Concerns and opportunities related to discontinuation of treatment in rheumatoid arthritis

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Discussion, conclusion and future perspectives

During the past decades, treatment outcomes of patients with RA have improved significantly due to earlier initiation of treatment, disease activity assessments with treatment to target strategies and the introduction of new medication classes. For patients who achieve remission, tapering and eventually discontinuation of antirheumatic treatment may be considered. Tapering and discontinuation may also be warranted in case of drug adverse effects. At the start of the SARS-CoV-2 pandemic in 2020, the risk for infections became a matter of concern whether some antirheumatic drugs should be used at all. These opportunities and concerns around tapering and discontinuation of antirheumatic medication were the subject of this thesis.

In part I of this thesis the focus was on the opportunity to taper antirheumatic drugs in patients with RA. To investigate and assess the evidence about different tapering strategies in both clinical trials and observational cohorts we conducted a review in **chapter 2**. To avoid confusion between drug tapering and drug discontinuation, we excluded studies in which all antirheumatic drugs were discontinued. We divided tapering strategies in three categories: tapering by discontinuation of one of the drugs while continuing the others in combination therapy, tapering by reducing the dose of one of the drugs in combination therapy and tapering by dose reduction of monotherapy. These tapering strategies were evaluated for 4 medication classes: csDMARDs, bDMARDs, tsDMARDs and glucocorticoids (GC). Tapering of csDMARDs appeared to be studied most often in combination therapy regimens (i.e. combination therapy with a bDMARD or another csDMARD). Tapering or stopping one or more of these csDMARDs in combination therapy, was associated with an increase in disease activity (flare). However, assessing the studies in our review that evaluated this method of tapering, it was seen that in most patients the stable disease activity state could be regained by reintroducing the tapered drug. Regarding bDMARDs tapering in the included studies, it appeared only safe to taper in patients with long lasting (sustained) remission (definitions of long lasting differed between 6 to 12 months in the included studies), whereas residual disease activity at the moment tapering is started was associated with flares. Only one trial existed at the moment of the review about tapering tsDMARDs. The RA-BEYOND trial evaluated tapering to half dose versus continuing full dose tsDMARDs in a clinical trial design. More patients in the continuing full-dose group maintained low disease activity and remission compared to the group that had tapered to half dose. Comparable to csDMARD tapering, stable disease activity state after a flare could be regained by restarting the stopped therapy in both b- as tsDMARD trials. Guidelines and recommendations agree on prescribing GC as short term as clinically feasible due to the cumulative dose response effect of GC. Unfortunately, no randomized controlled studies exist that specifically compare different GC tapering strategies. Data about effects of GC tapering are mainly derived from strategy trials in which detailed information on GC tapering is often lacking as GC tapering is not their main outcome. Only one (SEMIRA)

trial investigated the continuation of GC versus tapering and discontinuation of GC. It appeared that the patients that continued GC had more low disease activity control compared to the GC discontinuation group).(1)

In our review we also evaluated studies on patient opinions about tapering of antirheumatic drugs and we found that patients fear tapering because of the risk of flares and the expectation that access to healthcare will be limited once their treatment has been tapered and discontinued. Therefore, patients should be guaranteed that continued monitoring (at least for the first 4 months after discontinuation) is planned. Furthermore, they should be told that rapid treatment (re)escalation will be possible if necessary and they also should be reassured that in the majority of the patients restarting DMARDs, disease activity control is regained. Physicians should be aware that results of open label studies comparing tapering strategies may be sensitive to the nocebo effects that could play a role in flare rates and other outcomes. Placebo controlled RCTs with a long follow-up should be conducted to evaluate different tapering strategies in the most optimal situation with the least bias possible. For all DMARDs and GC it is still unclear in which patients tapering will be unquestionably successful. One could therefore argue, at least for now, to implement 'tapering and stopping' strategies in treatment plans of all patients, already at the initiation of therapy to also create awareness of the possibility and necessity of tapering both DMARDs and GC.

In part II we elaborated on the concerns related to treatment strategies involving tapering in RA by participating in the debate about the use of GC bridging therapy. As soon as patients are diagnosed with RA, initial therapy is started as quickly as possible because of the benefits of early treatment. Initial treatment of RA according to the 2022 updated EULAR recommendations consists of methotrexate (MTX) as cornerstone and GC should be considered. These recommendations don't include specifications about preferred route of administration and dose regimen of GC, but advise to always taper and stop GC as early as clinically feasible (short term, i.e. <3 months).(2) The 2021 updated ACR guidelines stated that the benefits of starting initial GC do not outweigh their disadvantages which consist of the risk of adverse events related to mainly long-term, high-dose GC use and the fear that patients cannot discontinue them.(3) These concerns were based on expert opinion only and led to a conditional recommendation against the use of GC bridging therapy in RA.

To investigate whether the concerns expressed in the 2021 updated ACR guideline regarding continued GC use after GC bridging could be justified, we have looked at GC bridging in 4 ways. In **chapter 3** we evaluated which literature existed about discontinuation of GC after using GC as bridging therapy in both clinical trials and observational research, with a systematic literature review (SLR). It appeared that no observational studies were available for answering

our research question as they did not make a distinction between patients who did start GC as initial bridging and those who started GC later in the disease course. In the search for clinical trials, ten trials were suitable for further analysis and a meta-analysis could be performed on two of our predefined outcomes: GC use at 12 months and at 24 months. In these protocolized clinical trials, discontinuation of GC after their use as bridging therapy was successful in the majority of the patients. The percentage of patients still or again using GC after the planned initial bridging therapy decreased over time, from 22% at 12 months to 10% at 24 months. In **chapter 4** we used a specific form of meta-analysis, an individual patient data (IPD) meta-analysis, to analyze the raw data we received from the principle investigators of 7 of the 10 clinical trials identified with the SLR. In these protocolized clinical trials the GC bridging schedules ranged from 10 to 36 weeks and follow up data reached until 12 or 24 months. We found that the probabilities of still or again using GC following those planned schedules were low and also decreasing over time. Furthermore, we tested baseline patient characteristics as well as bridging schedule characteristics on their associations with the outcomes. A higher initial GC bridging dose and a longer GC bridging schedule were associated with higher cumulative GC doses but also with more patients on GC at 18 months after bridging had ended. In **chapter 5** we compared GC use over 2 years follow up in patients randomized to treatment start with and without initial GC bridging, after the intended bridging schedule had ended. Three of the 7 clinical trials in chapter 4, which were identified with the SLR from chapter 3, were used in this second IPD meta-analysis as they all had at least one study arm with a csDMARD and GC bridging and one study arm with a csDMARD but without GC bridging (comparator arm). After the bridging schedules had ended, bridgers did not have an increased risk of using GC except for timepoint t=12 months. There was no difference in post-bridging cumulative GC dose and mean DAS28 was similar over time but bridgers had a more rapid decrease of DAS28 in the first 6 months and fewer DMARD changes over time than non-bridgers. Starting initial GC bridging or not, may in daily practice depend on general preferences or restrictions to GC use either stemming from patient characteristics and/or physician preferences. These may also affect the use of GC and bDMARDs later in the disease course. In **chapter 6** we therefore looked at outcomes of initial GC bridging in daily practice. We used data from the electronical health records (EHR) of the Leiden University Medical Center (LUMC) in the Netherlands. Patients who did and who did not start GC bridging as initial treatment were compared in terms of GC and bDMARD use later in the disease course. Patients in the group that started with GC bridging had a comparable probability of using a bDMARD later in the disease course but an increased risk of starting GC again later in the disease course, compared to patients from the group that did not start GC bridging.

GC are possibly the most debated antirheumatic drugs. Despite the benefits

of GC bridging next to csDMARD therapy which were confirmed in multiple RCTs and the IPD meta-analysis of chapter 5 (4-6), their use is still controversial. Both patients and physicians vary in their view on the need of GC in the long-term treatment of RA.(7, 8) Information about the view of patients on (short-term) GC bridging is unfortunately lacking. GC bridging ensures a more rapid decline of disease activity in the first months after start of treatment compared to csDMARD monotherapy (4-6), which is beneficial for patients in terms of regaining function and pain reduction. As a result of this early suppression of disease activity there are also other (long-term) beneficial effects such as prevention of irreversible radiographic damage and less chronic non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesic use.(9, 10) However, the concerns about GC bridging, which have led to the conditional recommendation against GC bridging in the 2021 updated ACR guidelines (3), are focused on two fears. First, there is the concern of adverse events which are suggested to be associated with (long-term, high-dose) GC use. Evidence about adverse events due to GC is mainly derived from observational studies. These observational studies carry the risk of confounding by indication and they mainly have focused on long term (low dose) GC use and not on (short-term) GC bridging with a high initial dose and rapid tapering schedule.(11) Furthermore, there is a fear that GC, used as bridging therapy, cannot be discontinued. In our analyses we showed that, at least in clinical trials, the majority of patients who start GC bridging can discontinue them after the intended bridging period has ended. The IPD analysis also provided a direction for research on the optimal GC bridging strategy in terms of the lowest cumulative GC dose and lowest GC use during the subsequent disease course. However, RCTs are needed for unbiased head-to-head comparisons of bridging strategies. These RCTs should unravel the most optimal bridging strategy for both clinical trials as daily practice in terms of lowest cumulative dose but still effective regarding DAS28 decrease and functional improvement.

The situation in clinical trials does not identically reflect real life due to the preselected patient population, protocolized treatment and in some cases sponsored treatment steps. Therefore we have also used observational data to investigate GC bridging. In this daily practice data it appeared the other way: patients who started with GC bridging had a higher chance of using GC in the subsequent disease course compared to non-bridgers. Important to note here is that despite the efforts undertaken to control for confounding by indication, there might still have been residual confounding due to comorbidities and/or disease severity which were not included in the multivariable adjusted analysis due to data limitations. To bring protocolized RCTs and daily practice more in line, it is important that after the establishment of an optimal bridging strategy by RCTs, international guidelines and recommendations (EULAR & ACR) should incorporate this strategy in their initial treatment recommendations for RA. If these two organizations are like minded in their viewpoint on GC bridging,

one could expect physicians (and possibly also patients) to be more adherent to these guidelines. Using GC bridging for a short and predefined amount of time will decrease the risk of possible adverse events and give patients the advantage of early disease activity control. As an alternative for GC bridging, one could think of using bDMARDs as initial therapy. bDMARDs are also rapidly active, comparable to GC.(5, 12) However, at this moment the drug costs of bDMARDs are still high and bDMARDs are also accompanied by a risk of adverse events.(13) So far, little is known about the long-term adverse events risk of different GC bridging strategies (different doses, administration routes and duration). This is an important knowledge gap that needs to be clarified before the definitive judgement over the risk/benefit ratio of GC bridging can be made. For now, GC bridging has advantages and disadvantages just as every other type of medication (class) and these disadvantages should be weighed against earlier disease control.

At the time this thesis was started (March 2020), the COVID-19 pandemic started as well. With this emerging COVID-19 pandemic it was urgent to find out what this pandemic meant for patients with RA and other autoimmune diseases. Especially for these immunocompromised patients there were many questions regarding their risk of (severe) COVID-19. In part III of this thesis we elaborated on this additional concern regarding treatment of RA patients, namely during a pandemic. As no information was available and everyone was in mandatory lockdown, we started a prospective cohort study with questionnaires about possible COVID-19 symptoms and their consequences. In **chapter 7** we evaluated if patients with an autoimmune disease or recipient of a transplant organ (IMIDT) had more COVID-19 like symptoms (CLS) compared to patients without such disease or condition. It appeared that in our observational cohort, patients with an IMIDT with or without immunosuppressive medication did not show an increased risk of having CLS compared to patients without such condition. Following this, it was important to evaluate how the immune response would evolve after a possible SARS-CoV-2 infection in IMIDT patients with and without immunosuppressive medication, compared to the control group. In **chapter 8** we described that approximately 30% of patients who reported CLS had SARS-CoV-2 antibodies. The distribution of this seroprevalence was similar among the patients with an IMIDT with and without use of immunosuppressive medication and patients without such condition.

The COVID-19 pandemic showed us how quickly knowledge can evolve once there is a 'need to know now'. As soon as the pandemic emerged, all questions about it were urgent. Possibly, new viruses or variants will again give concerns for patients with rheumatoid arthritis in the future, but for now the pandemic seems under control and guidelines have been generated to react quickly with scientific research in case of new life threatening (infectious) diseases.

Final conclusions

Based on the findings in this thesis we conclude that:

- It should be advised to include tapering and stop strategies in antirheumatic treatment plans. At the moment RA disease activity returns, remission can be re-achieved in most cases by restarting the stopped treatment.
- It is necessary that information about the success rate of GC bridging discontinuation in clinical trials and observational cohorts is reported.
- It is important to realize that the majority of RA patients in clinical trials starting with GC bridging are able to discontinue these GC.
- GC bridging schedules with a shorter duration and lower starting dose appeared to decrease the risk of GC use later in the disease course in clinical trials. Therefore, bridging schedules with these features should be further investigated.
- Regarding the comparison of GC use later in the disease course after GC bridging between bridgers and non-bridgers, there is conflicting data between clinical trials and an observational study. The advantages and disadvantages of both study designs should therefore always be kept in mind.
- It is reassuring that patients with an IMIDT (with or without use of immunosuppressive medication) in our cohort did not differ in reported CLS and seroprevalence of anti-SARS-CoV-2 antibodies following natural infection. Therefore, in our population, continuing immunosuppressant drugs as long as not ill, while following the lockdown rules, appears to be safe.

Summary of research agenda

- Randomized clinical trials (RCTs) comparing GC bridging schedules differing in administration route, starting dose and duration, are required to determine the best GC bridging strategy in terms of lowest cumulative dose, lowest GC use afterwards, early and long-term efficacy and risk of adverse events.
- More optimal methodological and/or statistical methods should be developed to be able to evaluate long-term adverse events in observational studies without such great risk of confounding by indication.
- When designing new RCTs comparing treatment strategies in RA, (secondary) outcome measures should be included that measure the success rate of discontinuation of the antirheumatic treatment.
- Placebo controlled RCTs with a long follow-up should be conducted to compare different tapering strategies of DMARDs in the most optimal situation with the least bias possible.
- Further research should be conducted to determine which patients are suitable for tapering antirheumatic treatment and at which timepoint (how long should the patient be in low disease activity or remission) this should be pursued.

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