Concerns and opportunities related to discontinuation of treatment in rheumatoid arthritis

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Introduction

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease which can be invalidating when not recognized and treated in time.(1) As with most autoimmune disorders, RA occurs mostly in women (2) and it typically manifests with inflammation in small and medium-sized joints symmetrically. Within the affected joint the synovium and the tendon sheaths are the primary sites of the inflammatory process.(3) Immune cells invade the synovial lining and, if present, the tendon sheaths of the joint, leading to the formation of inflammatory pannus. The inflammation causes pain, swelling and limitation of function.(1) The invasive nature of this process leads to bony erosions, cartilage breakdown and thereby to so called radiographic damage. Besides local joint symptoms, patients can have systemic complaints, which can be divided into early systemic effects such as morning stiffness, fatigue, malaise, fever and weight loss and late effects such as muscle weakness, nodules, vasculitis, general wasting and organ involvement, e.g. interstitial lung disease, glomerulonephritis, cardiovascular diseases and osteoporosis.(4) Leaving RA uncontrolled can therefore cause a high burden of disease and even a reduction in life expectancy (i.e. increased mortality). Due to substantial advances in treatment, significant improvements have been achieved in symptom reduction, burden of disease and prevention of damage, although in RA patients there is still increased mortality compared to the general population.(5, 6) Several factors have contributed to these advances in treatment strategies, of which, three important contributing factors will be discussed below: early start of treatment, disease activity steered treatment (a treatment goal, also known as 'treat-to-target') and (new) types of immunosuppressive medication.

These treatment advances have given rise to the possibility of drug tapering and eventually also reaching a state of drug free remission (DFR). However, using immunosuppressive medication to suppress rheumatoid inflammation can be associated with adverse events such as increased susceptibility for infections.(7) Most acutely, these concerns about infection risk arose with the outbreak of the COVID-19 pandemic in 2020. More chronic concerns about adverse effects of glucocorticoids were actualized by a change in the treatment recommendations for RA formulated by the American College of Rheumatology (ACR) in 2021. In this thesis both the concerns about negative effects as opportunities arising from antirheumatic treatment will be addressed.

Recent advances in antirheumatic treatment

Early start of treatment

In the nineties, three randomized controlled trials have been conducted to evaluate the value of early start of treatment. Patients were randomized into 'early start of treatment' or 'delayed start of treatment' and in all studies, patients in the 'early start' group had a milder disease course compared to the

'delayed start group'.(8-10) As these studies were conducted in the nineties, the investigated Disease Modifying Antirheumatic Drugs (DMARDs) were gold and hydroxychloroquine which are now obsolete (gold) or are no longer the first choice as initial treatment (hydroxychloroquine). In later conducted observational research with more modern drug regimens, it was confirmed that early treatment has greater beneficial effects on both radiological joint damage as well as on disease activity.(11) Therefore, the treatment strategy has changed from 'wait and see' during the initial stages of the disease towards 'treat-to-target' from the beginning of the disease, which involves early treatment steered by composite disease activity indices such as the Disease Activity Score (DAS) and 'tight control'. Early start of treatment has also been promoted by updating the ACR/ European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria (table 1), which facilitates the inclusion of patients in clinical trials in an earlier phase of the disease.(12) Earlier treatment start and better patients outcomes have stimulated further research on the 'window of opportunity' theory. This was first developed based on the effect of early start of treatment on prevention of radiological damage progression (13) and has since been expanded to the option that earlier treatment may even result in prevention of chronicity of inflammation and potentially the induction of cure. (14)

Disease activity steered treatment

The 'treat-to-target' approach in treatment of RA includes defining a preferred target at the beginning of therapy with 3 monthly adaptations of treatment if the treatment target is not achieved. Setting a target was greatly facilitated by development of the DAS (15) and other, later developed, composite scores such as the SDAI and CDAI.(16, 17) The prove of principle of this 'tight control' approach was then demonstrated in a randomized clinical trial.(18) The introduction of more effective drugs and drug combinations (see below) increased the proportion of patients meeting the new treatment targets, which in turn helped to aim for even stricter target definitions. Thus the treatment target moved from 'low disease activity' to 'remission', by various definitions. The ACR and EULAR organizations collaborated to form an 'ACR/EULAR remission' definition for clinical trials.(19) Benefits of using remission as treatment target were demonstrated in two early RA inception cohorts comparing 'treatment to DAS28 remission' and 'usual care'. The 'treat-to-target' strategy led to earlier DAS28 remission and also more remission after 1 year.(20) This 'treat-to-target' strategy has also been studied in several randomized controlled trials and proven successful.(21-23) Ultimately, the IMPROVED study incorporated 'drug free remission' as treatment target for patients with early RA.(24)

Available medication

The first drugs used as treatment for RA were non-steroidal anti-inflammatory drugs (NSAIDs) in the early twenties of the twentieth century. NSAIDs were the

Table 1. Classification criteria for RA

ACR 1987 criteria	ACR/EULAR 2010 criteria
Entry criteria: none	1. Entry criteria: Patient with at least one joint with definite clinical synovitis (swelling) 2. Synovitis is not better explained by another disease.
1. Morning stiffness (at least 1 hour) 2. Arthritis of three of more joint areas 3. Arthritis of hand joints (≥1 swollen joints) 4. Symmetrical arthritis 5. Rheumatoid nodules 6. Serum RF 7. Radiographic changes (erosions)	1. Joint involvement (0-5 points) - One medium-to-large joint (0) - Two to ten medium-to-large (1) - One to three small joints (large joints not counted) (2) - Four to ten small joints (large joints not counted) (3) - More than ten joints (at least one small joint) (5) 2. Serology (0-3 points) - negative RF and negative ACPA (0) - Low positive RF or low positive ACPA (2) - High positive RF or high positive ACPA (3) 3. Acute-phase reactants (0-1 points) - normal CRP and normal ESR (0) - Abnormal CRP or abnormal ESR (1) 4. Duration of symptoms (0-1 points) - Less than 6 weeks (0) - 6 weeks or more (1)
4/7 criteria must be present. Criteria 1-4 must be present for at least 6 weeks.	Cut-off for RA is 6 points or more.

Abbreviations: ACPA=anti-citrullinated protein antibodies; ACR=American College of Rheumatology; CRP=C-reactive protein; EULAR=European Alliance of Associations for Rheumatology; ESR=Erythrocyte sedimentation rate; RA=rheumatoid arthritis; RF=rheumatoid factor

first drug class that could actually give symptom relief, but they did not have an effect on the disease course. The subsequently developed drugs were disease modifying Antirheumatic Drugs (DMARDs), composed of synthetic chemical compounds and therefore known as conventional synthetic (cs)DMARDs. This class included injectable gold therapy, sulphasalazine, anti-malarials and D-penicillamine. Later on, also methotrexate (MTX) and leflunomide were added to this class. MTX is now considered as 'the anchor drug' in initial treatment of patients who are at risk for developing persistent disease, but importantly to note that the success of MTX is mainly due to the combination with glucocorticoids (GC). Strategy trials (e.g. COBRA and BeSt, (25, 26)) with study arms in which patients were treated with combination therapy (MTX+GC) showed better results regarding disease activity control, physical functioning and radiographic damage for combination therapy compared to csDMARD monotherapy. Furthermore, it has been shown that GC bridging together with a csDMARD (in all trials: MTX) gave similar responses as the combination MTX and a biological DMARD.(26-28)

Around the time of treatment strategy studies, new drugs were launched which were based on biological agents and therefore called biological (b)DMARDs. This class of bDMARDs consists of amongst others TNF blockers, T and B cell targeting agents (e.g. anti CD20), and interleukin (IL) inhibitors (e.g. anti IL-6). In

the 21st century, Janus-kinase inhibitors (JAK-i) were introduced, called 'targeted synthetic' (ts)DMARDs. These small molecule DMARDs inhibit cytokine and growth factor signaling by interfering with the JAK-STAT pathway. In clinical trials, both bDMARDs and tsDMARDs in combination with a csDMARD, have been demonstrated to result in more rapid clinical improvement and suppression of radiographic damage progression in more patients compared to csDMARD monotherapy.(29, 30) Limitations to their use as initial treatment are costs and concerns about adverse events, with information about the latter still being accumulated for the most recently introduced drugs. However, many patients who receive csDMARDs as initial treatment have to switch medication because of insufficient effect or intolerance. Despite the work on developing models for the response to methotrexate (31, 32), treating RA is still based on repeated trial and error. The EULAR 2022 recommendations for treatment of RA included several statements about the order to prescribe different types of DMARDs.(7) As stated previously, MTX is recommended to be part of the initial treatment of patients with RA and if there are contraindications for MTX, leflunomide or sulphasalazine should be considered. In case the preferred treatment target is not achieved with this first csDMARD, switching to, or adding other csDMARDs is the next suggested step. In case there are poor prognostic factors (persistently moderate or high disease activity despite csDMARD therapy, high c-reactive protein (CRP) or high Erythrocyte sedimentation rate (ESR), (high levels of) anti-citrullinated protein antibodies (ACPA) and or rheumatoid factor (RF), presence of early erosions and/or failure of ≥2 csDMARDs), a bDMARD or tsDMARD should be added. In general, a bDMARD or a tsDMARD should be accompanied by at least one csDMARD if these are tolerated.

Opportunities and concerns of antirheumatic treatment

Glucocorticoid bridging

GC are a separate class of medication used in patients with rheumatoid arthritis. Although they can be considered to be Disease Modifying Antirheumatic with a rapid effect, they are not recommended for chronic use because of the risk of adverse events, which can be serious, in particular prolonged and/or high dose use. The EULAR recommendations therefore suggest to use them only short term as 'bridging therapy' (2022 update).(7) Simultaneously with GC bridging therapy, one or more csDMARD(s) are started. As csDMARDs take longer to become effective, the idea is to reduce the starting dose of GC over time and to stop GC altogether (preferably ≤ 3 months) when the disease activity is sufficiently suppressed by the csDMARD alone. Unfortunately, in many patients the csDMARD proofs to be insufficiently effective once GC bridging has been discontinued, resulting in an increase in disease activity (33) and a need to optimize the treatment. Based on expert opinion and daily practice, it has been suggested that many patients continue or restart GC after the intended bridging period should have been ended. The ACR guidelines for treatment of RA, 2021 update, expressed these concerns about continued GC use after GC bridging

and included a conditional statement to not use GC bridging next to a csDMARD as initial treatment of patients with RA because the benefits of GC bridging do not outweigh the disadvantages according to their expert panel.(34) However, to what extent GC bridging results in long-term use of GC, in routine practice or in clinical trials that assign GC unbiased and include protocolized GC tapering, is still unknown and therefore a topic investigated in this thesis.

Tapering treatment

As gradually more patients achieved remission with adequate suppression of symptoms and prevention of radiographic damage due to treat-to-target strategies, tapering drug dosages and even discontinuation of medication became possible. Where in the past reduction of dosage or discontinuation of DMARDs was driven by (fear of) adverse effects, it can now also be considered in patients who have achieved sustained remission or low disease activity. Discontinuation of treatment is interesting as it can prevent adverse events, scheduled laboratory checks aimed at identifying toxicity and also lower the costs of use, checks and treatment of adverse events. Especially the newer medication types (several bDMARDs and the tsDMARDs) come with high treatment costs.(35) Before treatment can be discontinued, it is generally preferred to taper while monitoring the patient's disease activity as it is not desirable to discontinue medication immediately from the dose in which the state of sustained low disease activity have been achieved. Taking into account only moderate to high quality studies, a systematic literature review (SLR) found 5 to 24.3% as DFR percentages of all RA patients eligible for tapering.(36) These low DFR percentages could be explained by the gap of knowledge around drug tapering. A practical guide for tapering in clinical practice is lacking.

Treatment of RA patients during a pandemic

Besides the knowledge gaps in treatment strategies of RA patients that are encountered during 'normal times', other factors may also expose new challenges. An example of a new challenge the world had to face, started in December 2019 with the emergence and spread of a new coronavirus: 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2).(37) The disease this virus caused was named COVID-19 and brought many problems and uncertainties to the whole world when it became a pandemic. COVID-19 appeared to cause a range of symptoms and severities from mild flu-like symptoms (the area of symptoms expanded as more research was done) to severe organ involvement resulting in disability or death.(38) Several risk factors for a severe disease outcome were rapidly identified: cardiovascular disease including hypertension, diabetes, severe asthma, being male, higher age and previous bad health were associated with a higher risk of death due to COVID-19.(39) However, it was unknown if immunocompromised patients with an autoimmune disease and/or immunosuppressive medication were also more at risk for infection and/or severe complications after infection with this

new virus, either due to the illness itself or due to the immunosuppressive medication. This was a justified fear as it was known from earlier research about viral and bacterial infections in these patients that their susceptibility was higher than for the general population.(40-43) Regarding the medication classes, DMARDs were shown to have a higher risk of infection, in particular standard-dose and high-dose bDMARDs compared to the csDMARDs.(44) When the first COVID-19 cases were reported in the Netherlands, patients with immune mediated inflammatory disorders or post solid organ transplantation (IMIDT) who used immunomodulating treatment inquired if it would be better to stop their immunosuppressive medication, and whether it was safe for them to leave the house or to have contact with direct family members. To determine whether IMIDT patients, either on immunomodulating treatment or not, were at greater risk to become infected or had a worse disease course than controls, we set up a prospective symptom auto-registration and questionnaire study among IMIDT patients and controls to find evidence for this new knowledge gap. An extension of this study was done to also compare antibody presence after COVID-19 like symptoms between the IMIDT patients and the controls.

Aim and outline of this thesis

Where are we now? Remaining challenges

Despite the advances of antirheumatic treatment, we are not there yet. This thesis provides an overview of opportunities and concerns related to discontinuation of treatment in patients with RA.

Part I gives an overview about tapering DMARDs for daily practice, what is known and what is not. **Part II** focuses on the knowledge gap around GC bridging as part of the initial treatment of RA. We investigated how many patients were still using GC after their use as bridging therapy with both a conventional meta-analysis following a systematic literature review (SLR) (*chapter 3*), as well as an individual patient data (IPD) meta-analysis using raw data from the clinical trials identified with the SLR (*chapter 4*). Besides these analyses within the patients who used GC bridging, we have also compared this GC bridging group with patients who had not started GC bridging as initial therapy, regarding GC use and clinical outcomes (*chapter 5*). Next to these analyses with trial data also observational data was evaluated to see what the situation is in real life practice regarding whether or not a patient has started GC bridging as initial treatment: has it influenced GC and bDMARD use later during the disease course (*chapter 6*)? In **Part III** the focus is shifted towards treatment of RA patients and other patients with autoimmune diseases (IMIDT patients) during a pandemic and in particular during the COVID-19 pandemic. It is evaluated whether patients with an IMIDT with or without immunosuppressive medication were more susceptible to SARS-CoV-2 like symptoms compared to non-IMIDT patients (*chapter 8*). Furthermore, the seroprevalence of SARS-CoV-2 antibodies was compared between these groups (*chapter 9*).

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