Towards improved treatment of undifferentiated and rheumatoid arthritis

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General discussion and conclusions

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Major advances have been made in the treatment of rheumatoid arthritis (RA), an autoimmune inflammatory disease of still unknown etiology. The disease is characterized by inflammation of synovial joints, leading to symptoms of pain, swelling, and restriction of movement and ultimately progressive joint destruction, if effective treatment is not installed timely and continuously evaluated and adjusted.[1] RA poses a large burden on patients and society because prolonged inflammation leads to functional impairment, decreased quality of life, work loss and even increased mortality.[2-4] Fortunately, in recent years, the face and fate of RA have changed radically, by earlier initiation of disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX) as a prominent drug, the use of combination therapies, tight control of the disease by aiming at minimal disease activity and the use of new highly effective biologic drugs including tumor necrosis factor alpha (TNFα) inhibitors.[5] The development and validation of outcome measures, such as the disease activity score (DAS), health assessment questionnaire (HAQ) and the Sharp/van der Heijde score (SHS) has also contributed to this shift in managing RA.[6-9] As a result, sustained clinical remission with or even without DMARDs has become an achievable goal for a considerable number of patients.[10] Nevertheless, important challenges still remain to further improve the treatment and thereby the outcome of RA, with as ultimate goal cure or even prevention of this up till now still regarded chronic incurable disease. This thesis has focused on and made a start towards tackling several of these challenges.

I. Towards improved treatment of UA

One of the challenges of RA treatment is to start therapy as early as possible to increase the remission rate or even prevent the development of the chronic erosive state classified by the 1987 criteria for RA.[11] To this end, it is warranted to identify RA earlier, preferably close to its inception, addressing the hypothesis that with the right intervention, the disease course might be fundamentally altered or even brought to a halt. The hypothetical timephrame during which this might be accomplished has been called the 'window of opportunity'. However, it is not easy to determine when RA actually starts, as it probably composes a cascade of pathofysiological events, which still have to be fully elucidated and understood. Yet, clinically, it is known that a proportion of patients who present with undifferentiated arthritis (UA) are in an early phase of RA and have a comparable prognosis to patients who present with full-blown RA.[12,13] Therefore, in part I of this thesis the effect of MTX as remission induction therapy to prevent the development of RA was investigated in the first randomized placebo-controlled trial in UA: the 'PRObable rheumatoid arthritis Methotrexate versus Placebo Treatment' (PROMPT) study.

Conclusions from the PROMPT study

In the PROMPT study, patients with UA fulfilling the 1958 criteria for probable RA were treated for one year with either MTX or placebo. In chapter 2 it was shown that patients who were randomized to MTX had a delayed onset of RA, but eventually still fulfilled the 1987 RA criteria as often as patients who received placebo. Thus MTX did not prevent, but only postponed RA. Subanalyses clearly showed a difference in response to

MTX treatment between patients with and without antibodies to citrullinated proteins (ACPA). The RA-postponing effect of MTX was only observed in patients with and not in patients without ACPA. In chapter 3 a more detailed longitudinal analysis confirmed that MTX improved symptoms, function and delayed damage progression only in the ACPA-positive, but not in the ACPA-negative UA patients.
After one year MTX (or placebo) treatment, medication was tapered and discontinued in the UA patients who had not developed RA. This resulted in a flare of disease and ongoing radiographic progression, predominantly in the ACPA-positive patients, as described in chapter 4. This chapter further focused on the outcome drug-free remission. MTX therapy did not induce more drug-free remission than was observed in the placebo group and predictors for drug-free remission were similar to characteristics of self-limiting disease.
These results together suggest that one year MTX monotherapy did not induce a long-lasting change in the disease progression from UA to RA, certainly not for ACPA-negative UA, and only to a certain extent but not potent enough for ACPA-positive patients. Several new questions arise from these results. Was MTX monotherapy in itself insufficiently effective or was the duration of one year treatment too short? Should therapy have been steered at remission instead of low disease activity? Should ACPA-positive patients be treated differently than ACPA-negative patients? Or, irrespective of the above considerations, was the timing of the intervention just not early enough and was the window of opportunity missed? Accepting that a window of opportunity exists, we still don't know when it opens, when it closes again, nor how we can target it with optimal advantage.

When to treat?

The current pathophysiological concept of RA is a continuum that evolves from asymptomatic, next prodromal, early undifferentiated arthritis to full-blown polyarticular disease. Since it is not yet known which events mark the onset of RA or at which point the disease might still be reversible, the current idea is the earlier treatment is started the higher the chance for a successful outcome. Practically, however, it is not so easy to point out when this should exactly be. Since inflammation is the cause of clinical symptoms and the driving force behind the joint destruction that we want to prevent, it seems logical to start when clinical synovitis is present in at least one joint. In this thesis, the investigated starting point for treatment was UA defined according to the 1958 criteria for probable RA (chapter 1, table 1).[14] These criteria indicate a more advanced disease than for example a presentation of UA in only one joint. Therefore, the intervention in the PROMPT study might not have been early enough to yield a long-lasting benefit. Moreover, it has been shown with ultrasound, magnetic resonance imaging (MRI) and immunohistological methods that signs of synovitis can already be present subclinically, although the prognostic value of these observations is yet unclear.[15,16] Looking even earlier, before the onset of clinical synovitis, arthralgia appears to be a prodromal phase of RA in some patients, but only a small percentage of arthralgia patients will go on to develop RA.[17,18] In any case, moving towards earlier less well defined disease states as starting points for treatment holds a risk of overtreatment of

patients who will not develop RA. Clarification of the various immunological steps in the pathophysiological disease cascade, their specificity for RA and their prognostic implications will help to further characterize the window of opportunity for inducing remission, and thereby the optimal timing of DMARDs.

Who to treat? ACPA-positive versus ACPA-negative UA

The question 'who to treat' is partly inherent to the question 'when to treat', when interpreted in terms of different disease phases with accompanying symptoms, as described above. It is also related to the question what goal treatment should achieve, i.e. symptom relief or prevention of damage as well. Patients can be characterized according to specific genetic, serological and demographic factors, some of which have been associated with the progression and/or severity of the disease. Identification of subgroups of UA patients with self-limiting or other diseases and those who will go on to develop chronic erosive RA, is crucial to prevent overtreatment associated with possible toxicity and costs, while avoiding undertreatment. Starting from UA, several prediction models have been developed to help determine the risk for RA.[19,20] Although these models perform reasonably well, still the risk for RA cannot be classified accurately for a considerable number of patients. Increased knowledge and identification of genetic risk factors, their pathophysiological effects and the development of specific biomarker tools will probably improve individual prediction in the future.[21]

In the meantime, in UA one of the strongest predictors for RA is the presence of ACPA. ACPA can be present years before the disease becomes clinically apparent, are highly specific for RA and 93% of ACPA-positive patients with UA go on to develop RA within three years.[22-24] This was also shown in the PROMPT study, where almost all ACPA-positive UA patients eventually developed RA. Since also the course of ACPA-positive disease, once developed into RA, is clinically more severe and more destructive than ACPA-negative disease, it is clear that ACPA-positive UA warrants early DMARD treatment.[25]

DMARD treatment of ACPA-negative UA is more controversial, since it may represent a variety of diseases, with a different genetic background and variable disease prognosis.[26,27] With the current prediction models the risk for RA is particularly difficult to determine in ACPA-negative UA patients, as they lack one of the most important factors adding to the prediction score. In addition, the risk of joint destruction is less than in ACPA-positive patients.[25] Nevertheless, the burden of ACPA-negative UA can be considerable. In the PROMPT study, ACPA-negative patients presented with a similar amount of tender and swollen joints as ACPA-positive patients, 35% of them fulfilled the 1987 criteria for RA during the study and 14% had persistent UA. Furthermore, the relationships between disease activity, functional ability and radiographic joint damage, which form part of the rationale for treatment in RA, also exist in ACPA-negative (and ACPA-positive) UA (chapter 3). Thus, at least for symptom relief, and in some ACPA-negative UA patients for prevention of damage progression, these patients are also in need of early treatment. A great challenge for the future is the search for distinct genetic or serological factors that might distinguish between ACPA-negative patients who are prone to developing RA or who will have other diseases, and disentangle this heterogeneous patient group.

How to treat?

Chapter 2-4 showed that MTX monotherapy, administered as a one year treatment course in UA patients, did not induce a permanent change of the disease. Besides the issues of timing and patient population, one can hypothesize that a different treatment strategy is needed to induce a more profound chance. A few randomized short-term intervention studies have tried to alter the course of early UA. In the STIVEA trial, three-weekly intramuscular methylprednisolone injections in inflammatory polyarthritis of 4-10 weeks duration postponed the need for DMARDs and resulted in more resolved disease after 12 months, but longer follow-up is not yet available.[28] In the larger SAVE study in a similar patient population, a single 120 mg intramuscular methylprednisolone injection was not effective in inducing remission or delaying development of RA.[29] A tapered high oral dose of prednisone has not yet been evaluated for this purpose, but proved to be an important element of effective combination therapies in established RA. Two other powerful antirheumatic therapies, infliximab (a TNF-blocker) and abatacept (a T-cell co-stimulation inhibitor), have been tested in two, small (probably underpowered), studies in UA patients, but none were able to prevent the progression to RA.[30,31] Together, these data show that we need more randomized controlled trials with sufficient power and follow-up, to search for an effective strategy that prevents the development of RA or at least modifies the course into a milder disease with a higher chance for remission. Subanalyses on ACPA-positive and ACPA-negative patients should be pre-specified as it is clear that these represent different disease entities which might respond differently. Such trials might use the DAS as an outcome, as chapter 5 showed that the DAS is a valid measure for use in UA, or even a DAS-driven strategy, proven superior to routine treatment evaluations in RA.[32]

New ACR criteria for RA

In a joint effort of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) new classification criteria for RA have just been developed[33], to replace those of 1987, which have been criticized for their lack of sensitivity and diagnostic value for early RA. The new 2010 criteria aim to identify patients with undifferentiated inflammatory arthritis who have a sufficient risk of persistence to be considered for DMARD therapy. The new criteria redefine the disease, as the label 'RA' is actually moved towards an earlier stage. Not denying the valuable effort, this has several consequences. It is questionable whether the sensitivity and specificity (and thus predictive value) of the new criteria will be high enough to accurately classify all patients. In that respect, the criteria face the same difficulties as the current prediction models, in that we do not yet fully understand the inflammatory processes leading to RA and not know all the predictive variables. We went back to the inclusion data in the PROMPT study and found that 64 out of the 110 patients (58%) included as UA fulfilled the 2010 RA criteria at baseline. These patients included all 27 ACPA-positive patients and 37 out of 83 ACPA-negative patients. After repeating the principal analyses only in this subgroup of 64 patients, we found a comparable remission rate and a comparable incidence of fulfilling the 1987 criteria for RA as seen in the total PROMPT group. Extrapolation of existing data on available therapies to this newly defined 'RA' population will be

difficult, as these come from trials with patients fulfilling the 1987 ACR criteria for RA. The value and therapeutic consequences of the new criteria for RA will have to be evaluated in the upcoming years by post-hoc analyses of established studies or in new trials using them as inclusion criteria.

II. Current treatment of RA: recommendations for methotrexate use

Moving from UA to diagnosed RA, methotrexate has been firmly described as a cornerstone of RA treatment as initial monotherapy, as anchor drug in combination therapies and as reference drug against which new therapeutics are evaluated.[34] Its efficacy (within limits of past definitions of 'efficacy') and toxicity profile of MTX has been well established in randomized controlled trials in the early 1980s and in longitudinal cohort studies in the 1990s.[35-38] However, more recent studies have shown that, with tight control of treatment and DAS-based definitions of efficacy, actually only 30-50% of patients maintain sufficiently low disease activity on MTX monotherapy.[39,40]

Despite this widespread use and long-term experience, considerable variation exists among rheumatologists in prescribing and managing MTX and few countries have specific clinical guidelines. Therefore, evidence and consensus based recommendations would be valuable to harmonize the use of MTX in daily practice, increase the comparability of trial results, for education purposes and ultimately to improve patient care. In part II, the 2nd multinational 3E (Evidence, Expertise, Exchange) Initiative undertook the task of reviewing a large part of the available literature on MTX in rheumatic disorders and combined the evidence with expert opinion of a large group of rheumatologists from 17 countries. The results were 10 multinational recommendations for the use of MTX in daily clinical practice (chapter 6).

Summary of methotrexate recommendations

A profound level of evidence was found for the optimal dosing strategy of MTX, the supplementation of folic acid, mono- versus combination therapy and the long-term safety of MTX. The results showed that to obtain higher clinical efficacy, higher start doses of MTX (>10-15 mg/wk) should be used and the dose should be rapidly escalated (with 5mg every 2-4 weeks) to a maximum of 25-30 mg/wk (chapter 7). In addition, folic acid in a dose of at least 5 mg/wk is strongly recommended, as a meta-analysis showed a significant reduction in gastrointestinal and liver toxicity, without lowering efficacy.[41] Findings from another large meta-analysis suggested a significant advantage of conventional DMARD combination therapy (excluding prednisone or anti-TNF) for patients who already failed on previous MTX therapy, but not for DMARD-naive patients.[42] Only the triple combination of MTX, sulphasalazine and hydroxychloroquine showed a better efficacy/toxicity ratio. Another review established the acceptable safety profile of MTX.[43] For the remaining topics the evidence was more limited or even absent. Regarding the use of MTX during elective orthopedic surgery three trials suggest that continuation of low-dose MTX is safe, as it resulted in equal or less postoperative complications and RA flares in comparison with stopping MTX.[44] A review of six databases/surveys suggested an increased risk for miscarriages and congenital malformations if MTX is used during pregnancy.[45] No evidence was found for a direct recommendation

how and how often to screen and monitor laboratory results in order to prevent severe toxicity in patients treated with MTX (chapter 8).

Strength and weakness of systematic reviews

Systematic literature review is a crucial part of evidence-based approaches, but the success is predominantly determined by the availability of evidence in the literature. Regarding the 3E project on MTX, for several areas evidence from high-quality randomized controlled trials was found and even meta-analyses could be performed, while for other topics no data were available at all. Additional limitations of studies included the lack of uniform outcome measures, underreporting of data necessary for statistical pooling (such as standard deviations), the absence of correction for confounders, or suboptimal study designs. These are important items to take into account when designing and reporting on new trials. In addition, many studies were old and addressed long-standing RA patients, who received low dosages of MTX without folic acid supplementation, which does not reflect current practice and might hamper translation of the results to the present time. On the other hand, the identification of evidence gaps created new research opportunities. In the case of MTX, future follow-up studies and trials with higher dosed MTX might reveal new safety data. A randomized trial evaluating low versus high dosed folic acid with higher dosed MTX might clarify the observation that folic acid did not significantly reduce gastrointestinal toxicity with MTX >10mg/wk. Other still unanswered questions concern whether and how often liver enzymes should be monitored and whether or not the dose of MTX should and can be tapered. Indeed, new studies have already been published and, as with all guidelines, the recommendations will have to be periodically adapted to keep them up-to-date.[46,47]

III. Towards improved treatment of RA

Three fundamental changes have improved the treatment of recent-diagnosed RA in the past decade and form the basis from which even further improvement might be achieved: early start of DMARDs, use of initial combination therapy including prednisone or anti-TNF, and tight control of therapy.[5] While part I of this thesis has focused on the timing of DMARD therapy, part III dealt with further challenges regarding combination therapy and tight control. An important remaining question is how to translate the beneficial results achieved with combination therapies on the group level to individual treatment choices. Individual patients differ in their disease course, drug metabolism and response to therapy, thus some might be less in need of initial intensive, costly and possible toxic treatments than others. Vice versa, some patients would benefit from direct start of biologicals but are now obliged to first use (and fail) conventional DMARDs, as these expensive drugs are not yet reimbursed as initial therapy. Therefore, if we would be able to predict the prognosis and the response to different treatment strategies for individual patients, this would be helpful for rheumatologists in weighing the initial treatment choice and it might have implications for health economics.

Combination versus monotherapy: individualized treatment choice

A step towards more individualized treatment decisions was made in chapter 9, where

a practical matrix model has been developed for the prediction of rapid radiographic progression in recent-onset RA patients, using data from the BeSt 'Behandel Strategieen in RA' study.[48] In contrast to previously developed algorithms or models, the matrix model is easy to use, needs only a limited number of clinical variables and originates from a dynamically treated patient population (aimed at achieving and maintaining a DAS ≤2.4) resembling clinical practice. In addition, the matrix has included the treatment choice as one of the most important predictors for outcome, something which is not often acknowledged. Furthermore, the matrix takes conventional logistic regression one step further, by filling in the prediction rule (regression formula) and visualizing the individual risks associated with all possible combinations of risk factors.
As a result, from the matrix, for patients with various combinations of risk factors, including ACPA and/or rheumatoid factor (RF) status, C-reactive protein and the presence of baseline erosions, the risk for rapid radiographic progression can be estimated for initial monotherapy or initial combination therapy including prednisone or anti-TNF (infliximab). Numbers-needed-to-treat were calculated to give an indication on how many patients would have to be treated with initial combination therapy to prevent one patient from rapid progression. The results confirmed that in many patients the risk was reduced with initial combination therapy compared with monotherapy and numbers-needed-to-treat were relatively low for high risk profile patients.[48] However, the matrix also showed a subgroup of patients with a milder risk profile who were not prone to show damage progression with 91% certainty, if treated with initial monotherapy. This allows speculation on which might be worse: initial undertreatment or initial overtreatment.
It is obvious that the choice of treatment is not only governed by the need to prevent radiographic progression, but also to rapidly improve symptoms and functional ability. Investigated, but not included in this thesis, is a second matrix model to identify patients with a high risk for functional impairment after three months of treatment, defined as a HAQ >=1.[49] Predictors were different from the first matrix and included a high baseline HAQ, high self-reported pain, high Ritchie Articular Index, and the initial treatment choice. Numbers-needed-to-treat were relatively low for all subgroups, while after 1 year in both the monotherapy and the combination therapy groups, the majority of patients achieved a HAQ<1. With the knowledge that HAQ is influenced by multiple factors, is partly reversible and in contrast to radiographic damage, is not a cumulative reflection of disease activity, it is probably less well suited to use in a matrix prediction model.
Still, patients benefit in several ways if the initial treatment is chosen correctly on the basis of individual risk profiles: they can have earlier functional improvement and can look forward to better functional and radiographic outcomes in the long-term. After validation of the matrix model in other cohorts, it might be used for identification of patients with a substantial risk for a worse disease course as potential candidates for early intensive treatment.

Tight control

Another challenge regards tight control, meaning frequent treatment evaluations and adjustments aiming at a pre-defined level of minimal disease activity. A recent international task force has proclaimed tight control as the optimal management of RA and has formulated recommendations for 'treating to target', as this improves the outcome of RA.[32,50] Clinical remission, defined as the absence of signs and symptoms of inflammatory disease activity, is chosen as the primary target of treatment, and should be periodically assessed by a validated (composite) measure such as the DAS.[7] Ideally, clinical remission is maintained even after discontinuation of treatment, resulting in what could be called 'cure'. Such a state of drug-free remission has been reported in RA patients in which the disease might have faded out[51-53], but the BeSt study has shown that drug-free remission can also be achieved in recent-onset RA patients after intensive DAS-driven therapy.[10] Thus, an important remaining question is whether DAS-driven therapy leads to more sustained drug-free remission, earlier in the disease course, or in patients with more severe disease than routine non-DAS-driven therapy adjustments.

Drug-free remission

The ideal methodological setting to test this hypothesis would be a randomized controlled trial evaluating DAS-driven versus non-DAS-driven therapy. However, such a trial would now be considered unethical given the established superiority of DAS-driven therapy on clinical and radiographic outcomes. Therefore, in chapter 10 of this thesis, two existing cohorts were compared, one representing DAS-driven therapy (the BeSt cohort) and one representing non-DAS-driven therapy (the Leiden Early Arthritis Cohort). This comparison, however, was not straightforward, due to differences in baseline characteristics, follow-up systematics and remission definitions. Nevertheless, the DAS-driven cohort comprised patients with worse prognostic outlook, while the patients in the non-DAS-driven cohort appeared to have milder RA. Still, the drug-free remission percentages were similar (around 10%) in both cohorts, as were predictors for drug-free remission. Acknowledging the difficulties comparing these two cohorts, one can speculate whether DAS-driven therapy might counterbalance the poor prognosis at baseline by systematically suppressing inflammation, resulting in remission which is sustained even after discontinuation of antirheumatic drugs.

However, the absolute number of patients with sustained drug-free remission is still low and an important question is if and how we can attain more sustained drug-free remission in the future. Is it intrinsically limited to certain patients, or should we be able to induce this in all patients? Some of our observations may point towards the latter: the fact that with DAS-driven treatment drug-free remission was achievable in patients with more poor prognosis ACPA-positive RA, and the finding of short symptom duration as a determinant of drug-free remission, which may indicate a 'window of opportunity'. Thus, possibly, with earlier, more effective, more stringently steered treatment, higher success rates can be achieved.

Future perspectives

One of the major challenges in RA research will be the continuing search for effective strategies that can alter the disease course of UA patients towards a milder disease, more remission or even prevention of the development of chronic destructive RA. A second major focus will be the shift towards more personalized medicine by enhancing our knowledge on determinants of individual disease courses, treatment efficacy and toxicity. By continuing the fruitful collaboration between researchers covering the entire spectrum from basic molecular research to clinical patient-based studies, we can enhance our understanding of the principal mechanisms underlying RA, translate these into new therapeutic modalities and ultimately implement them into clinical practice. This will hopefully enable us to effectuate the window of opportunity and target RA at the right time, in the right patients, with the right intervention.

Important advances in basic genetic research have been the genome-wide association studies, from which, next to confirmation of known genetic loci, new genes have been identified which are associated with disease susceptibility or progression, such as TRAF1-C5 and STAT4.[54] Replication studies, sequencing and ultimately functional studies will provide us insight into how genetic variants of genes and their functionally derived proteins contribute to disease processes in RA. Other researchers follow a more hypothesis-driven approach of studying candidate genes, encoding for proteins known to be involved in important immunological pathways, such as complement, cytokines or T- and B-cell structures. Irrespective of the search strategy, identified candidate molecules might show promising targets for future treatment. With the help and innovations of drug engineering companies, new drugs can actually be manufactured. Current developments include Blys inhibition (atacicept), IL-6 antagonism (rather than IL-6 receptor blockade), and protein kinase inhibitors (tofacitinib, fostamatinib), but also newer-generation B-cell-depleting agents and TNF-inhibitors (certolizumab and golimumab) are being produced.[55] As a result, we can expect the choice of therapy to broaden rapidly in the upcoming years.

The value and place of these new drugs in the existing armamentarium, once approved for use, preferably have to be evaluated through large randomized clinical trials. Despite extensive experience with trials in the rheumatology field, this will not be an easy task. A first question is whether to evaluate new drugs as first line therapy, second line therapy after failure to conventional DMARDs, or as treatment for persistent non-responders? Finding a therapy for patients who are refractory to current treatment modalities poses a challenge, but if prevention of the development of chronic erosive RA is the treatment goal, this would have to be evaluated in an as early as possible disease phase, the definition of which, as discussed previously, in itself is still controversial. Using the new 2010 ACR criteria for RA as inclusion criteria would enhance comparability between trials and generalization to clinical practice. But shouldn't patients with earlier undifferentiated arthritic disease be included too? Weighing the risk of progression to RA with the risk of treatment toxicity and costs, there is reluctance to move too far away from the first presentation of a patient with an inflamed joint, as starting point for treatment. With the help of translational research, in the coming years, hopefully the early stages of RA will be further characterized in biological terms (gene-ex-

pression, antibody repertoire, cytokine patterns, bone markers). This might provide us with more specific tools to enhance our prediction models and improve our diagnostic criteria, so we can better select patients for clinical trials or pre-specify subgroups for statistical analyses.

Instead of comparing new therapies against other treatment modalities in a head to head fashion, it would be more valuable from a clinical point of view to evaluate strategies of various combinations and/or orders of drugs, in multi-arm trials, following the example of the BeSt study. This would yield valuable information for daily clinical practice, and provide the opportunity to sort out optimal therapeutic strategies as a basis for developing guidelines. Difficulties, however, are the increasing number of drugs to be included, the need for extensive logistics and dedication of doctors and research nurses cooperating in large trials, the high costs involved with the use of medication in a stage for which it is not reimbursed (yet) and reluctance of the pharmaceutical industries to engage in such comparative trials. Still, innovative trials have proved to take clinical research and patient-care to a higher level, which emphasizes the importance of investigator-driven independently-sponsored research.

Finally, the choice of statistical analysis can also be a matter of debate. One could argument that trials should be performed separately for ACPA-positive and ACPA-negative patients, or designed with sufficient power to investigate distinct subgroups in a post-hoc manner. However, the more predictive factors and characteristics will emerge, the more fractured analyses will become, resulting in weak associations due to loss of power. Until distinct subgroups can be clearly specified and associations have been validated in multiple studies, traditional primary analyses can be performed on the group level, with additional graphical or numerical demonstration of individual responses to give better insight into the variation within the group. In combination with basic studies and pharmacogenetic data, this will add to the identification of relevant subgroups.

Since we are not there yet, an important step now is to continue the investigation of intensive remission-induction strategies, with currently available DMARDs and biological therapies, within the boundaries of what is ethically, clinically and financially manageable. Importantly, short courses of intensive therapy, followed by tapering and discontinuation of the anti-rheumatic medication in case of remission should be investigated. This provides both the chance to see whether the therapy has induced a fundamental change in the disease course of those patients who were prone to show progressive disease, and prevents continuation of overtreatment of patients with self-limiting disease, especially those among ACPA-negative patients.

One of the promising trials that are currently underway is the IMPROVED 'Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease' study, designed following results of the PROMPT and BeSt study. In this study, recent-onset UA and RA patients with at least one swollen and one painful joint are included and receive a common initial induction therapy with MTX and a high-tapered-to-low dose of prednisone for four months. The aim is to achieve clinical remission (DAS<1.6), in which case tapering and discontinuation of medication follows. The hypothesis is that with this strictly steered induction therapy RA can be prevented in the UA patients (both ACPA-positive and ACPA-negative) and longstanding remission or cure

might be induced in both the UA and RA patients. If this is not achieved with the initial induction therapy, the study continues as a randomized controlled, single blind trial, making a head to head comparison which would be the next best treatment step: extended DMARD combination therapy (with MTX, sulphasalazine, hydroxychloroquine and prednisone) versus the combination of MTX and the TNF-blocker adalimumab, two of the most relevant currently available combination therapies. The aim continues to be remission. In addition to data on remission induction and drug-free remission, the IMPROVED study will also provide results on the HAQ, radiographic progression, the impact on quality of life, work productivity, costs, and safety associated with these tightly controlled treatment strategies. At the time of the writing of this thesis, more than 600 patients have already been included in the IMPROVED trial and first analyses and results can be expected soon.

In the meantime, rheumatologists are confronted with early arthritis patients and treatment choices on a daily basis. How do the results of this thesis help them? Among other studies, the PROMPT study has contributed to the awareness of the benefit of starting early DMARD treatment in UA patients. For ACPA-positive UA, initial MTX therapy has shown efficacy and safety, although the effect was limited and the disease course was not profoundly changed. For ACPA-negative UA, MTX appears not to be the therapy of choice, but is it yet unclear which other strategy should be followed. Therefore, preferably, newly diagnosed UA patients should enter clinical trials, the participation of which in itself has shown to be beneficial. The recommendations for the management of MTX presented in this thesis will guide rheumatologists to more uniform use of this drug and are currently being translated into national guidelines in several countries.[56-59] The guidelines of the Dutch Association of Rheumatology have already recently been updated.[60] For recently diagnosed RA patients, it is still a challenge to translate existing guidelines and recommendations into individual treatment choices. The matrix model presented in this thesis, although not yet sufficiently validated, may help to estimate the risk of progressive, or even better non-progressive disease in terms of radiographic damage. This will reduce unnecessary costs and toxicity associated with 'suboptimal treatment choices' and will enhance rapid effective suppression of the disease. Irrespective of the treatment choice, tight control and steering at remission is being advocated and implemented more and more in clinical practice.

What remission really beholds both clinically and biologically will hopefully become clear in the next few years. Will we be able to find a so called 'master switch', a critical immunological event that may mark a point of no return in the inflammatory cascade, before which lies an opportunity to stop the disease process and beyond which chronicity is bound to occur? Whether such an event exists or whether with the right intervention inflammation can be controlled or even reversed, yet remains to be seen.

Ultimately, with early effective induction therapies in UA and intensive tightly controlled therapies in RA, which are tailored to the individual patient, we will hopefully be able to move away from the age old concept of RA as a chronic, progressive, disabling disease and attack it as a condition of emergency, to be stopped or cured at the earliest possibility.

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