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CHAPTER 10

Summary and conclusions
To date, only limited evidence is available to answer the question whether starting treatment already in the phase of undifferentiated arthritis (UA) is more effective than waiting until a patient meets classification criteria for rheumatoid arthritis (RA). As shown in chapter 2, the available evidence is not only limited, but there is also a huge heterogeneity in performed treatments and treatment strategies and in outcomes. Furthermore, the follow up duration of all trials is restricted and long term effects of the applied treatment strategies are not known.

The IMPROVED study, in which both patients with early RA and patients with UA were included, provides a valuable addition to the limited evidence for the beneficial effect of treating patients in early phases of RA, even before classification criteria are met.

**THE IMPROVED STUDY: AN OVERVIEW OF OUTCOMES**

In the IMPROVED study, patients with in an early phase of RA are intensively treated with combination treatment, introduced as early as in the phase of UA or early RA, and treatment is subsequently steered at the stringent goal of achieving remission. If remission was not achieved, medication was extended, either by adding more synthetic disease modifying anti-rheumatic drugs (DMARDs) to the initial treatment of prednisone and methotrexate (MTX), or by replacing prednisone with the biologic agent adalimumab. If remission was achieved medication was tapered, even until patients were in drug free remission. As early as one year after starting therapy, this goal was achieved in 20% of the patients. More than 50% of all patients were in remission and radiological damage progression was found in only 5% of the patients after one year. Also patient reported outcomes concerning functional ability and health related quality of life improved, and in a proportion of the patients even normalized, during the first year.

**STUDY POPULATION**

**Inclusion**

By protocol, DMARD-naïve patients with UA, defined as having at least one joint clinically diagnosed as arthritis and one other painful joint, not fulfilling the 1987 classification criteria for RA but in the opinion of the treating rheumatologist clinically suspect of early RA, and patients with early RA according to the 1987 criteria ¹ and with a symptom duration of less than 2 years, were included. In chapter 3 is shown that, compared to previous clinical trials in patients with early RA, ²-⁵ we included patients with a relatively mild baseline disease activity (mean Disease Activity Score (DAS) 3.2), short symptom duration (median symptom duration 18 (9-32) weeks) and almost no radiological damage present (median baseline Sharp-van der Heijde Score (SHS) 0 (0-0) and 12% of the patients had erosions). Mean age (52 years)
and percentages female and rheumatoid factor (RF) positive patients (respectively 70% and 56%) were comparable with previous trials. The percentage of patients with a positive test for anti-citrullinated protein antibodies (ACP A) (55%) was also comparable with previous trials, although in most previous trials ACP A status was not known at baseline, but measured afterwards. As ACP A nowadays can be routinely measured in the Netherlands, rheumatologists were often aware of the ACP A status of patients they included in the IMPROVED study. This may explain why the percentage of ACP A positive patients was higher than one might expect in patients with early arthritis.

Reclassification

As in 2010 new ACR/EULAR classification criteria for RA were introduced,6 we reclassified all patients participating in the IMPROVED study according to these new criteria. The new criteria aim to classify patients earlier in the disease course and give a lot of weight to the presence of ACP A and/or the presence of many arthritic joints. In chapter 3 we showed that 60% of the total study population fulfilled the 1987 classification criteria for RA and 40% were included as UA. Based on the new criteria 79% were classified as RA and 20% remained classified as UA. Thus, 19% of the patients were classified as RA by the 2010 criteria but not (yet) by the 1987 criteria. Compared to patients who were classified as RA according to the 1987 criteria,1 these 19% had a comparable symptom duration, but they had a slightly lower baseline disease activity (mean DAS 3.3 versus 3.5), mainly due to a lower median swollen joint count (7 (3-11) versus 8 (4-12)) and a somewhat lower median erythrocyte sedimentation rate (ESR) level (26 (12-41) versus 29 (15-45)). Other clinical variables were comparable.

In conclusion, compared to using the 1987 criteria, reclassification using the 2010 criteria did not result in identifying patients with a shorter symptom duration, but in classifying patients with a lower disease activity. Other studies, performed in early arthritis cohorts, showed similar results.7,8 These findings seem to challenge some of the intentions of the new criteria.

Undifferentiated versus early rheumatoid arthritis

Although we expected that UA patients we included would have a shorter symptom duration than RA patients, this was not the case, as was shown in chapter 3. UA and RA patients had a median symptom duration of respectively 16 (8-28) and 18 (9-34) weeks. Included UA patients had lower baseline disease activity than RA patients (mean baseline DAS 2.7 (0.7) versus 3.3 (0.9)), and only a few UA patients were ACP A and/or RF positive compared to almost 70% of the RA patients. Another difference was apparent in the distribution of affected joints. Sixty-eight percent of UA patients and 73% of RA patients had involvement of large joints, but 6% of the UA patients had involvement of only large joints compared to none of the RA patients. UA patients with only large joint involvement might have had other
rheumatic diseases than RA, such as osteoarthritis or spondylarthropathy, in particular when ACPA and RF were negative.

ACPA negative patients who were still classified as RA differed from ACPA positive RA patients. To meet the 2010 classification criteria, ACPA negative RA patients had to have a higher disease activity than ACPA positive patients, mainly based on more affected joints. At time of classification, ACPA negative RA patients also had a longer symptom duration than ACPA positive RA patients.

**MAIN OUTCOMES OF THE FIRST STUDY YEAR**

**Remission, drug free remission and joint damage progression**

In chapter 3 we showed that, after 4 months of remission induction therapy with MTX and a tapered high dose of prednisone, as many as 61% of patients with early arthritis achieved remission (early remission, defined as DAS<1.6), regardless of fulfilling the 2010 criteria. Ninety percent of patients had no radiological progression and in those who had progression it was minimal (median progression score 1(1-1)). In chapter 4 we demonstrated that after one year of remission steered treatment, 54% of patients in the IMPROVED study were in remission and only 5% of the patients had radiological damage progression of more than 0.5 SHS points. Remission was most often achieved in patients who achieved early remission after four months (68%) and 32% of these patients were able to taper all medication and achieved drug free remission as soon as after one year. Patients who did not achieve early remission and were randomized, less often achieved remission after one year. Those randomized to treatment with MTX and adalimumab, with an increased dose of adalimumab as possible next step, more often achieved remission after one year (40%) than patients who were randomized to the extended combination of DMARDs with continued low dose prednisone, reserving adalimumab as possible next step (25%). Radiographic progression and functional ability were similar between randomization arms.

Compared to previous trials in patients with early RA, percentages of patients achieving remission during the first year of the IMPROVED study were high and joint damage was more effectively suppressed. In other studies reporting similar high remission percentages after 1 year medication was not tapered. On the other hand, these studies included patients with early or established RA with a higher baseline disease activity than patients in the IMPROVED study. Drug free remission was previously reported in 17-29% in clinical trials, but never as soon as after one year. These results may be explained by the treatment strategy we used, starting early in disease course with combination therapy consisting of MTX 25 mg/week and a tapered high plus continued low dose of prednisone, followed by extending medication in those who did not achieve remission. Previously the beneficial effect of low dose corticosteroids compared to placebo was shown, and several trials showed the benefit
of DMARD combination including prednisone compared to DMARD mono therapy.\textsuperscript{2,3,5} In the recently published CAMERAII trial, a randomized placebo controlled trial in patients with early RA aimed at achieving remission, treatment with MTX was compared with MTX plus low dose prednisone. After 2 years of remission steered therapy, patients treated with MTX plus low dose prednisone had less radiological damage progression and more often and sooner achieved remission than patients treated with MTX alone. Remission percentages in this trial were comparable with percentages we found in the IMPROVED study, although in contrast with the IMPROVED study, there was no ability to taper medication as soon as remission was achieved.\textsuperscript{16}

However, other explanations for the high (drug free) remission rates and nearly absence of radiological damage progression in the IMPROVED study may also be possible, such as the fact that early arthritis patients with a low disease activity at baseline may not have damage progression (yet) and may easier achieve the treatment goal of a DAS < 1.6. Also, some UA patients and patients who fulfilled the 2010 classification criteria may have had self-limiting forms of early arthritis, that would have gone into spontaneous remission without the use of medication.

Compared to the DAS-remission criteria that we used to steer treatment adjustments in the IMPROVED study, the Boolean based ACR/EULAR preliminary definition published in 2011\textsuperscript{17} appeared to be a more stringent definition, as fewer patients achieved remission according to this definition after 4 months (26%) and after 1 year (24%). In patients who were in DAS-remission but did not fulfill the Boolean based remission definition, this was most often due to a VAS global health ≥ 10. Recently, similar results were observed in the DREAM study,\textsuperscript{18} in which also was shown that residual disease activity was only present in the minority (32%) of these patients. Thus, although the Boolean based definition is more stringent, the question raises whether it may be too stringent, resulting in patients in clinical remission not fulfilling this definition.

**Never achieving remission during the first year**

Results of chapter 4 showed that despite of the progressive treatment strategy aiming at remission, still 16% of patients did not achieve remission during the first year of treatment. Also, 5% of the patients had radiological damage progression after 1 year, although with a limited progression rate (median progression score of 1 and only one patient had rapid radiological progression of 18 SHS points). Patients who never achieved remission throughout the first year were characterized by a higher mean baseline disease activity (mean DAS 3.7 (0.9) versus 3.2 (0.9)), a longer symptom duration (24 (12-44) versus 17 (8-31) weeks) and included more females (89% versus 63%) compared to patients who achieved remission at least once. It is possible that these patients might have benefitted from starting treatment earlier when disease activity was still lower, or from treatment with other drugs. Follow up
therapy with other biologic therapies than adalimumab might have been more effective in these patients.  

**Patient reported outcomes**

In chapter 5 we showed that patient reported outcomes (PROs) at baseline, such as functional ability measured by the Health Assessment Questionnaire (HAQ) and McMaster Toronto Arthritis questionnaire (MACTAR) and health related quality of life measured by the Short Form-36 (SF-36), were lower in this population of early arthritis patients than in the general population. Only mental health, measured by the mental component score (MCS) of the SF-36, seemed not to be affected, since mean MCS in the IMPROVED study participants were comparable to the general population throughout the first year. During the first year, functional ability and physical health improved, with the greatest improvement occurring in the first four months. Improvement was largest in patients who achieved early remission. In this group, mean or median values of the HAQ and SF-36 after one year returned to levels comparable to those in the general population. In randomized patients, no differences were seen between treatment arms. In all patients, achieving remission during the first year was associated with better functional ability and health related quality of life than not achieving remission. These results suggest that with the current treatment strategy, PROs reflecting functional ability and physical health improve, and in part of the patients even normalize within one year after diagnosis. Achieving early remission after four months and achieving remission throughout the whole year improved PROs most.

Results of chapter 7 showed that minimal depressive symptoms were present among patients participating in the IMPROVED study. Depressive symptoms severity decreased with lower disease activity and was significantly lower in patients who achieve remission than in patients who did not. Mostly, this was due to symptoms of arthritis, such as pain and unwell being, rather than signs of inflammation, suggesting that depressive symptoms in RA patients may improve if symptoms of RA are optimally suppressed.

**Metacarpal bone mineral density**

In chapter 9 we explored changes in metacarpal bone mineral density (BMD) loss during the first year of remission steered treatment. The IMPROVED study is the first clinical trial in which metacarpal BMD was monitored this intensively and this early in the disease course of RA. These data however have to be interpreted with care, because they were imputed because of many missing values and most differences found were small. The data suggested that over half of the patients had metacarpal BMD loss after 4 months after 1 year (respectively 56% and 55%), and some patients might even have metacarpal BMD gain after 1 year (14%).

Our finding that more than half of these patients early arthritis, having a relatively mild disease activity and being treated intensively, may have had metacarpal BMD loss after 4 months, may be due to the initial treatment with a tapered high dose of prednisone. Only
a minority (13%) of the patients seem to totally regain this metacarpal BMD loss during the subsequent months. Longer follow data are needed to see whether this loss may be regained in the other patients in the second year or later. Another explanation may be the initial disease activity, although in these data, baseline disease activity was not found to be predictive of metacarpal BMD loss after 4 months.

The data may also suggest that patients who had achieved early remission and tapered medication, showed more metacarpal BMD loss than patients who were randomized to extended combination therapy. This may be explained by the intensive combination therapy randomized patients achieved, either including low dose prednisone or adalimumab. On the other hand, the fact that patients who achieved early remission tapered medication and that part of them lost remission, might also explain this possible difference. Although based on small numbers, the original data may furthermore suggest that patients treated with adalimumab may show the smallest loss in metacarpal BMD and most often metacarpal BMD gain after 1 year (54%, compared to 21% in patients randomized to combination therapy including prednisone and 12% of early remission patients). This is in line with previous research, showing that anti-TNF alpha inhibitors may reduce generalized as well as localized bone loss in patients with RA. 20-23

Adverse events
Adverse events were reported in 56% of the patients during the first 4 months, as was shown in chapter 3. Most adverse events were mild and temporary, but in 3% of the patients serious adverse events occurred including the death of two patients, one of a pneumonia left untreated by wish of the patient and one of a myocardial infarction later found to be caused by a giant cell arteritis. None of the serious adverse events were suspected unexpected serious adverse events (SUSARs). In general, initial combination therapy with MTX and a tapered high and continued low dose of prednisone appears to be safe on the short term. However, fourteen of sixteen serious adverse events (infections, cardiovascular disease, femoral head necrosis, diabetic complications) might have been related to the use of prednisone. Further follow up will show whether there are long term consequences of this induction therapy. Previous data of the COBRA trial, in which the same tapered high dose of prednisone was used, suggest that a tapered high dose of prednisone, in combination with MTX and SSZ, can be used safely. 2,24 Previously, no evidence has been found for long term complications of short term use of low dose prednisone. 15

In chapter 4 we showed that from 4 months two one year adverse events were reported in 57% of the patients. The lowest percentage of adverse events was reported in the early remission group (53%) and adverse events were reported in similar percentages in the randomization arms (74% in arm 1 and 68% in arm 2). Adverse were generally mild. Serious adverse events were reported in 4% of the patients, including 3 patients who died; one of a squamous cell carcinoma of the tongue (early remission group), one of a cerebral tumor (arm
2) and one of an ovarian carcinoma (OP group). Serious adverse events that were possibly related to the use of adalimumab were: pneumonia, cerebral tumor, percutaneous coronary intervention for myocardial infarction, exacerbation of chronic obstructive pulmonary disease and cerebrovascular accident. None of the serious adverse events were SUSARs. In summary, also after 1 year, adverse events were generally mild and combination treatment with multiple DMARDs and low dose prednisone seemed to be equally safe as treatment with MTX and adalimumab.

LIMITATIONS OF THE IMPROVED STUDY

No control group
To avoid the need of excessive patient numbers, no control group was included in the IMPROVED study to verify the superiority of the initial combination treatment. Instead of finding the best initial treatment, we decided to use a combination of two drugs, proven very effective as initial treatment for patients with active RA, in all patients and focus on identifying the best follow up treatment when the initial treatment did not result in remission. This means we also do not know how many UA and RA patients would actually have achieved remission spontaneously and thus which part achieved remission and drug free remission due to the applied therapy.

Single blind study
This study was a single blind study. For practical reasons, only research nurses who did the four monthly assessments were blinded, while patients and doctors were aware of the allocated treatment. Several years after the introduction of biological agents, patients participating in the BeSt study were shown to have a preference for combination therapy including infliximab and disliked taking prednisone. In the IMPROVED study, patients might also have had a preference for combination therapy including a biological agent, in this case adalimumab, which might have biased our results. However, almost none of the patients randomized to the combination of multiple DMARDs and low dose prednisone refused to start with this therapy.

Definition of remission: DAS <1.6
Remission was defined as a DAS <1.6 and treatment was steered at this definition. In the past, it has been shown to correspond well to the 1981 ACR preliminary criteria for clinical remission. However, because this definition allows for one or two swollen or painful joints, some say that it reflects low disease activity rather than remission. Recently two new definitions for remission have been proposed. In the IMPROVED study, the Boolean based definition for remission appeared to be more stringent than the DAS-definition. In future,
one of the provisional definitions may best be used to reach uniformity among clinical trials. However, it remains questionable whether the various remission definitions are associated with significant differences in clinical and radiological outcomes.\textsuperscript{38}

**Protocol deviations**

Protocolized treatments adjustments in the IMPROVED study were integrated in daily practice, which led to a considerable amount of protocol deviations for several reasons. Sometimes the treating rheumatologist disagreed with the required treatment step or with the DAS evaluation by the research nurse. For example, a DAS might have been high due to an elevated ESR or painful joints due to other reasons than RA activity. In this case rheumatologist deviated from the protocol because the patient was clinically in remission. Also, the fact that we steered at remission defined as a DAS <1.6 might have caused protocol deviations. When for example the DAS was 1.6 or just >1.6, treatment had to be intensified according to the protocol but sometimes rheumatologists hesitated to do so. Or sometimes they might have hesitated to taper medication when the DAS was <1.6 but they felt there still was some residual disease activity.

In 50 patients who did not achieve remission after 4 months, the protocol was not followed and patients were not randomized (Outside of Protocol group, OP group). In 17 of these patients prednisone was tapered, probably because these patients were estimated by the rheumatologist to be in clinical remission, but the DAS was >1.6 due to other reasons. In other patients several other treatment steps were taken for different reasons. In most cases treatment remained steered at remission, but this was clinical rather than DAS-remission. After 1 year, outcomes of the patients in the OP group were similar to patients who had been randomized to arm 1, suggesting that following the current treatment strategy may lead to better disease outcomes than treatment outside of protocol.

**UA versus RA**

We included UA patients ‘clinically suspect for RA’ because we expected that these patients would represent RA patients with a shorter disease duration than classifiable RA patients and might achieve remission in a higher rates. This would support the window of opportunity theory.\textsuperscript{25,26} Our results in chapter 3 however showed that UA patients did not have shorter symptom duration at inclusion of the study than RA patients (median (IQR) 16 (8-28) versus 18 (9-34) weeks, respectively). It is thought that the first twelve weeks after symptom onset offer the best opportunity to stop or reverse the disease process that otherwise may become chronic and destructive. This means that for 64% of the UA patients as well as for 66% of the RA patients with a symptom duration ≥ 12 weeks, the window of opportunity may have been missed.
UA patients also may have had a favorable outlook compared to the RA patients because on average they were included with a lower disease activity, and almost all were auto-antibody negative, possibly including patients with self-limiting forms of arthritis. However, as shown in chapters 3 and 4, we found no differences between UA and RA patients in percentages (drug free) remission, functional ability or radiological joint damage progression after 4 months or 1 year. Besides having missed the window of opportunity, some UA patients may not have had self-limiting arthritis but rather a type of rheumatic disease that did not respond to the given therapy (for example osteoarthritis or spondylarthropathy).

**PRESENCE VERSUS ABSENCE OF ANTI-CITRULLINATED PROTEIN ANTIBODIES**

The presence of ACPA is known as a factor associated with a higher disease activity, more functional disability and more radiological damage progression in patients with RA. Therefore we were surprised to find that after one year in the IMPROVED study, as described in chapter 6, ACPA positive patients achieved remission and drug free remission equally often as ACPA negative patients and also functional ability and radiological damage progression both were similar in ACPA positive and negative patients. After the initial combination therapy of MTX and a tapered high dose of prednisone, ACPA positive patients even achieved remission more often than ACPA negative patients. This might suggest that ACPA positive patients responded better to the initial combination therapy than ACPA negative patients. Previously, results of the PROMPT study showed that in ACPA negative UA patients MTX was not superior to placebo treatment, while in ACPA positive patients MTX resulted in suppression of progression to classifiable RA and suppression of joint damage progression. This suggests that ACPA negative UA responds less well to anti-inflammatory treatment than ACPA positive UA, and therefore may be driven by different disease pathways.

Furthermore, results of chapter 6 showed that of those patients who achieved early remission, and by protocol of the IMPROVED study were able to achieve drug free remission (DFR) after 1 year, 32% actually achieved DFR after 1 year. Of those, 55% were ACPA positive, compared to 61% of the patients who achieved early remission but not DFR after 1 year (no significant difference). Patients in DFR after 1 year were less often RF factor positive than patients not achieving DFR (50% versus 62%).

In the following 4 months, 30% of the patients who had achieved DFR after 1 year, lost it. These patients were more often ACPA positive than patients who did not lose DFR (72% versus 47%), and ACPA positive patients less often sustained DFR than ACPA negative patients (58% versus 80%). This suggests that compared to ACPA negative patients, ACPA positive patients have a similar likelihood of achieving and maintaining remission, even while medication is tapered. But after having successfully tapered and discontinued medication, ACPA positive patients show more relapses in disease activity in the next 4 months.
CHAPTER 10

PREDICTION OF DISEASE OUTCOME BY METACARPAL BONE MINERAL DENSITY

We showed in chapter 8 that metacarpal bone mineral density (BMD) loss in the first 4 months after diagnosis was predictive for radiological damage progression after 1 year of remission steered treatment in the IMPROVED study, independent of several known predictors. The presence of baseline erosions was found to be the only other predictor, but 86% of the total study group had no erosions at baseline and 17 (5%) still developed radiological progression (63% of all 27 patients with radiological progression). In patients without baseline erosions no predictors other than metacarpal BMD loss after 4 months were found.

Preferably, an outcome predictor would be present at baseline. But with the lack of baseline predictors, especially in patients without baseline erosions, and with achieving remission after 4 months also not being predictive for future joint damage, metacarpal BMD loss after 4 months may be a useful new predictor in patients with early arthritis.

Furthermore, several known predictors of (rapid) radiological progression, such as ACPA and/or RF positivity and baseline CRP or ESR level, were not found to be predictive of progression in this population with almost no progression present after 1 year. This may be explained by the treatment strategy we applied, starting early in disease course with combination treatment and steering at remission, which may have prevented progression of radiological damage. But it may also be possible that radiological progression would, also without medication, hardly be present in this early arthritis population with a relatively low disease activity.

In conclusion, early metacarpal BMD loss may be used in clinical practice or may be added to known prediction models of disease outcome in patients with RA to steer early treatment decisions with the ultimate goal of preventing radiological joint damage.

FUTURE PERSPECTIVES

Data in this thesis suggest that, with the treatment strategies applied in the IMPROVED study, disease outcomes have indeed been further improved in early phases of RA. Remission and even drug free remission can be achieved in higher proportions of patients and earlier in disease course than before. Future results of the IMPROVED study will show for how long and in which patients remission and drug free remission can be sustained, if tapering of medication and achieving drug free remission is also possible in patients who were randomized, how many and which patients will have radiological progression, and what will be the best follow up treatment strategy in patients who did not achieve remission within the first year. After one year, remission was achieved in approximately half of the patients, of which about one third were in drug free remission. To achieve these goals in the majority, or ultimately even in all patients, treatment strategies still need further optimization.
Even including results of the IMPROVED study, the current evidence of treating patients in the stage of undifferentiated arthritis is limited and very heterogeneous. Further research has to elucidate the optimal period to start treatment and the optimal treatment strategy. Starting therapy within twelve weeks after symptom onset may further improve outcomes, but may also increase overtreatment of patients with a self-limiting type of arthritis. In these patients, tapering medication as soon as remission is achieved may further minimize the risk of side effects.

Targeting treatment to low disease activity has been shown to benefit patients with RA and our results as well as data from the FINRA-Co and NEORA-Co study suggest that remission as treatment target may be even better. However, a randomized trial with a head to head comparison of the same treatment strategy aiming either at low disease activity or at remission has not been done. Until such a trial has been performed, no definitive statement can be made on the superiority of remission over low disease activity as treatment goal.

Adding short term prednisone to one or more DMARDs may become a new cornerstone in the treatment of RA. It has been shown to suppress disease activity and radiological damage as effectively as combination therapy including a biologic agent, but may offer a less expensive alternative. However, the optimal dosage and duration of therapy has still to be determined and future research has to ensure that short and long term side effects are indeed acceptable.

In patients who do not achieve remission on initial DMARD therapy in combination with prednisone, follow up treatment with early introduction of a biological agent seems to result in more patients achieving remission. Whether drug free remission is also achieved more often or whether damage progression is more effectively suppressed still has to be determined. If this is the case, exchanging prednisone for a biologic agent in these patients may be the best next step in their treatment strategy.

There is an ongoing search for new predictors to further optimize current prediction models for disease outcome in patients with RA. Early bone loss may be a candidate for further improvement of predicting the disease course in individual patients. To improve prediction even more, future research has to reveal more new predictor candidates. Being able to accurately predict disease outcome in all patients with RA will offer the best opportunity to choose the most advantageous treatment strategy for all individual patients.

In conclusion, the current treatment strategy, including early start of combination therapy and steering treatment at remission, may have contributed to the high remission and drug free remission rates and the nearly absence of radiological damage progression after one year in patients with early arthritis. However, current treatment strategies still need further optimization with the ultimate goal of achieving these outcomes in the future in every patient in an early phase of RA.
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SUMMARY AND CONCLUSIONS


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