ID group;
 MODEL DAS=group time group*time/S CHISQ;
 RANDOM Intercept/TYPE=VC SUBJECT=ID G V;
```

In addition to the statistics, I created associated graphs, again with the help of SPSS. I used scatter plots, because box plots or other graphical methods did not deliver a good visual solution in regards to the data. I considered calculating mean disease activity scores for each observed year to be able to create better box plots, but eventually dismissed the idea, because the scatter plots offered a good visualisation of the interdependencies.

3 Results

3.1 Epidemiologic data and documentation findings

3.1.1 Results for the epidemiologic data

The first epidemiologic question I wanted to answer was how many individual rheumatoid arthritis patients visited the outpatient clinic of the rheumatology department at least once during the time span of mid-2004 (implementation of RCQM) and June 2015 (point of time data was collected). As it can be seen in table 4, the total number of RA-patients came up to 1,839 individuals of which 1,378 (74.9%) were women and 461 (25.1%) were men. Overall, the department registered 23,744 unique visits associated with rheumatoid arthritis during that time. The average number of visits per year was 2,158. I also looked at the average age of the patients and found that it was 59.3 years for the entire collective. Women were slightly older than men with 59.5 compared to 58.7 years. The numbers for the mean age (x̄Age) can also be found in table 4.

Table 4. Number and mean age of patients from mid-2004 to June 2015

	n	%	x̄Age
Women	1,378	74.9	59.5
Men	461	25.1	58.7
Total	1,839	100	59.3

Eventually, I also evaluated how many rheumatoid arthritis patients were treated with biologic DMARDs at least once during their observation time in the outpatient department. I decided to only use those 1,166 patients who had visited the department twice for this calculation. The individual numbers per year included patients who received different treatments at various points throughout their therapy. This means that, for example, a patient who had been treated with a synthetic DMARD in 2005, but was later switched to a biologic in 2006 was included in the numbers of both of those years.

A look at the data revealed that 419 unique patients received a bDMARD or combination at least once. That translates to 35.9% of the patient collective of 1,166 patients. However, I decided to take a closer look at each year and evaluate

the trend of how many patients were prescribed such bDMARDs. In 2004 approximately 23.7% of the RA-patients were treated with biologics. By the end of 2014 that number was already at 43.8%. Table 5 summarises these findings. In order to quickly see if this prescription behaviour in combination with the new disease management concepts might have had an effect on the DAS ESR, I calculated the mean DAS-values for each observed year and contrasted them with the prescription percentages. In 2004 the x̄DAS equalled 3.67 while in 2014 the average DAS dropped to 3.03. The difference ΔDAS was eventually 0.64 points. In figure 13 and 14 you can see these trends.

Table 5. DAS28 and % of patients treated with bDMARDs for 2004 versus 2014

	n	bDMARDs	%	x̄DAS
2004	304	72	23.7	3.67
2014	509	223	43.8	3.03
ΔDAS 2004-2014 = 0.64				

Figure 13. % of RA-patients treated with bDMARDs per year from 2004 to 2014

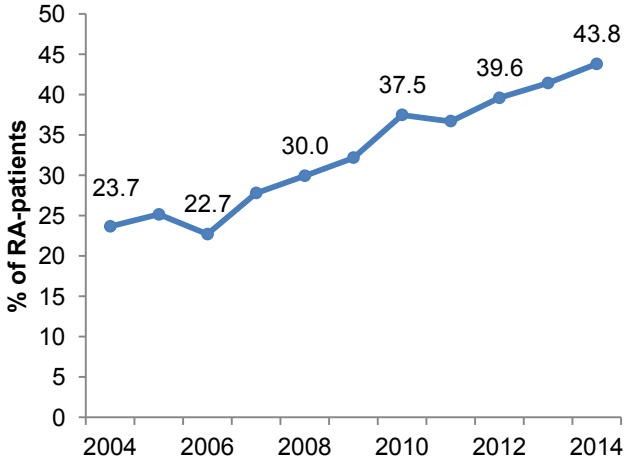
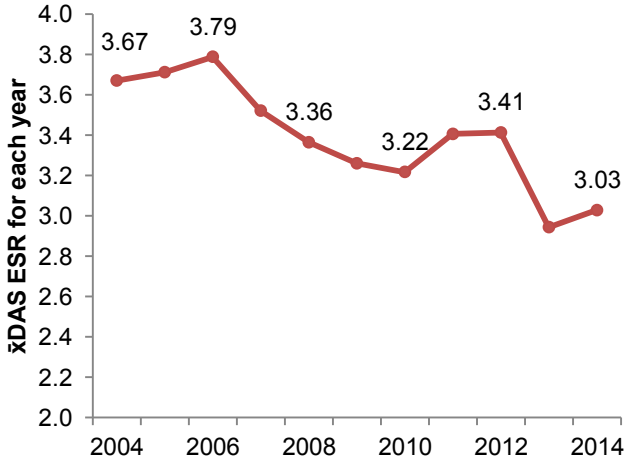


Figure 14. Mean DAS ESR per year from 2004 to 2014



3.1.2 Results for the documentation data

For the secondary objective of evaluating the documentation in RCQM I took a look at how often certain parameters were documented for the patient visits. This included numbers for the DAS28 calculated with ESR and CRP, for the sDAI and cDAI as well as for the health assessment questionnaire (HAQ) and the medication. I found that the disease activity scores were documented averagely in 60 to 70% of the visits with the cDAI coming in most reported at 72.4% and the sDAI lowest at 62.4%. The HAQ on the other hand was reported astoundingly low with only 31.8%. A baseline therapy was recorded in RCQM in 82% of the visits. Table 6 provides a quick overview of these numbers as percentages of the total visits.

Table 6. % of documentation of all RA-patient visits

	n	%
DAS ESR	15,083	63.5
DAS CRP	16,084	67.7
sDAI	14,807	62.4
cDAI	17,193	72.4
HAQ	7,544	31.8
Therapy	19,462	82.0
Total visit number: 23,744		

Additionally, I calculated these numbers for the observation group. It turned out that with this limited rheumatoid arthritis patient collective that was followed up over more than ten years the documentation was slightly higher for all parameters. Having been documented in 41.1% of the visits of this group, the HAQ was noticeably documented more frequently than for the group of all patients. Table 7 shows the results for the observation group.

Table 7. % of documentation of observation group visits

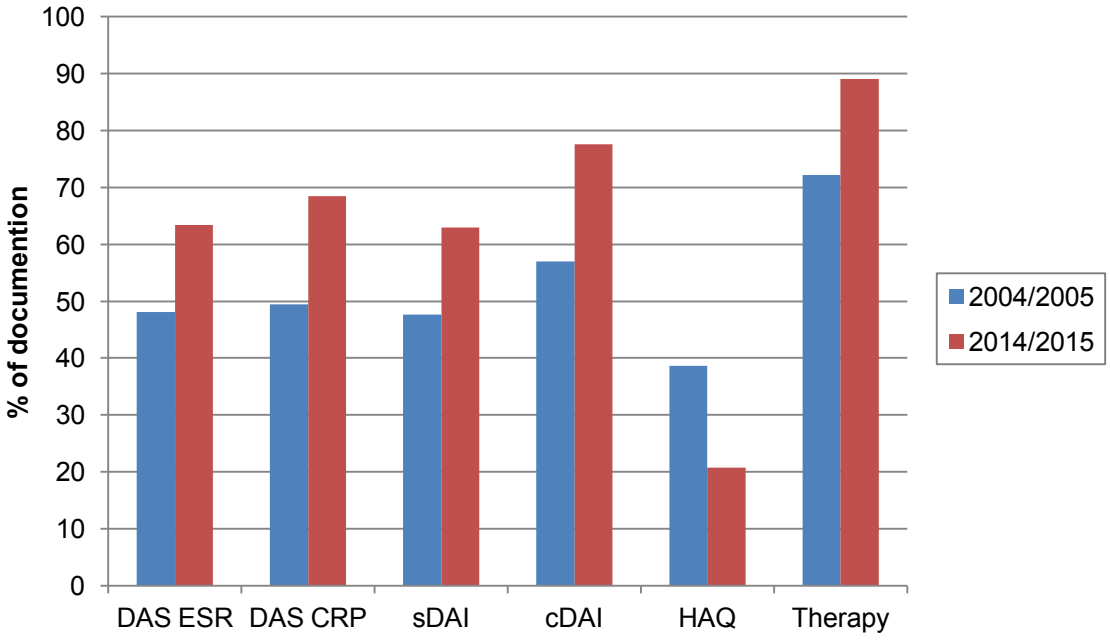
	n	%
DAS ESR	4,737	69.1
DAS CRP	4,873	71.0
sDAI	4,466	65.1
cDAI	5,214	76.0
HAQ	2,814	41.0
Therapy	6,085	88.7
Total visit number: 6,859		

It was also interesting to see if there was a trend in the documentation behaviour of the physicians over the observed ten years, so I decided again to evaluate that question by comparing the data at the beginning right after the implementation of RCQM (2004/2005) and at the end of the observed time period (2014/2015). It became apparent that with the exception of the HAQ the documentation of all parameters was higher in 2014/2015 than it was in 2004/2005. The documentation for the HAQ was low from the beginning but dropped even further. By the end of the observation time it was almost half of the value that it had been in 2004/2005. The biggest increases can be seen for the cDAI and DAS CRP. Numbers for the other scores have also increased significantly. The therapy documentation was again highest and came in at almost 90% in 2014/2015. I included all of these numbers into table 8 and figure 15 offers a bar chart for visualisation.

Table 8. Documentation data of all RA-patients 2004/2005 versus 2014/2015

	2004/2005		2014/2015	
	n	%	n	%
DAS ESR	1,515	48.1	1,924	63.4
DAS CRP	1,555	49.4	2,078	68.5
sDAI	1,500	47.6	1,907	62.9
cDAI	1,795	57.0	2,354	77.6
HAQ	1,215	38.6	629	20.7
Therapy	2,274	72.2	2,703	89.1
3,150 total visits for 2004/2005; 3,034 for 2014/2015				

Figure 15. % of documentation for all patients 2004/2005 versus 2014/2015

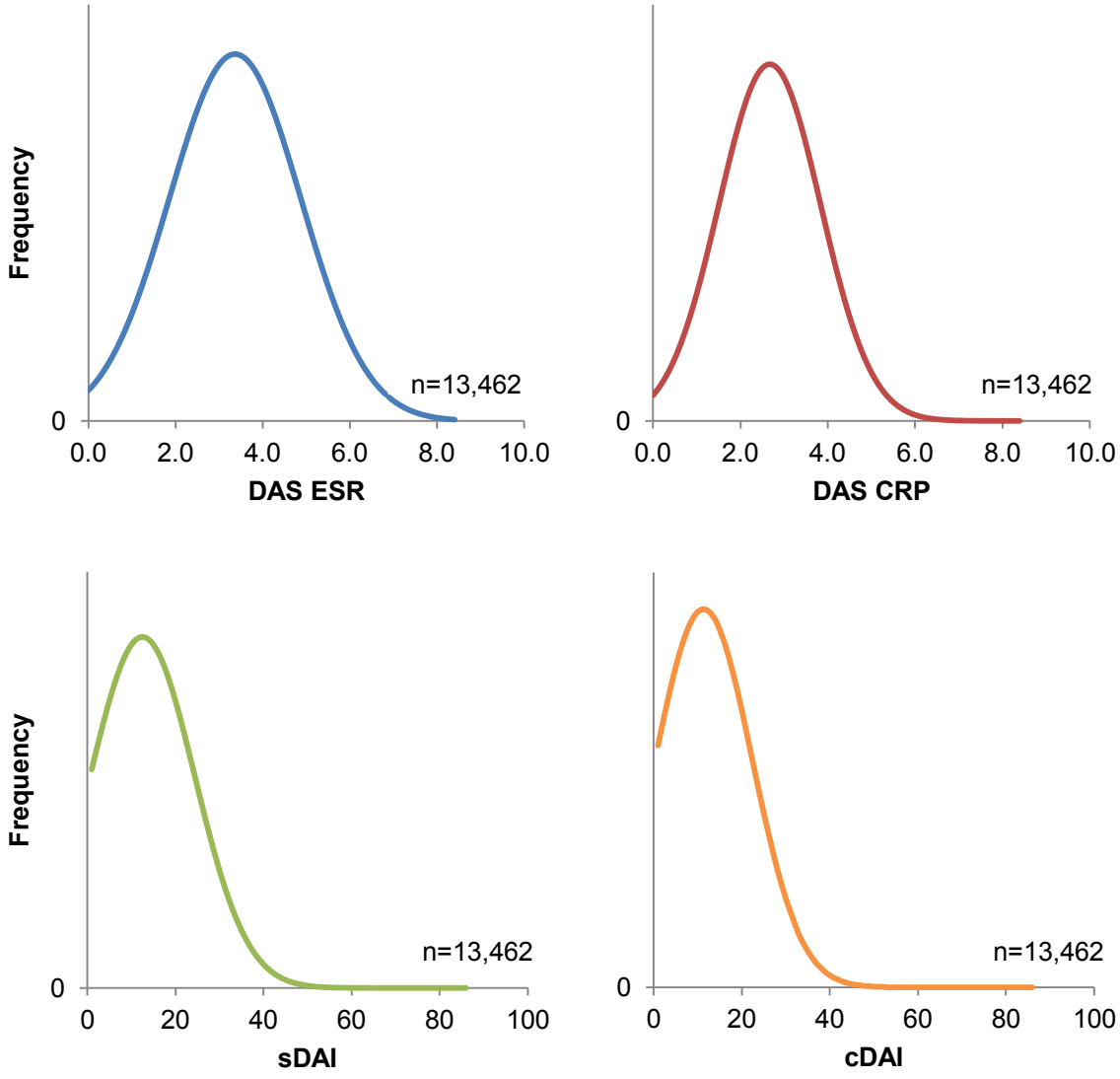


3.2 Correlation of DAS and DAI findings

3.2.1 Checking for normal distribution

Before I could calculate the correlation coefficients it was necessary to check if the variables I wanted to compare in these statistics were normally distributed. This is important in order to determine what method should be used for assessing the correlation, as explained in chapter 2.3.4 of this work. It is important to note that for this model I only considered visits where all four scores (DAS ESR, DAS CRP, sDAI and cDAI) were reported in RCQM. Eventually, I illustrated them as histograms with normal distribution lines and it became apparent that only the DA8 ESR values were distributed normally. You can see the associated graphs in figure 16.

Figure 16. Distribution curves of DAS ESR, DAS CRP, sDAI and cDAI



3.2.2 Correlation coefficients between DAS and DAI

Eventually, I applied the Spearman-Rho procedure to the data. The amount of observed parameters was 13,462 (n=13,462). In the results the coefficients showed strong and significant positive correlation between all disease activity scores. All variables had a correlation coefficient of approximately 0.9, which means that an estimated 90% of the values of one parameter correlated with the other. The strongest correlation was found between the sDAI and cDAI with almost 99%. Interestingly, the lowest result was 86.9% for DAS ESR and cDAI, which is still very high though. The coefficients can be viewed in table 9 and the associated scatter plots in figure 17 and 18.

Table 9. Results of the Spearman rank correlation between DAS and DAI

		DAS ESR	DAS CRP	sDAI	cDAI
DAS ESR	Spearman coefficient	1.000	.895	.885	.869
	Sig. (2-tailed)	.	.000	.000	.000
DAS CRP	Spearman coefficient	.895	1.000	.926	.894
	Sig. (2-tailed)	.000	.	.000	.000
sDAI	Spearman coefficient	.885	.926	1.000	.986
	Sig. (2-tailed)	.000	.000	.	.000
cDAI	Spearman coefficient	.869	.894	.986	1.000
	Sig. (2-tailed)	.000	.000	.000	.
The coefficient ranks from -1 (strong negative) to 1 (strong positive correlation)					

Figure 17. Correlation graphs of cDAI to DAS ESR and DAS CRP

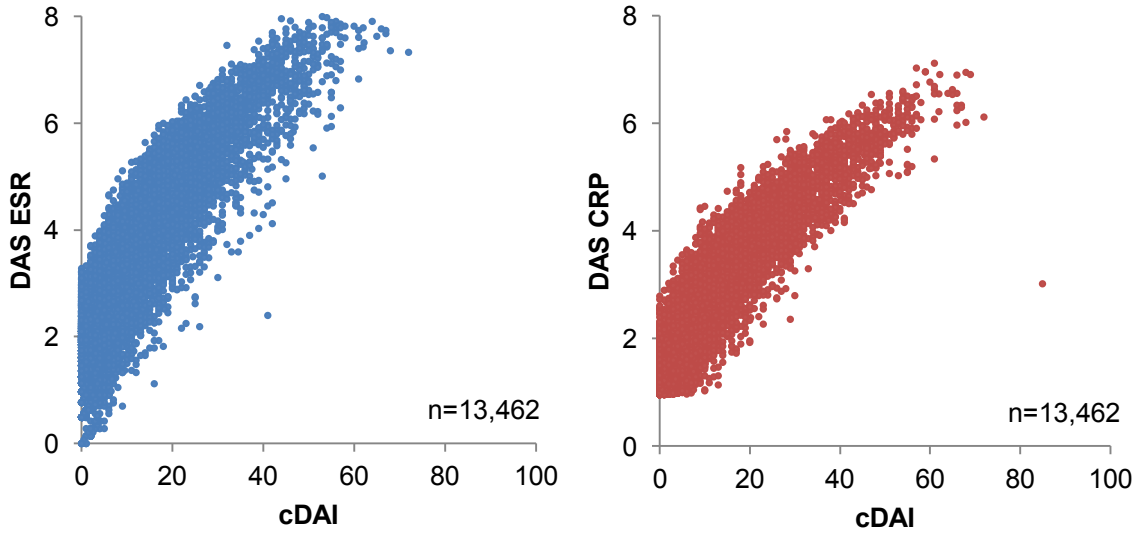
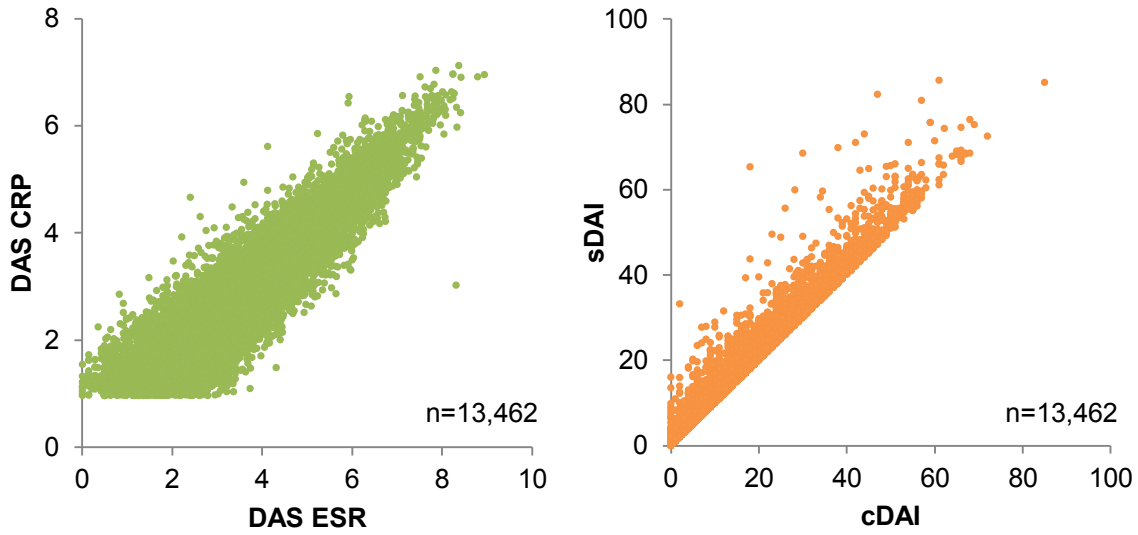


Figure 18. Correlation graphs of DAS ESR to DAS CRP and cDAI to sDAI



3.3 Disease activity versus time findings

3.3.1 Disease activity over time of the observation group

I retrospectively evaluated the disease activity of 103 patients who had been under stringent control from at least 2004/2005 until 2014 (observation group). In figure 11 (chapter 2.3.2) an overview of the various subgroups I formed for these calculations and that are presented in the results can be found. In table 10 I listed the number of individuals and the differences (Δ) between the mean DAS values for each DAS-group at the beginning (2004/2005) and at the end (2014) of the observed time span. The mean standard error was ±0.1 DAS points for all groups. The scatter plots in figure 19 (green dots), 20 (yellow) and 21 (red) are the associated graphs for these results of $Group_{1\text{-}3}$. Each data dot represents one visit and its associated DAS value. Green dots stand for the patients of $Group_1$ (initial low DAS), the yellow dots for $Group_2$ (initial moderate DAS) and the red dots for $Group_3$ (initial high DAS). The graphs also show cubic regression lines of the mean DAS with their according standard errors and DAS interpretation lines at 5.1 (high disease activity), 3.2 (low disease activity) and 2.6 (remission) DAS points.

Table 10. Differences (Δ) of mean DAS 2004/2005 versus 2014 for $Group_{1\text{-}3}$

	n	2004/2005	2014	Δ
$Group_1$	51	2.9 (±0.1)	3.0 (±0.1)	+0.1
$Group_2$	32	4.5 (±0.1)	3.2 (±0.1)	-1.3
$Group_3$	20	5.4 (±0.1)	3.0 (±0.1)	-2.4

Figure 19. DAS ESR trend over time of $Group_1$ (n=51)

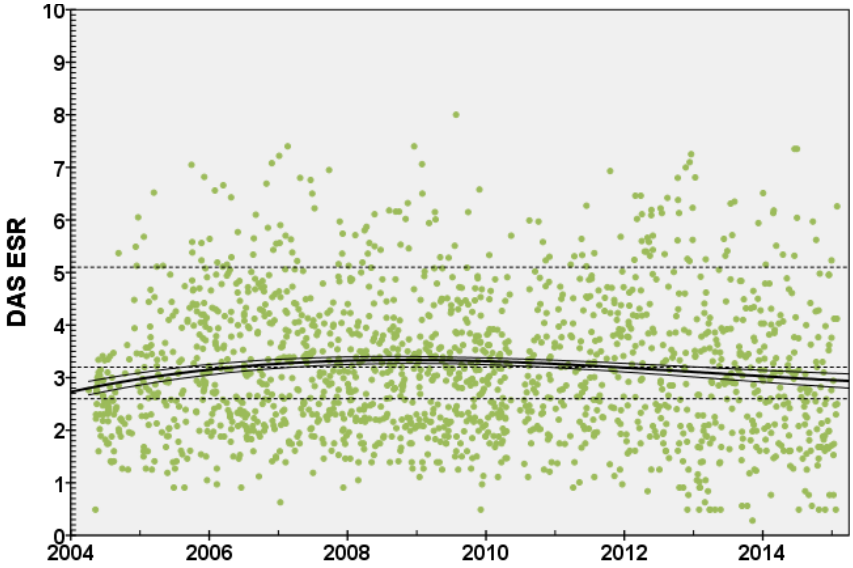


Figure 20. DAS ESR trend over time of $Group_2$ (n=32)

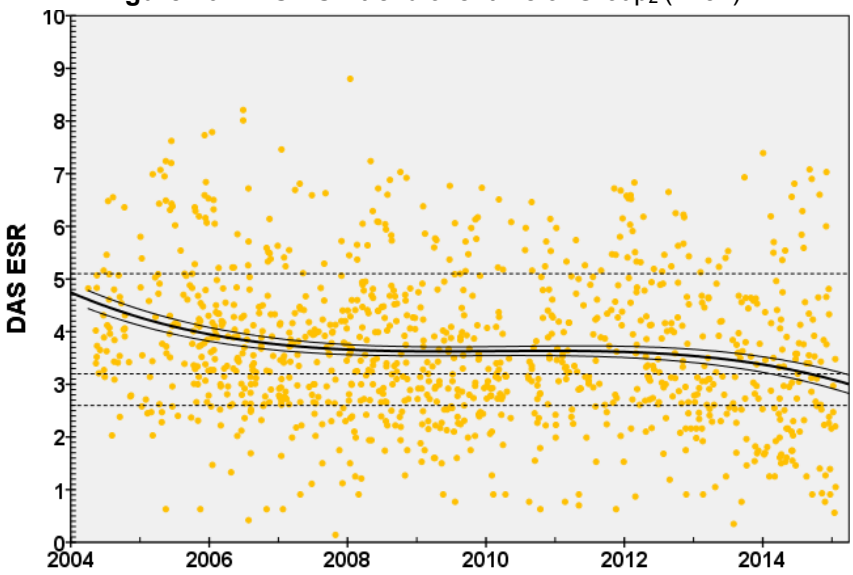
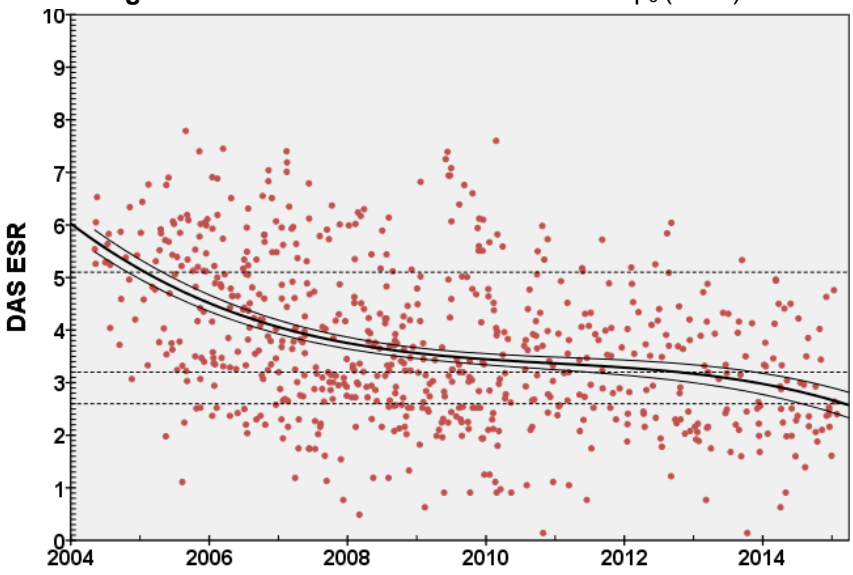


Figure 21. DAS ESR trend over time of $Group_3$ (n=20)



For $Group_1$ the DAS values remained at approximately the same level around the 3.2 mark, indicating continuously low disease activity. $Group_2$ and $Group_3$, however, showed a visible decrease of disease activity over time. These findings correlate with the basic principles of therapy (tight control, Treat-to-Target) for each of these groups and the change in prescription behaviour of the physicians outlined before. Additionally, I would like to show the results for the statistical evaluation of the linear mixed effects model for the subgroups of the observation group. A total of 3,386 visits (n=3,386) were included with 1,650 for $Group_1$, 1,065 for $Group_2$ and 671 for $Group_3$. The variable "*t*" stands for the time component calculated into the model. In table 11 I summarised the statistical results. They can be interpreted that all subgroups had a significant decrease of disease activity. When considering $Group_1$ to be the baseline, $Group_2$ and $Group_3$ showed a stronger decrease in comparison. The random effect (intercept) was also significant, implying that there was a wide variety of different disease courses over time in the patient collective.

Table 11. Outcome of the linear mixed effects model for $Group_{1-3}$

Effect	Estimated Parameter	Standard Error	p-Value
Intercept	3.58079	0.4801	<0.0001
$tGroup_1$	0	.	.
$tGroup_2$	-0.00020	0.000041	<0.0001
$tGroup_3$	-0.00052	0.000051	<0.0001
Time t	-0.00004	0.000026	0.1298
Residual	1.2825	0.03166	<0.0001

n=3,386 visits; t = time component

3.3.2 Disease activity over time by gender

The data material of the department gave me the opportunity to evaluate if there were differences in the disease course of women and men and if so what those would look like. I therefore split the observation group by gender resulting in 21 individuals for the male groups ($Group_{1M-3M}$) and 82 for the female groups ($Group_{1F-3F}$) and created scatter plots accordingly. These can be seen in figure 22 and 23. The most striking difference that I found was that with men the disease activity does not decrease as much as with women after the initial therapy-induced bend. In the male moderate ($Group_{2M}$) and high activity group ($Group_{3M}$) the

disease activity remained at the 3.0 mark after some time. In the low activity group ($Group_{1M}$) the activity even increased noticeably at the end of the course.

The women, on the other hand, showed the same patterns that the non-divided group had already shown as presented in the chapter before. The scatter plot for the female high disease activity group ($Group_{3F}$) even shows the pattern of a negative correlation between the DAS and the time. The graphs indicate though that the sample sizes for the male groups may be too small to make decisive statements about them. This is visible as the intervals of the standard error are larger than in the female groups. However, the general trend of therapy success is also apparent when looking at the course of disease activity distinctively in men.

Figure 22. DAS ESR trend over time of $Group_{1F-3F}$ (Women)

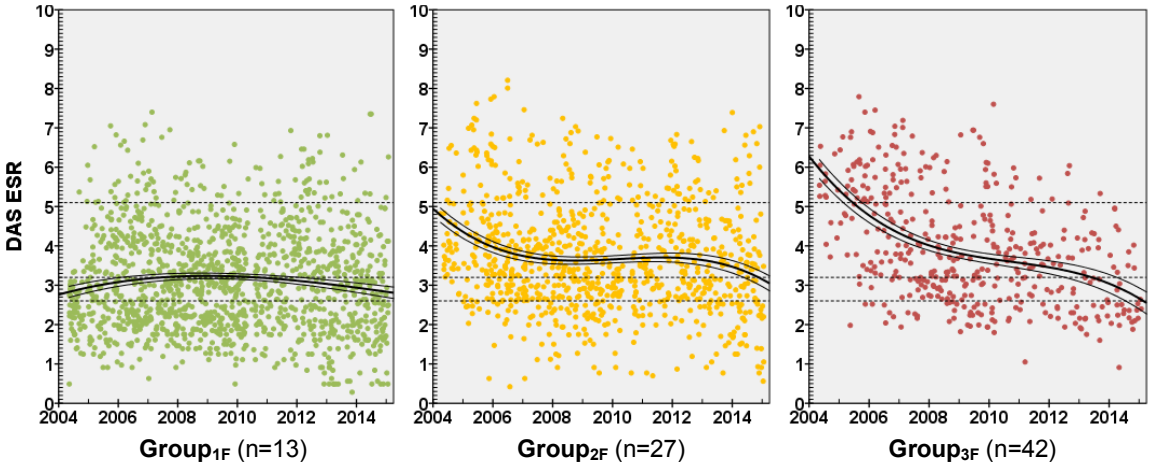
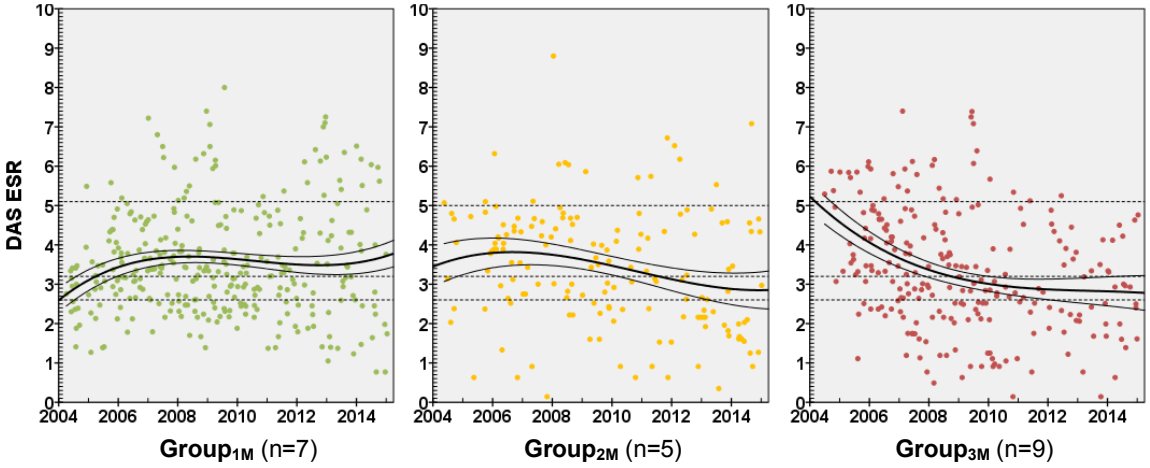


Figure 23. DAS ESR trend over time of $Group_{1M-3M}$ (Men)



I applied the linear mixed effects model to the separate gender groups as well and found that all the statistics for each of these groups were similar to the model for the overall observation group. All p-values were below 0.05, which means that the decrease of disease activity was significant when looking at women and men

independently. The intercept, however, showed a relatively weak significance of p=0.025 for the male group, which again highlights that the male sample was less variant than the female group's sample. In this calculation a total of 719 visits were included for the male group (n_M=719; nG_{1M}=322; nG_{2M}=157; nG_{3M}=240) and 2,667 for the female group (n_F=2,667; nG_{1F}=1,328; nG_{2F}=908; nG_{3F}=431). All the resulting numbers from these statistics are summarised in table 12.

Table 12. Gender-specific outcome of the mixed effects model for $Group_{1-3}$

Effect	Estimated Parameter	Standard Error	p-Value
$Intercept_F$	3.9944	0.5206	<0.0001
$Intercept_M$	2.9341	1.1974	0.0247
$tGroup_{1F}$	0	.	.
$tGroup_{2F}$	-0.00016	0.000044	<0.0001
$tGroup_{3F}$	-0.00054	0.000061	0.0002
$tGroup_{1M}$	0	.	.
$tGroup_{2M}$	-0.00036	0.000110	0.0010
$tGroup_{3M}$	-0.00057	0.000101	<0.0001
Time t_F	-0.00005	0.000028	0.0517
Time t_M	0.000033	0.000065	0.6058
$Residual_F$	1.2376	0.03443	<0.0001
$Residual_M$	1.4481	0.07770	<0.0001

n_F=2,667 visits; n_M=719 visits; t = time component

3.3.3 Disease activity over time of the collective cohort

I decided to run the linear mixed effects model on the larger patient group, in order to check back if there were noticeable differences when looking at the collective cohort of 1,166 patients compared to the observation group. This was the only purpose this short evaluation should serve. I included all patients who had at least two visits with a documented DAS at the outpatient clinic from 2004/2005 to 2014 into the calculation. This larger collective was split again into the three subgroups depending on the disease activity level upon the patient's first reported visit. Overall, I found 14,816 visits of 1,166 individual patients that fell under these criteria and fitted them into the model. Broken down into the DAS-groups this accounts for 5,929 visits for the first group (486 patients), 4,928 for the second group (397 patients) and 3,959 for the third group (283 patients). The results can be found in table 13. The DAS-subgroups are labelled $Group_{1E-3E}$ there.

Table 13. Outcome of the mixed effects model for the collective cohort

Effect	Estimated Parameter	Standard Error	p-Value
$Intercept_E$	3.2343	0.6149	<0.0001
$tGroup_{1E}$	0	.	.
$tGroup_{2E}$	-0.00023	0.000024	<0.0001
$tGroup_{3E}$	-0.00052	0.000026	<0.0001
$Time\ t_E$	-0.00001	0.000015	0.3989
$Residual_E$	1.2728	0.01538	<0.0001

n=14,816 visits; t = time component

As expected, in comparison to the observation group this more extended group showed the same statistical significance for the decrease of disease activity. All p-values measured below 0.0001 indicating a strong significance. I also looked at the numbers for women and men separately, but couldn't find any noticeable differences to the observation group either. For the gender specific groups I will thus not provide another separate table. I also forgo graphs for the larger group, because I think they are not suitable for this highly imbalanced data set.

3.3.4 cDAI observations for disease activity over time

The results of the correlation statistics showed that in the cohort the DAS ESR and cDAI activity scores were highly correlated by approximately 87 per cent. It was therefore interesting to see if there were different results when applying the cDAI instead of the DAS ESR in the statistical and graphical solutions. Contrary to the DAS the cDAI does not include the inflammation parameters CRP or ESR in its calculation. I evaluated this question with exactly the same methods that I used for the DAS ESR models, including the division into subgroups. In table 14 I outlined the sample sizes and mean cDAI differences from 2004/2005 to 2014 for the three groups. Figure 24, 25 and 26 show the associated scatter plots that use the same colour pattern as before. The interpretation lines are adapted to the cDAI scale though.

Table 14. Differences (Δ) of mean cDAI 2004/2005 versus 2014 for $Group_{1-3}$

	n	2004/2005	2014	Δ
$Group_1$	51	9.5 (±0.1)	11.5 (±0.1)	+2.0
$Group_2$	32	18.5 (±0.1)	12.0 (±0.1)	-6.5
$Group_3$	20	24.0 (±0.1)	9.5 (±0.1)	-14.5

Figure 24. cDAI trend over time of Group$_1$ (n=51)

Figure 25. cDAI trend over time of Group$_2$ (n=32)

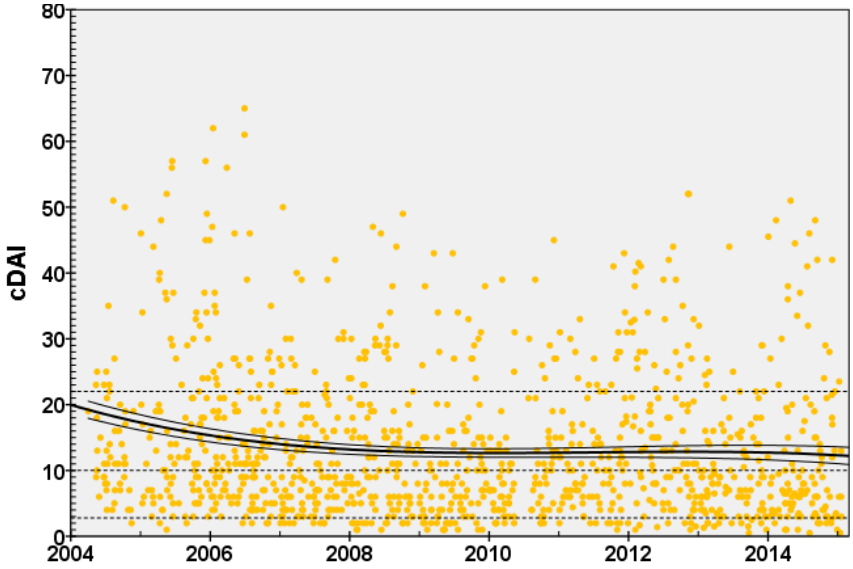
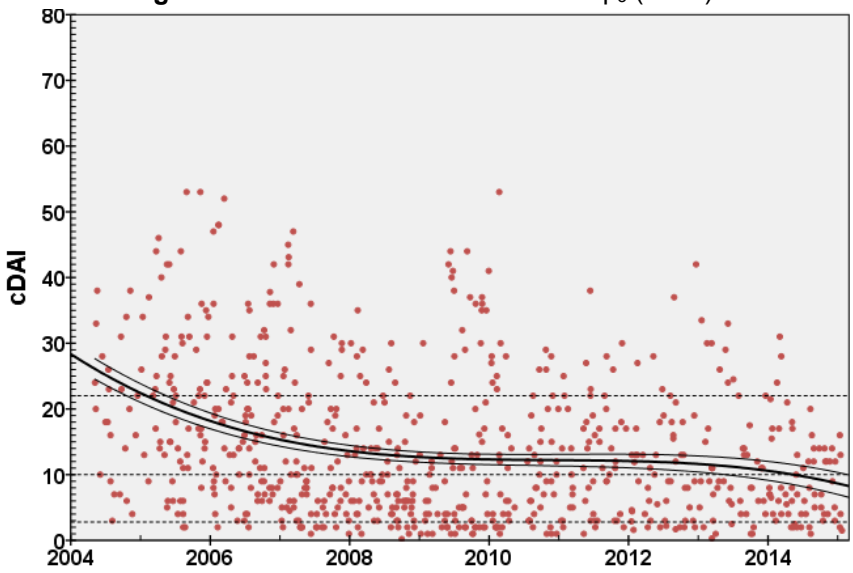


Figure 26. cDAI trend over time of Group$_3$ (n=20)



The general patterns and results that can be seen in the table and figures resemble those of the DAS ESR calculations. There are no major discrepancies noticeable between the separate results of the two scores. Small differences include that with the cDAI the disease activity is generally estimated slightly higher than with the DAS and that $Group_1$ (low initial disease activity) does not show a decrease trend by the end of the observed time with the cDAI. However, I do not consider these findings to have a significant meaning. The numbers from the statistical evaluation can be found in table 15. They are higher than the DAS numbers, because of the more extended cDAI value scale. Moreover, higher documentation of the cDAI is the reason why the sample size in this model was larger. Other than that no irregularities could be found and all p-values were highly significant.

Table 15. Mixed effects model results for the observation group with cDAI

Effect	Estimated Parameter	Standard Error	p-Value
Intercept	11.5802	3.5194	0.0014
$tGroup_1$	0	.	.
$tGroup_2$	-0.00139	0.000303	<0.0001
$tGroup_3$	-0.00334	0.000366	<0.0001
Time t	-0.00010	0.000189	0.5915
Residual	81.9547	1.9023	<0.0001
n=3,816 visits			

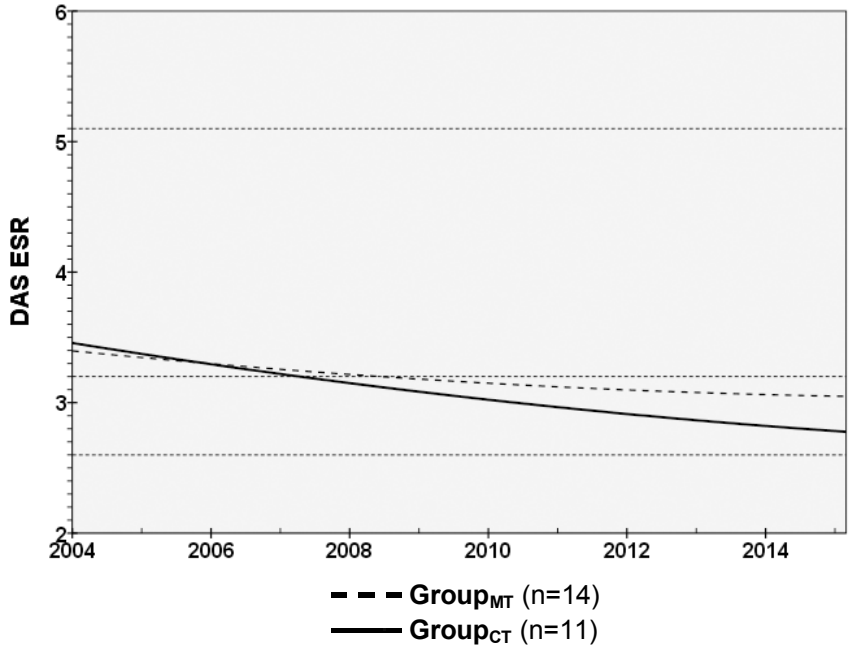
3.3.5 Disease activity over medication

As a last side objective, I wanted to explore the hypothesis that a combination therapy of sDMARDs with biologics shows a better therapy outcome than the sDMARDs-monotherapy. I therefore scanned the observation group further and found 25 individuals who did not undergo a significant change in their medication plan throughout the observed time period of ten years. I divided these patients into two groups according to their therapy plan. $Group_{MT}$ (n=14) consisted of patients who received a synthetic DMARDs monotherapy (MT). These sDMARDs included methotrexate, leflunomide and sulfasalazine. $Group_{CT}$ (n=11), on the other hand, was comprised of patients with a combination therapy (CT). The bDMARDs that were included can be found under chapter 1.2.6 in table 3. I did not include

patients who were treated with other drugs and there was no further division of the groups according to initial DAS.

In figure 27 you can see the curves of the disease activity trends for both groups. The dashed line (- - -) represents the sDMARDs-monotherapy group ($Group_{MT}$) and the solid line (——) stands for the combination therapy group ($Group_{CT}$). I also added again the three dotted lines to the charts that indicate the 5.1, 3.2 and 2.6 DAS-marks for an easier interpretation of the disease activity. For the sake of simplicity I erased the data dots from the graphs and did not include the standard error intervals of the curves. For a more distinctive visualisation I additionally narrowed the DAS-scale on the y-axis down to only show the area of 2 to 6.

Figure 27. DAS ESR trend over time of therapy-groups



As it can be seen in the graph, both therapies reduced the disease activity noticeably. The mean DAS at the beginning of the observed period was approximately the same for both groups at 3.5 points. While the combination therapy was able to lower this value to 2.7, the synthetic monotherapy lowered it down to 3.0 DAS points. It is therefore apparent that in this patient collective the combination therapy reduced the mean DAS stronger than the sDMARDs-monotherapy by 0.3 points. However, the statistical evaluation did not show that the decrease was more significant in the CT-group than in the MT-group. The small sample size might be a reason for this. All the numbers and statistical results for this observation are summarised in table 16 and 17.

Table 16. Differences (Δ) of mean DAS for therapy-groups over time

	n	2004/2005	2014	Δ
sDMARDs MT	14	3.5 (±0.2)	3.0 (±0.2)	-0.5
Combination	11	3.5 (±0.2)	2.7 (±0.2)	-0.8

Table 17. Mixed effects model results for therapy-groups over time

Effect	Estimated Parameter	Standard Error	p-Value
Intercept	4.4201	0.9462	0.0001
tsDMARDs MT	0	.	.
tCombination	-0.00006	0.000070	0.3910
Time t	-0.00007	0.000051	0.1816
Residual	0.8172	0.04791	<0.0001

n=609 visits; t = time component

4 Discussion

4.1 Discussing epidemiology, documentation and correlation

4.1.1 Evaluation of epidemiologic results

Rheumatoid arthritis therapy is one the major parts of medical routine at the rheumatology outpatient department. In the year 2014 2,040 visits by 625 individual rheumatoid arthritis patients were registered there. That would translate to approximately ten RA-patients coming to the outpatient clinic on a normal working day. It is interesting that the number of patient visits has not changed significantly over the last ten years; in 2005 the clinic saw 699 individual patients with 1,976 visits. A rise of the incidence of the disease, mostly caused by environmental factors, is suggested by several sources (18,127), though. I could not find signs of a noticeable increase of patients at the rheumatology department of the Medical University of Graz, but this might be, because patients are followed up increasingly often outside of the hospital at their general practitioners.

As mentioned before, RA is a disease that predominately affects women. It is well-established that the ratio between women and men in rheumatoid arthritis patients is 3:1 (12,128). Looking at the results in this work, I can say that for our department the patient collective matches this ratio almost exactly with 74.9% female and 25.1% male RA-patients who visited the outpatient clinic over the last ten years. It is not yet fully understood where this discrepancy comes from, but it might be linked to female hormones. Studies have shown that the gender gap among RA-patients is especially striking in the age group prior to the menopause (until 50 years of age) where the women-men ratio is 5:1 (128–130). After the age of 50 the incidence for both genders is much closer. Another possible factor that plays a role in this case might be that women generally seek more medical attention than men (131). In rheumatoid arthritis, however, we know that women suffer from more severe courses of the disease (132), which would naturally lead female RA-patients to consult with their doctors more often. On all accounts, with the data at hand I can clearly confirm that women are more often affected by RA than men.

Looking at the mean age of the patients, I found out that with approximately 60 years it lay at the end of the suggested main age range of 30 to 60 years (1), indicating that the patient collective was generally older than the average. Women were slightly older than men by 0.8 years on average, which is not a large difference. RA is prevalent in all age groups with juvenile and late onset forms, which I could see in our data as well. Scientific findings suggest that the age of the patient, especially at the onset of rheumatoid arthritis, might have a strong influence on the course and severity of the disease (133,134). However, the studies I could find dealing with this question were from the early 1990s. I consider it therefore interesting for the future to evaluate our patient cohort more thoroughly in regards to age. The data would definitely allow such a study.

An important epidemiologic aspect of the patients Professor Graninger and I wanted to evaluate was the number of patients who were treated with biologics (bDMARDs) in the department, because this would also deliver information about how the therapeutic behaviour of the physicians has changed during that time in terms of prescriptions. Biologics are new pharmaceutical agents that have become more popular in RA-therapy over the last few years due to their more targeted approach in the treatment of the disease. Observing the prescription trend in our patient data, the increase of the percentage of patients treated with bDMARDs was tremendous. In the year 2004 this percentage was 23.7% of all patients. By the year 2014 that number has already risen to 43.8%, which means that the amount of biologic prescriptions has almost doubled throughout the decade. Beneficial to that development was certainly that the national healthcare providers in Austria have become more cooperative in approving and financing these drugs.

The majority of these bDMARDs-treated patients at the department were treated with a combination therapy consisting of at least one biologic and one synthetic DMARD, such as methotrexate or leflunomide. This is important, because recent data show that the combination therapy results in a better outcome, which will be discussed later on. From the data, I calculated that a biologic monotherapy was registered in 17.8% of all patient visits compared to 32.2% for the combination therapy. I concluded that the combination therapy in general had a higher approval in the department than the monotherapy. For comparison, in other centres approximately 30% of the patients received a monotherapy (135).

4.1.2 Evaluation of documentation results

Another purpose of this work was to see if the documentation in RCQM was carried out thoroughly and professionally. During the last ten years the team responsible for the outpatient clinic of the Medical University of Graz included the same four rheumatology specialists and one or two alternating residents who were in training. These doctors learned how to the use the software mostly by themselves.

According to the data, a disease activity score was assessed and documented in RCQM at 60 to 70% of all reported visits of rheumatoid arthritis patients during the observed time period. I could not obtain such documentation numbers from other centres, but I believe that the missing 30 to 40% are made up by quick follow-up visits where a physical examination is not needed. These visits only serve the purpose of e.g. quickly assessing the patient's reaction to a treatment change or notifying the patient of their blood test results. The data also revealed that such visits often occur right after a visit with actual activity documentation. This is also backed up by the data of the observation group where the documentation was generally more complete as a result of the more thorough monitoring of that group.

The apparent discrepancy between the DAS ESR and DAS CRP documentation is also easily explainable. Testing the ESR usually takes longer than the CRP blood tests in the hospital's laboratories. That is why the ESR results often come in later than the CRP levels of the patient and are then not reported into RCQM. The ESR is, however, documented in the hospital's information system MEDOCS. A later transfer of the data to RCQM would be very time-consuming. It is therefore not practical and thus not performed at the department. The discrepancy is rather small though and the problem should be solved with the next version of RCQM, which is supposed to have automatic synchronisation with MEDOCS.

More interesting is the very low documentation of the health assessment questionnaire (HAQ) in the department. In 2014/2015 it was reported in only 20% of all patient visits. This percentage almost halved in comparison to the time of the RCQM implementation where apparently the enthusiasm for the test was much higher. The HAQ itself is a well-thought-out tool to evaluate the restraints a patient experiences from the disease in daily life and would have also been helpful for supporting the findings in this work and for further investigating our objectives. A

reason for the low documentation of the HAQ might be the relatively high time and patient effort necessary for its completion.

The three page questionnaire for RA consists of eight main parts with several subquestions concerning the restraints in daily life. Each answer is awarded points that are eventually added up for the final result of the test (136). It is thus not possible for the HAQ to be assessed during the doctor-patient visit due to time limitation. That is why the test is supposed to be filled out alone by the patients during their waiting time, but for many elderly patients this is too difficult without help. Moreover, while the test can give an overview of the patient's quality of life, it has almost no clinical significance for the patient's treatment plan, which is oriented mostly by the disease activity scores. This situation apparently led to the neglect of the test throughout the years and because of the general lack of time and capacities in the hospital routine this might not change in the near future.

For the department it was also interesting to see if the documentation in RCQM has increased after its implementation. I therefore compared the numbers from the years 2004/2005 to 2014/2015 and the results showed that the documentation was indeed higher by the end of the time period. I already mentioned the numbers for the HAQ. For the disease activity scores and therapy the percentages were higher by 15 to 20 per cent points in 2014/2015 than they were at the beginning of the use of RCQM. This shows that the implementation of the software worked well and the physicians use it in their daily routine. I can confirm this also from my observations when I visited the outpatient department. All physicians there, regardless of their medical position, were well-trained in using the software and thoroughly documented all findings. The patient assessment was performed professionally and according to the standard of procedure in place at the department.

My personal experience with RCQM was mostly positive. I think the system clearly makes the assessment of rheumatology patients easier and allows a better handling of all the information. Overall, it became apparent that the programme was developed by physicians. The interface is very intuitive for a medical software like this with a few exceptions of course, such as the missing synchronisation with MEDOCS or the complicated handling of printing documents with the software. These flaws should be tweaked with the next version of RCQM, though.

4.1.3 Evaluation of correlation between DAS and DAI results

The two inflammation parameters erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be assumed to correlate well with each other. That correlation can be variable and dependent on the disease and form of infection, leading to discordance between the two measures (137). Concerning rheumatoid arthritis it is established though that CRP-levels correlate highly with ESR (138,139). There is, however, an important difference between both parameters in RA-patients. CRP reflects acute phases of the disease better than ESR. On the other hand, ESR also mirrors the activity of immunoglobulins and rheumatoid factor and can therefore express disease activity more accurately (138). The correlation I calculated for our patient data between the DAS ESR and DAS CRP scores accounted to approximately 90%. This led me to the conclusion that with our data a high correlation between these two scores can be confirmed.

Our goal, however, was to evaluate how the clinical disease activity index (cDAI) would perform in comparison to the gold standard of DAS ESR, considering that the cDAI does neither include the measurement of CRP nor the ESR. A study conducted in Hungary even suggested that because it does not take acute reactants into account the cDAI would outperform the DAS ESR in certain cases, especially during remission (140). Our data showed that 86.9% of the documented cDAI scores correlated with the reported DAS ESR, which is a very high percentage. Other recent studies suggest similarly high numbers (141,142). Despite these results, I found that the correlation between the cDAI and DAS ESR was the lowest of all activity scores but only by a few per cent. I considered this discrepancy not relevant enough to change my assumption on the matter and concluded that the correlation between the two scores is excellent, proving the hypothesis made before to be true.

Additionally, I decided to evaluate the main objective with the DAS ESR as well as the cDAI and performed the statistical model for the disease versus time objective with both scores. The visualisation via scatter plots did not reveal significant differences. All disease activity patterns of the observed groups became equally apparent with both measurements. There was only the small difference that the cDAI slightly overestimated the disease activity in comparison to the DAS ESR, which would imply that the scale for the cDAI might be set too low. However, this

discrepancy was not significant, but it would be interesting to investigate it more thoroughly in the future. In the statistical evaluation the results from the cDAI calculations were equally significant in all groups. These findings let me conclude that using the cDAI is sufficient for assessing the disease activity of RA in daily clinical routine or a general practise. However, it is, of course, recommendable to (additionally) evaluate the DAS ESR when possible.

4.2 Discussing change in disease activity and therapy outcome

4.2.1 Evaluation of disease activity versus time results

It was our main objective to scrutinise the disease activity of rheumatoid arthritis patients depending on the therapeutic behaviour of the physicians, including therapy concepts and prescriptions. This question was interesting to us, because of the rapid treatment advances of the last ten years. In the early 2000s, the tight control concept as well as the emergence of biologic agents started to shape a new approach to RA-therapy. The treatment of RA evolved to be more targeted and patient-centred, which was one of the reasons for the creation of RCQM. Throughout the years, the tight control concept became the standard for RA-therapy, eventually leading to the formulation of the simplified Treat-to-Target and EULAR guidelines I presented before. However, it should be noted that the new therapy concepts were not introduced universally at one point, but much rather came into effect gradually over the years. The data I used in this work covered precisely this decade and I would now like to look into the findings from the study.

The most important goal of RA-therapy today is to maintain a low level of disease activity. This prevents joint destruction and allows patients to enjoy more functionality in their daily lives (143). These effects were not only proven by low disease activity scores (113,114), but also by showing how patients with continuously low RA-activity present with less detectable joint damage in radiologic imaging (144). We wanted to see if the department had been able to achieve this goal of RA-treatment with its long-time patients. In order to do so, I looked at the longitudinal disease activity of 103 patients over ten years and found that with the therapeutic behaviour in the department the mean DAS of the patients was indeed reduced.

In all observed groups the DAS ended up at the 3.2 mark or lower by the end of the observed time span. Under chapter 3.3.1 I summarised these results and showed the associated graphs. It became clear that the therapy concept in place at the department showed to be effective, especially with patients who suffered from a high initial disease activity. This high DAS group even experienced an impressive mean DAS decrease of 2.4 points during the last ten years and not a single one of these patients presented with a DAS higher than 5.1 by the end of the observed disease course. This pattern was also apparent in the moderate disease activity group but the decrease was not as strong. In the low disease activity group not much change was detectable and the patients' mean DAS remained around the 3.2 mark throughout the observed time. It is therefore debatable if these patients might be treated not tightly enough. There is also the question if the effect of a more intense therapy with all its side effects and restraints benefit these patients and their function enough to make a tighter therapy justifiable. A more thorough look into this matter would be necessary to answer this.

Overall, the trend patterns of disease activity I found in the observation group allowed me to conclude that the gradual implementation of the tight control therapy concept in combination with new pharmaceuticals, which I will discuss later, had a positive effect on the average disease activity and can therefore be regarded as a beneficial concept in RA-treatment. The hypothesis made in the introduction that the change in therapeutic behaviour of the physicians in the last decade boosted the therapy success can therefore be confirmed.

Eventually, the data gave me the opportunity to break these results down by gender in order to see if I could find differences in the response of the disease to therapy between women and men. It is generally believed that women suffer from a more severe course of RA more often than men, which is not a result of women over-reporting symptoms (132,145). To provide a quick overview, I looked at our observation group and found that 51.1% of the female patients started with a high disease activity against 42.8% in the male group. When the moderate group is added, the numbers come up to approximately 84.1% of women and 66.7% of men falling under the moderate and high disease activity category. I noticed that women also indeed started with a higher mean DAS than men (6.0 against 5.2).

This data thus confirms the aforementioned statement, but it should be noted that this is of course only a simple approach to this question.

I also observed the disease course for each gender group and saw that men showed a slightly diverging pattern from women. After the initial decrease of disease activity, which was the same for all patients, men presented stagnation or even increase over the following years. As an explanation for this I thought that men may show a weaker compliance after the treatment has resulted in positive effects, but this would be contrary to the fact that all of these patients turned up to regular check-ups. Another reason could be that some of the male patients refused to intensify their therapy according to tight control. I can also not exclude that the effect comes from the small sample size of the male group, albeit showing statistical significance though. In any way, to further investigate the effect it would be necessary to ask the patients directly about it. I consider the effect to be only very little though so that this is not an important matter for the immediate future. Apart from these specific gender diversities, I could not find any more noticeable differences between women and men in this evaluation.

4.2.2 Evaluation of disease activity versus medication results

With our data we initially planned to formulate a second main objective, in which we wanted to scrutinise the effects of biologics and the disease response to them. Unfortunately though, we were dealing with retrospective data where the patients underwent frequent therapy plan changes throughout their medical record, which is actually very positive in regards to the tight control and T2T concepts described before, but this confounder would impede a clear statement about the effects of biologics in RA-therapy. A prospective study design would therefore be required for an objective like this.

However, I thought this was too interesting to just dismiss the idea. I therefore looked more closely into the data and found 25 patients out of the initial 103 who did not see a major therapy change over the observed ten years. This means that looking into the records their treatment had not been changed from a synthetic DMARD to a biologic monotherapy or combination therapy or vice-versa. They received the same therapy during this period. I was able to form two groups, one sDMARDs-monotherapy and one combination therapy group. A biologic

monotherapy group was dismissed, because I could only find four patients who would have been eligible to that group.

It is generally assumed and acknowledged that biologics show a better outcome than methrotrexate, leflunomide and other such synthetic disease-modifying drugs. Study results from the Swiss SCQM study group back this assumption up (146,147). The data from Switzerland showed that patients treated with biologics had a lower DAS outcome and better HAQ scores. Moreover, it turned out that these patients presented with less joint damage in radiologic imaging. Another conclusion of the Swiss researchers was that the combination of biologics and sDMARDs leads to an even better outcome in comparison to a biologic or sDMARDs-monotherapy (148). This is also backed up by a variety of other studies, in which colleagues dealt with this subject (149–151).

For our smaller group the line graph in chapter 3.3.5 alludes to a trend that biologic combination treatment reduces the DAS stronger than a monotherapy of sDMARDs. The combination lowered the DAS by 0.3 points further down than the monotherapy. I could not prove these observations to be statistically significant though, but I think that the visual pattern allows for making this conclusion. Additionally to that, as described in chapter 3.1.1, I looked at the larger cohort and contrasted its mean DAS development with the prescription rate of biologics. With these graphs it becomes apparent that the higher percentage of bDMARDs-prescriptions might have a positive influence on lowering disease activity. While this rate almost doubled throughout ten years, the mean DAS decreased by an average 0.64 points.

I consider these findings to be significant enough to conclude that biologics have a beneficial effect on reducing the disease activity in comparison to sDMARDs. Their prescription in combination with the tight control therapy concept is the preferable therapeutic behaviour, most notably in patients with higher disease activity. However, it is important to always weigh in the benefits and undesired side effects and restraints for the patients that come with a more intensified therapy. Eventually, the last hypothesis I proposed in the introduction about how biologics positively influence the outcome of RA-therapy, especially in combination with a synthetic DMARD, can also be considered true.

4.3 Key messages and conclusion

During the course of this retrospective study we formulated and explored several questions concerning the clinical characteristics and therapy of rheumatoid arthritis. We tried to answer them by evaluating the data of the patients, which the department of rheumatology of the Medical University of Graz had collected over ten years. I would now like to express the summarised key findings from this study in regards to the treatment and course of RA:

- The therapy concept in place at the department is effective in lowering disease activity and maintaining a low level over a longer period of time.
- Gradually implementing the tight control and eventually Treat-to-Target concepts has improved therapy success significantly. These are therefore recommendable treatment concepts
- Combining biologics with synthetic DMARDs improves therapy outcome better in comparison to an sDMARDs-monotherapy.
- The clinical disease activity index (cDAI) functions well as an activity scoring measurement for RA in comparison to the gold standard of DAS28.

These key messages are supposed to help understand rheumatoid arthritis and its therapy better and also demonstrate in which direction the development of the medical care for RA-patients is heading. Moreover, with this study we opened a data pool that allows us to research this matter further in the future. Based on the trends I was able to present in this work, I think it would be interesting to design a real-life or register study as a national effort in Austria on the effects of new biologic treatments in order to back up our retrospective findings. This would probably also lead to a re-evaluation of the HAQ and its importance for the department. Furthermore, I hope that all rheumatology centres in Austria will be able to establish a nationwide information system for rheumatology patients much like the one in place in Switzerland, because it would certainly lead to a simpler exchange of experience and ideas. In any way, there are many tasks to be fulfilled in rheumatoid arthritis research in the future.

5 References

1. Dunky A, Graninger W, Herold M, Smolen J. Praktische Rheumatologie. 5th ed. Springer Science+Business Media S.A.; 2012. 916 p.
2. Aceves-Avila FJ, Medina F, Fraga A. The antiquity of rheumatoid arthritis: a reappraisal. J Rheumatol. 2001 Apr 1;28(4):751–7.
3. Entezami P, Fox D a., Clapham PJ, Chung KC. Historical Perspective on the Etiology of Rheumatoid Arthritis. Hand Clin. 2011;27(1):1–10.
4. Keitel W. The High Priest of gout - Sir Alfred Baring Garrod (1819-1907). Zeitschrift für Rheumatol. 2009 Dec;68(10):851–6.
5. Waaler E. On the Occurrence of a Factor in Human Serum Activating the Specific Agglutination of Sheep Blood Corpuscles. Acta Pathol Microbiol Scand. 1940 Aug 10;17(2):172–88.
6. Rose HM, Ragan C, Pearce E, Lipman MO. Differential Agglutination of Normal and Sensitized Sheep Erythrocytes by Sera of Patients with Rheumatoid Arthritis. Exp Biol Med. SAGE Publications; 1948 May 1;68(1):1–6.
7. Singer J, Plotz C. The latex fixation test. I. Application to the serologic diagnosis of rheumatoid arthritis. Am J Med. 1956 Dec;21(6):888–92.
8. Terzani G, Recchia O, Olivieri M, Pica R. Comparison of the Waaler-Rose reaction and the optimized Singer-Plotz reaction. Minerva Med. 1981 Jan 14;72(1):33–9.
9. Aggarwal R, Liao K, Nair R, Ringold S, Costenbader KH. Anti-citrullinated peptide antibody assays and their role in the diagnosis of rheumatoid arthritis. Arthritis Rheum. 2009 Nov 15;61(11):1472–83.
10. Ajeganova S, Huizinga TWJ. Rheumatoid arthritis: Seronegative and seropositive RA: alike but different? Nat Rev Rheumatol. 2015 Jan;11(1):8–9.
11. Aho K, Palosuo T, Niemelä N, Takala J. Rheumatoid factor seroconversions in relation to clinical rheumatoid arthritis. Ann Clin Res. 1985 Jan;17(1):15–8.
12. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care. 2012 Dec;18(13 Suppl):S295–302.
13. Sacks JJ, Luo Y-H, Helmick CG. Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001-2005. Arthritis Care Res (Hoboken). 2010 Apr;62(4):460–4.
14. Dowman B, Campbell RM, Zgaga L, Adeloye D, Chan KY. Estimating the burden of rheumatoid arthritis in Africa: A systematic analysis. J Glob Health. 2012 Dec;2(2):020406.
15. MacGregor AJ, Riste LK, Hazes JM, Silman AJ. Low prevalence of rheumatoid arthritis in black-Caribbeans compared with whites in inner city

Manchester. Ann Rheum Dis. 1994 May;53(5):293–7.

16. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014 Jul 18;73(7):1316–22.

17. Zink A, Huscher D, Westhoff G. Versorgungsforschung im Kompetenznetz Rheuma – Was leistet sie für die Verbesserung der Versorgung? Z Rheumatol. 2014 Feb 21;61(1):3–12.

18. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum. 2010 Jun;62(6):1576–82.

19. Sangha O. Epidemiology of rheumatic diseases. Rheumatology. 2000 Dec 1;39(suppl 2):3–12.

20. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014 Aug;35(3):347–69.

21. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet. 2010 Sep 25;376(9746):1094–108.

22. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature. 2003 May 15;423(6937):356–61.

23. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum. 2000 Jan;43(1):30–7.

24. Seldin MF, Amos CI, Ward R, Gregersen PK. The genetics revolution and the assault on rheumatoid arthritis. Arthritis Rheum. 1999 Jun;42(6):1071–9.

25. Eyre S, Bowes J, Diogo D, Lee A, Barton A, Martin P, et al. High-density genetic mapping identifies new susceptibility loci for rheumatoid arthritis. Nat Genet. 2012 Dec;44(12):1336–40.

26. Fox DA. The role of T cells in the immunopathogenesis of rheumatoid arthritis. New perspectives. Arthritis Rheum. 1997 Apr;40(4):598–609.

27. Aho K, Heliövaara M. Risk factors for rheumatoid arthritis. Ann Med. 2004 Jan;36(4):242–51.

28. Waksman BH, Pearson CM, Sharp JT. Studies of arthritis and other lesions induced in rats by injection of mycobacterial adjuvant. II. Evidence that the disease is a disseminated immunologic response to exogenous antigen. J Immunol. American Association of Immunologists; 1960 Oct 1;85(4):403–17.

29. Van Eden W, Waksman BH. Immune regulation in adjuvant-induced arthritis: possible implications for innovative therapeutic strategies in arthritis. Arthritis Rheum. 2003 Jul;48(7):1788–96.

30. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol. 1996 Jan;14:397–440.

31. Kong YY, Feige U, Sarosi I, Bolon B, Tafuri A, Morony S, et al. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. Nature. 1999 Nov 18;402(6759):304–9.

32. Pettit AR, Ji H, von Stechow D, Müller R, Goldring SR, Choi Y, et al.

TRANCE/RANKL knockout mice are protected from bone erosion in a serum transfer model of arthritis. Am J Pathol. 2001 Nov;159(5):1689–99.

33. Romas E, Gillespie MT, Martin TJ. Involvement of receptor activator of NFkappaB ligand and tumor necrosis factor-alpha in bone destruction in rheumatoid arthritis. Bone. 2002 Feb;30(2):340–6.

34. Geusens P. The role of RANK ligand/osteoprotegerin in rheumatoid arthritis. Ther Adv Musculoskelet Dis. 2012 Aug;4(4):225–33.

35. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum. 1996 May;39(5):732–5.

36. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006 Jan;54(1):38–46.

37. Heliövaara M, Aho K, Knekt P, Impivaara O, Reunanen A, Aromaa A. Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis. Ann Rheum Dis. 2000 Aug;59(8):631–5.

38. Doran MF, Crowson CS, O'Fallon WM, Gabriel SE. The effect of oral contraceptives and estrogen replacement therapy on the risk of rheumatoid arthritis: a population based study. J Rheumatol. 2004 Feb;31(2):207–13.

39. Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. Arthritis Rheum. 2004 Nov;50(11):3458–67.

40. Jaakkola JJK, Gissler M. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. Int J Epidemiol. 2005 Jun;34(3):664–71.

41. Brennan P, Bankhead C, Silman A, Symmons D. Oral contraceptives and rheumatoid arthritis: results from a primary care-based incident case-control study. Semin Arthritis Rheum. 1997 Jun;26(6):817–23.

42. Di Giuseppe D, Bottai M, Askling J, Wolk A. Physical activity and risk of rheumatoid arthritis in women: a population-based prospective study. Arthritis Res Ther. 2015 Jan;17:40.

43. Colebatch AN, Edwards CJ. The influence of early life factors on the risk of developing rheumatoid arthritis. Clin Exp Immunol. 2011 Jan;163(1):11–6.

44. Spector TD, Roman E, Silman AJ. The pill, parity, and rheumatoid arthritis. Arthritis Rheum. 1990 Jun;33(6):782–9.

45. Pope JE, Bellamy N, Stevens A. The lack of associations between rheumatoid arthritis and both nulliparity and infertility. Semin Arthritis Rheum. 1999 Apr;28(5):342–50.

46. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. Eur J Radiol. 1998 May;27 Suppl 1:S18–24.

47. Fleming A, Crown JM, Corbett M. Early rheumatoid disease. I. Onset. Ann Rheum Dis. 1976 Aug;35(4):357–60.

48. Sierakowski S, Cutolo M. Morning symptoms in rheumatoid arthritis: a defining characteristic and marker of active disease. Scand J Rheumatol Suppl. 2011 Jan;125:1–5.

49. Veys EM, De Keyser F. Rheumatoid nodules: differential diagnosis and immunohistological findings. Ann Rheum Dis. 1993 Sep;52(9):625–6.

50. Helliwell PS, Hetthen J, Sokoll K, Green M, Marchesoni A, Lubrano E, et al. Joint symmetry in early and late rheumatoid and psoriatic arthritis: comparison with a mathematical model. Arthritis Rheum. 2000 Apr;43(4):865–71.

51. Gorin AA, Smyth JM, Weisberg JN, Affleck G, Tennen H, Urrows S, et al. Rheumatoid arthritis patients show weather sensitivity in daily life, but the relationship is not clinically significant. Pain. 1999 May;81(1):173–7.

52. Apfelberg DB, Maser MR, Lash H, Kaye RL, Britton MC, Bobrove A. Rheumatoid hand deformities: pathophysiology and treatment. West J Med. 1978 Oct;129(4):267–72.

53. Shi K, Tomita T, Hayashida K, Owaki H, Ochi T. Foot deformities in rheumatoid arthritis and relevance of disease severity. J Rheumatol. 2000 Jan;27(1):84–9.

54. Welsh RP, Hastings DE. Swan neck deformity in rheumatoid arthritis of the hand. Hand. 1977 Jun;9(2):109–16.

55. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular Manifestations in Rheumatoid Arthritis. Mædica. 2010 Dec;5(4):286–91.

56. Al-Ghamdi A, Attar SM. Extra-articular manifestations of rheumatoid arthritis: a hospital-based study. Ann Saudi Med. Jan;29(3):189–93.

57. Calgüneri M, Ureten K, Akif Oztürk M, Onat AM, Ertenli I, Kiraz S, et al. Extra-articular manifestations of rheumatoid arthritis: results of a university hospital of 526 patients in Turkey. Clin Exp Rheumatol. Jan;24(3):305–8.

58. Mielants H, Van den Bosch F. Extra-articular manifestations. Clin Exp Rheumatol. Jan;27(4 Suppl 55):S56–61.

59. Turesson C, Matteson EL. Management of extra-articular disease manifestations in rheumatoid arthritis. Curr Opin Rheumatol. 2004 May;16(3):206–11.

60. Chan KW, Felson DT, Yood RA, Walker AM. The lag time between onset of symptoms and diagnosis of rheumatoid arthritis. Arthritis Rheum. 1994 Jun;37(6):814–20.

61. Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. Am J Med. 2007 Nov;120(11):936–9.

62. Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol. 1989 May;16(5):585–91.

63. Kellgren JH. Radiological signs of rheumatoid arthritis; a study of observer differences in the reading of hand films. Ann Rheum Dis. 1956 Mar;15(1):55–60.

64. van der Heijde DMFM. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillieres Clin Rheumatol. 1996 Aug;10(3):435–53.

65. Grassi W, Tittarelli E, Pirani O, Avaltroni D, Cervini C. Ultrasound Examination of Metacarpophalangeal Joints in Rheumatoid Arthritis. Scand J Rheumatol. Taylor & Francis; 2009 Jul 12;22(5):243–7.

66. Lopez-Ben R, Bernreuter WK, Moreland LW, Alarcon GS. Ultrasound detection of bone erosions in rheumatoid arthritis: a comparison to routine radiographs of the hands and feet. Skeletal Radiol. 2004 Feb;33(2):80–4.

67. Cheung PP, Dougados M, Gossec L. Reliability of ultrasonography to detect synovitis in rheumatoid arthritis: a systematic literature review of 35 studies (1,415 patients). Arthritis Care Res (Hoboken). 2010 Mar;62(3):323–34.

68. Ostergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol. 2003 Jun 1;30(6):1385–6.

69. Suter LG, Fraenkel L, Braithwaite RS. Role of magnetic resonance imaging in the diagnosis and prognosis of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2011 May;63(5):675–88.

70. Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum. 2000 Dec;43(12):2762–70.

71. McQueen FM, Stewart N, Crabbe J, Robinson E, Yeoman S, Tan PLJ, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. Ann Rheum Dis. 1998 Jun 1;57(6):350–6.

72. Backhaus M, Kamradt T, Sandrock D, Loreck D, Fritz J, Wolf KJ, et al. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. Arthritis Rheum. 1999 Jun;42(6):1232–45.

73. Westwood OMR, Nelson PN, Hay FC. Rheumatoid factors: what's new? Rheumatology (Oxford). 2006 Apr 1;45(4):379–85.

74. Nishimura K. Meta-analysis: Diagnostic Accuracy of Anti–Cyclic Citrullinated Peptide Antibody and Rheumatoid Factor for Rheumatoid Arthritis. Ann Intern Med. American College of Physicians; 2007 Jun 5;146(11):797.

75. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315–24.

76. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580–8.

77. van der Linden MPM, Knevel R, Huizinga TWJ, van der Helm-van Mil AHM.

Classification of rheumatoid arthritis: comparison of the 1987 American College of Rheumatology criteria and the 2010 American College of Rheumatology/European League Against Rheumatism criteria. Arthritis Rheum. 2011 Jan;63(1):37–42.

78. Mackenzie AH. Differential diagnosis of rheumatoid arthritis. Am J Med. 1988 Oct;85(4):2–11.

79. Fam AG. Paraneoplastic rheumatic syndromes. Baillière's best Pract Res Clin Rheumatol. 2000 Sep;14(3):515–33.

80. Fallahi S, Collins RD, Miller RK, Halla JT. Coexistence of rheumatoid arthritis and sarcoidosis: difficulties encountered in the differential diagnosis of common manifestations. J Rheumatol. 1984 Aug;11(4):526–9.

81. van der Heijde DM, van 't Hof M a, van Riel PL, Theunisse L a, Lubberts EW, van Leeuwen M a, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990;49(11):916–20.

82. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken). 2012 May;64(5):640–7.

83. Prevoo MLL, Van'T Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LBA, Van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44–8.

84. Wells G, Becker J-C, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythr. Ann Rheum Dis. 2009 Jun 1;68(6):954–60.

85. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28-C-reactive protein threshold values. Ann Rheum Dis. 2007 Mar 1;66(3):407–9.

86. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005 Jan;23(5 Suppl 39):S100–8.

87. Aletaha D, Ward MM, Machold KP, Nell VPK, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum. 2005 Sep;52(9):2625–36.

88. Fransen J, van Riel PLCM. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am. 2009 Nov;35(4):745–57, vii – viii.

89. Kiely PDW, Brown AK, Edwards CJ, O'Reilly DT, Ostör AJK, Quinn M, et al.

Contemporary treatment principles for early rheumatoid arthritis: a consensus statement. Rheumatology (Oxford). 2009 Jul;48(7):765–72.

90. Sokka T, Pincus T. Rheumatoid arthritis: strategy more important than agent. Lancet (London, England). 2009 Aug 8;374(9688):430–2.

91. Voshaar MJH, Nota I, van de Laar MAFJ, van den Bemt BJF. Patient-centred care in established rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2015 Jan;29(4-5):643–63.

92. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2015 May 12;annrheumdis – 2015–207524 – .

93. Hall J, Skevington SM, Maddison PJ, Chapman K. A randomized and controlled trial of hydrotherapy in rheumatoid arthritis. Arthritis Care Res (Hoboken). 1996 Jun;9(3):206–15.

94. Minor MA, Webel RR, Kay DR, Hewett JE, Anderson SK. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 1989 Nov;32(11):1396–405.

95. Van den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM. Dynamic exercise therapy in rheumatoid arthritis: a systematic review. Rheumatology. 1998 Jun 1;37(6):677–87.

96. Luqmani R, Hennell S, Estrach C, Basher D, Birrell F, Bosworth A, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). Rheumatology (Oxford). Oxford University Press; 2009 Apr 1;48(4):436–9.

97. Smith-Petersen MN, Larson CB, Aufranc OE. Osteotomy of the spine for correction of flexion deformity in rheumatoid arthritis. Clin Orthop Relat Res. 1969 Jan;66:6–9.

98. Clayton ML. Surgical Treatment at the Wrist in Rheumatoid Arthritis: A Review of Thirty-Seven Patients. J Bone Joint Surg Am. The American Orthopedic Association; 1965 Jun 1;47(4):741–50.

99. Ranawat CS, O'Leary P, Pellicci P, Tsairis P, Marchisello P, Dorr L. Cervical spine fusion in rheumatoid arthritis. J Bone Joint Surg Am. The American Orthopedic Association; 1979 Oct 1;61(7):1003–10.

100. Kirwan JR, Currey HLF, Freeman MAR, Snow S, Young PJ. Overall Long-Term Impact of Total Hip and Knee Joint Replacement Surgery on Patients with Osteoarthritis and Rheumatoid Arthritis. Rheumatology. 1994 Apr 1;33(4):357–60.

101. da Silva E, Doran MF, Crowson CS, O'Fallon WM, Matteson EL. Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. Arthritis Rheum. 2003 Apr 15;49(2):216–20.

102. Steultjens EMJ, Dekker J, Bouter LM, van Schaardenburg D, van Kuyk M-AH, van den Ende CHM. Occupational therapy for rheumatoid arthritis: a systematic review. Arthritis Rheum. 2002 Dec 15;47(6):672–85.

103. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016 Jan;68(1):1–25.

104. van Laar M, Pergolizzi J V, Mellinghoff H-U, Merchante IM, Nalamachu S, O'Brien J, et al. Pain treatment in arthritis-related pain: beyond NSAIDs. Open Rheumatol J. 2012 Jan;6:320–30.

105. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: An analysis of serious adverse events. Am J Med. Elsevier; 1994 Feb 1;96(2):115–23.

106. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995 Jul 20;333(3):142–6.

107. Bakker MF, Jacobs JWG, Welsing PMJ, Verstappen SMM, Tekstra J, Ton E, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med. American College of Physicians; 2012 Mar 6;156(5):329–39.

108. Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewé R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis. 2014 Jan;73(1):3–5.

109. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625–39.

110. Morrow T, Felcone LH. Defining the difference: What Makes Biologics Unique. Biotechnol Healthc. 2004 Sep;1(4):24–9.

111. Li F, Vijayasankaran N, Shen AY, Kiss R, Amanullah A. Cell culture processes for monoclonal antibody production. MAbs. 2010 Jan;2(5):466–79.

112. Ramanan S, Grampp G. Drift, evolution, and divergence in biologics and biosimilars manufacturing. BioDrugs. 2014 Aug;28(4):363–72.

113. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet (London, England). 2004 Jan;364(9430):263–9.

114. Bakker MF, Jacobs JWG, Verstappen SMM, Bijlsma JWJ. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis. 2007 Nov 1;66 Suppl 3(suppl_3):iii56–60.

115. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010 Apr 1;69(4):631–7.

116. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs.

Ann Rheum Dis. 2010 Jun 1;69(6):964–75.

117. Schoels M, Knevel R, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas DT, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis. 2010 Apr;69(4):638–43.

118. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis. 2016 Jan 19;75(1):16–22.

119. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014 Mar 25;73(3):492–509.

120. Aletaha D, Nell VPK, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005 Jan;7(4):R796–806.

121. Über SCQM - SCQM Foundation [Internet]. [cited 2016 Mar 3]. Available from: http://www.scqm.ch/uber-scqm

122. Simonic KM, Bloice M. A Clinical Information System to Improve the Outcome of Rheumatoid Arthritis Treatment. (Unpublished Manuscript). 2007;

123. Finckh A, Neto D, Iannone F, Loza E, Lie E, van Riel P, et al. The impact of patient heterogeneity and socioeconomic factors on abatacept retention in rheumatoid arthritis across nine European countries. RMD open. EULAR; 2015 Jan 1;1(1):e000040.

124. Artusi R, Verderio P, Marubini E. Bravais-Pearson and Spearman correlation coefficients: meaning, test of hypothesis and confidence interval. Int J Biol Markers. 2002 Jan;17(2):148–51.

125. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. 2nd ed. Wiley series in probability and statistics. 2011. 740 p.

126. Hill T, Lewicki P. Statistics Methods and Applications. 1st ed. StatSoft; 2007. 815 p.

127. Crowson CS, Matteson EL, Davis JM, Gabriel SE. Contribution of obesity to the rise in incidence of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013 Jan;65(1):71–7.

128. Kvien TK, Uhlig T, Ødegård S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci. 2006 Jun;1069:212–22.

129. Goemaere S, Ackerman C, Goethals K, De Keyser F, Van der Straeten C, Verbruggen G, et al. Onset of symptoms of rheumatoid arthritis in relation to age, sex and menopausal transition. J Rheumatol. 1990 Dec;17(12):1620–2.

130. Brennan P, Silman A. Why the gender difference in susceptibility to rheumatoid arthritis? Ann Rheum Dis. 1995 Sep;54(9):694–5.

131. Wang Y, Hunt K, Nazareth I, Freemantle N, Petersen I. Do men consult less

than women? An analysis of routinely collected UK general practice data. BMJ Open. 2013 Aug 19;3(8):e003320–e003320.

132. Katz PP, Criswell LA. Differences in symptom reports between men and women with rheumatoid arthritis. Arthritis Care Res. 1996 Dec;9(6):441–8.

133. Inoue K, Shichikawa K, Nishioka J, Hirota S. Older age onset rheumatoid arthritis with or without osteoarthritis. Ann Rheum Dis. 1987 Dec;46(12):908–11.

134. Pease CT, Bhakta BB, Devlin J, Emery P. Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors. Rheumatology (Oxford). 1999 Mar;38(3):228–34.

135. Detert J, Klaus P. Biologic monotherapy in the treatment of rheumatoid arthritis. Biologics. 2015 Jan;9:35–43.

136. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Jan;23(2):137–45.

137. Costenbader KH, Chibnik LB, Schur PH. Discordance between erythrocyte sedimentation rate and C-reactive protein measurements: clinical significance. Clin Exp Rheumatol. 2007 Jan;25(5):746–9.

138. Wolfe F. Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. J Rheumatol. 1997 Aug;24(8):1477–85.

139. Walsh L, Davies P, McConkey B. Relationship between erythrocyte sedimentation rate and serum C-reactive protein in rheumatoid arthritis. Ann Rheum Dis. 1979 Aug;38(4):362–3.

140. Futó G, Somogyi A, Szekanecz Z. Visualization of DAS28, SDAI, and CDAI: the magic carpets of rheumatoid arthritis. Clin Rheumatol. 2014 May;33(5):623–9.

141. Slama I Ben, Allali F, Lakhdar T, El Kabbaj S, Medrare L, Ngeuleu A, et al. Reliability and validity of CDAI and SDAI indices in comparison to DAS-28 index in Moroccan patients with rheumatoid arthritis. BMC Musculoskelet Disord. 2015 Jan;16:268.

142. Singh H, Kumar H, Handa R, Talapatra P, Ray S, Gupta V. Use of clinical disease activity index score for assessment of disease activity in rheumatoid arthritis patients: an Indian experience. Arthritis. 2011 Jan;2011:146398.

143. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum. 2001 Sep;44(9):2009–17.

144. Welsing PMJ, Landewé RBM, van Riel PLCM, Boers M, van Gestel AM, van der Linden S, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum. 2004 Jul;50(7):2082–93.

145. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther.

2009 Jan;11(1):R7.

146. Zufferey P, Dudler J, Scherer A, Finckh A. Disease activity in rheumatoid arthritis patients at initiation of biologic agents and 1 year of treatment: results from the Swiss SCQM registry. Joint Bone Spine. 2013 Mar;80(2):160–4.

147. Ciubotariu E, Gabay C, Finckh A. Joint damage progression in patients with rheumatoid arthritis in clinical remission: do biologics perform better than synthetic antirheumatic drugs? J Rheumatol. 2014 Aug 15;41(8):1576–82.

148. Gabay C, Riek M, Scherer A, Finckh A. Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. Rheumatology (Oxford). 2015 Sep;54(9):1664–72.

149. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet (London, England). 1999 May 8;353(9164):1568–73.

150. Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii13–6.

151. Emery P, Kvien TK, Combe B, Freundlich B, Robertson D, Ferdousi T, et al. Combination etanercept and methotrexate provides better disease control in very early (<=4 months) versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the COMET study. Ann Rheum Dis. 2012 Jun;71(6):989–92.

Image directory

Figure 2: Cush J. Rheumatoid arthritis [Internet]. 2007 [cited 2016 Jan 18]. Available from:
https://commons.wikimedia.org/wiki/File:Arthrite_rhumatoide.jpg

Figure 3: Steinhoff M. Rheumatoide Arthritis AP [Internet]. 2008 [cited 2016 Mar 23]. Available from:
https://commons.wikimedia.org/wiki/File:RheumatoideArthritisAP.jpg

All other figures and tables drafted by the author of this diploma thesis