Review
Aspects of early arthritis
Definition of disease states in early arthritis: remission versus minimal disease activity

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Abstract

With regard to rheumatoid arthritis, remission as currently used in the literature can have two meanings: either a state with persistent absence of clinical and radiological signs of disease activity without being treated for a specific time period, or it may point to a disease state with minimal disease activity during antirheumatic treatment. A risk factor for the first is absence of autoantibodies, with the anti-CCP-antibodies as best predictors, whereas risk factors for achieving a drug-induced state of minimal disease activity are not well defined. These definitions of remission refer to different disease states; therefore, we propose that the term remission is reserved for patients that are not treated with antirheumatic drugs.

Introduction

Since it was first named by Sir AB Garrod in his treatise of 1859 [1], rheumatoid arthritis (RA) has been considered a chronic disease, which implies that the curing of it or longstanding remission from it is an uncommon course of the disease. Although remission has always been the ultimate goal of treatment, during the times of the pyramid treatment strategy the prevalence of remission was low and the main effect of therapy was to slow the progression of the disease. The observation that even patients with low disease activity exhibit an increase in disability as well as radiographic progression has prompted the rheumatological community to perform trials that have shown that tight control of disease activity is the best way to prevent disability [2]. The availability of more aggressive treatment strategies, including the use of biologics, has increased the ability to achieve remission. This has pressed rheumatologists to reconsider the description of a remission.

Within the concept of remission, two clinical states must be separated (Figure 1). First, remission can be defined as a state in which there is absence of disease activity without any concomitant use of drugs, which seems compatible with the curing of RA. This state necessitates the absence of clinical evidence for arthritis and no progression of radiological damage during a specific time period without the use of disease modifying antirheumatic drugs (DMARDs). Today, this form of remission is achieved by only a small percentage of patients and is either drug-induced or the result of the natural disease course (natural remission). Patients with a pure natural remission have never been treated with DMARDs. Second, the term remission is often used to describe a disease state in which RA patients have a (very) low disease activity while using DMARDs. In this case, remission is considered as a disease state at the lower end of the continuum of disease activity and signifies that a patient is optimally treated. The present article reviews the currently used definitions for, and characteristics associated with, these different disease states with a focus on recent-onset arthritis.

Natural remission

Recent-onset arthritis bears the inherent problem that classification of the disease is difficult [3]. In an analysis of the first 1,000 patients included in the Leiden Early Arthritis Clinic at 2 weeks, only 10% fulfilled the criteria for RA, and a about a third of the patients presented with an undifferentiated arthritis (UA) [4]. From several inception cohort studies it is known that some of these UA patients remit spontaneously, some (about one-third) develop RA and the rest remain undifferentiated or develop other rheumatological diagnoses [4].

The development of RA seems to be a multistage process, in which a number of genetic and environmental factors trigger the development of UA and a subsequent amount of triggers is required for progression towards RA (Figure 2). The number and the identity of the triggers needed for the development of RA are only partly known, but the chance to remit spontaneously is lower in established RA than in UA. It

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ACR = American College of Rheumatology; CCP = cyclic citrullinated peptide; DAS = disease activity score; FDA = US Food and Drug Administration; RA = rheumatoid arthritis; TNF = tumour necrosis factor; UA = undifferentiated arthritis.

Figure 1
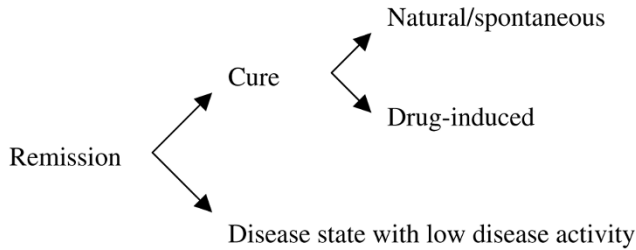
Different clinical states that are indicated as remission in the current literature. The 'cure' state necessitates the absence of clinical evidence for arthritis and no progression of radiological damage during a specific time period without the use of disease modifying antirheumatic drugs. In the 'disease state with low disease activity' definition of remission, treatment with disease modifying antirheumatic drugs is allowed and this points to a disease state at the lower end of the continuum of disease activity and signifies that a patient is optimally treated.

must be realised that in the literature there is no accepted definition or classification criterion for natural remission. Thus, the observed prevalence of natural remission depends on the definition that is chosen, the setting (community or hospital) or patient population (UA or RA) and the duration of follow-up. In this perspective, it is relevant to emphasize important data from population-based studies from the 1960s (reviewed in [5]) in which a profound difference was observed in patients in clinical settings compared to population-based settings. Intriguingly, it was observed that RA identified in population-based settings is often a self-limited process because in the group of individuals with RA that were reviewed 3 to 5 years later, RA could still be observed in only about 30% of them, indicating the relevance of the setting for the frequency of natural remission.
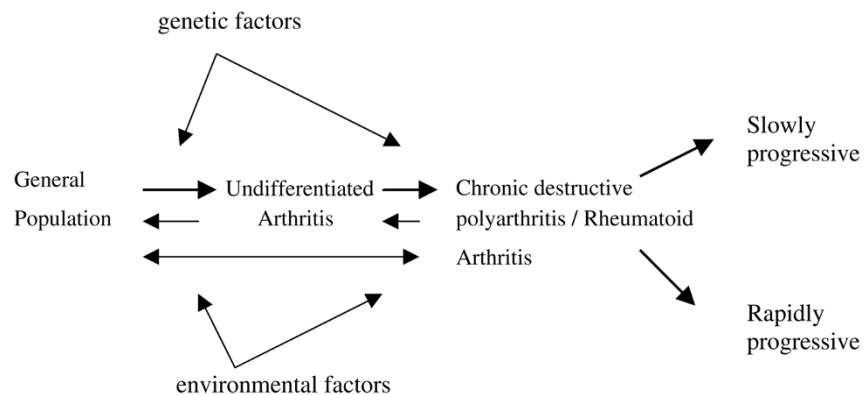
Natural remission in undifferentiated arthritis

Harrison and colleagues [6] defined natural remission as the absence of arthritis at physical examination after cessation of DMARDs, including steroids, for at least 3 months. In this study, 358 patients with early arthritis that were included in the Norfolk Arthritis Register were examined; assessing the subgroup of patients that presented with UA revealed that 42% of them had achieved natural remission after 2 years follow-up [6]. A group of 112 patients with UA was followed in Birmingham, UK, and after one year a remission rate (defined as complete resolution of symptoms) of 55% was found [7]. Van Aken and colleagues [8] studied the first 1,064 patients with an early arthritis that were included in the Leiden Early Arthritis Cohort. At presentation, 330 patients had an UA and after one year follow-up about one-third of these patients was in remission (persistent absence of arthritis at examination) and, therefore, were discharged from the outpatient clinic [8]. In a study including 100 patients with UA (Leeds, UK) a lower remission rate was observed in comparison with the above-mentioned studies [9]. Remission (absence of symptoms in patients receiving no treatment) was observed in 13% after 1 year follow-up [9]. In conclusion, the frequency of natural remission in UA seems to vary between 13% and 55%.

Risk factors for natural remission in undifferentiated arthritis

Both Harrison and colleagues [6] and Tunn and Bacon [7] performed logistic regression analyses to identify factors that were independently associated with natural remission. Although the number of swollen joints, male gender [6] and the absence of rheumatoid factor [7] were recognized as independent predictive variables to achieve a natural remission, the explained variability of these analyses was too low to result in a model that, in UA patients, adequately predicts the chance to remit spontaneously [6,7]. Notably, the presence of HLA class II alleles, in particular DR4, was associated with persistency of disease [10].

Figure 2

Multiple hit model for the development of rhematoid arthritis.

A recent analysis using early arthritis patients included in the Leiden Early Arthritis Cohort revealed that, of a total of 1,700 patients, 570 patients had an UA at inclusion and that, after 1 year of follow-up, 150 patients (26%) were discharged from the outpatient clinic because of the repeated absence of signs and symptoms of arthritis. Assessing clinical and serological characteristics in a logistic regression analysis with the presence/absence of remission as dependent variable revealed that the number of swollen joints, the absence of anti-cyclic citrullinated peptide (CCP) antibodies and the level of sedimentation rate were independently associated with the chance to achieve a remission (unpublished data, Van der Helm-van Mil). Also in this analysis, however, the fraction of explained variance was low and the three independent predictive variables had insufficient discriminative ability to be used in clinical practice for the identification of the patients with a high risk to achieve a natural remission. It is intriguing that the original observation of Salmon and colleagues from 1993 [10] is reproduced and explained by our recent data from 2005/2006. In fact, HLA class II alleles such as DR4 that form the 'shared epitope' are not primarily a risk factor for RA but for the presence of CCP antibodies [11,12]. With respect to the population-based cohorts studied in the 1960s, a similar observation was made. Rheumatoid factor was observed in only about 20% to 30% of the patients and these individuals were characterized by persistent disease [5]. In summary, the absence of anti-CCP antibodies is a strong risk factor for natural remission in UA.

Natural remission in rheumatoid arthritis
The rate of natural remission in patients with RA is evidently lower compared to patients with UA. In 1985, Wolfe and colleagues [13] investigated 458 patients with RA that were followed for 1,131 patient years. Of these patients, 14% achieved remission without being treated. In addition, in 1996, Prevoo and colleagues [14] described a cohort of 227 early RA patients with a median follow-up of 4 years and remission was observed in 9.5% of them. In a Swedish cohort of 183 RA patients with a follow-up of 5 years, a remission rate of 20% was described; 11% had a natural remission and 9% was drug-induced [15]. Linn-Rasker and colleagues [16] examined 285 RA patients and found that remission (in the absence of DMARDs for at least 1 year) was achieved in 10% of patients after a mean disease duration of 4.6 years. Some of the patients included in this study had been treated with DMARDs before achieving remission, although this involved mild drugs, such as penicillamine and hydroxychloroquine, which are expected to have little potency to induce a remission. A number of clinical characteristics between the patients that did and did not enter remission were compared, and only the presence of anti-CCP antibodies was associated with a lower risk to achieve remission [16]. In the above-mentioned studies, remission was defined by the absence of clinical characteristics. In a Finish study, the prevalence of radiological remission during an impressive follow-up period of 20 years was assessed;

102 rheumatoid factor positive, erosive RA patients were included and radiological remission (absence of radiological progression measured using the Larsen score) was found in 26% of patients [17]. However, some of the patients still had swollen joints at the time of the radiological remission, and the absence of both arthritis and radiological progression was observed in 19% of patients after a disease duration of 20 years [17]. In this study, the baseline ESR and number of swollen joints were not significantly associated with the chance of remission, the autoantibody status was not described, and a lower rate of joint destruction at inclusion did correlate with a higher percentage of remission [17].

In conclusion, the prevalence of natural remission in RA is reported to be about 10% and the absence of anti-CCP antibodies is correlated with natural remission in RA.

Drug-induced remission in rheumatoid arthritis
The effect of stopping DMARD therapy (several second line drugs but no tumour necrosis factor (TNF) inhibitors) in RA patients with a good long-term therapeutic response was assessed in a 52 week, randomised, double-blind, placebo-controlled study [18]. The 285 patients either continued the second-line drug (n = 142) or received a placebo (n = 143); the endpoint was a flare defined as recurrence of arthritis. At the study entry patients had been treated with DMARDs during (median) 5 years and at 52 weeks the cumulative incidence of a flare differed significantly between the placebo group (38%) and the continued therapy group (22%). The same trend was found for each second-line drug separately (antimalarial, parenteral gold, sulphasalazine, or metho-trexate), with the exception of d-penicillamine [18]. As the participants of this study were RA patients that already had low disease activity during therapy, the rate of drug-induced remission in the general population of RA patients cannot be deduced from it. Disease characteristics significantly associated with a flare were, in logistic regression analysis, the presence of rheumatoid factor and swollen joints [18].

Risk factors for natural or drug-induced remission in rheumatoid arthritis
Characteristics associated with natural or drug-induced remission in RA are the absence of anti-CCP antibodies/rheumatoid factor, a low number of swollen joints and a low level of radiological joint destruction at baseline [16-18]. Some genetic risk factors for RA, PTPN22 and HLA class II alleles, have been investigated in relation to the development of remission in RA. The absence of the PTNP22 T allele (risk allele) was not associated with a higher level of remission [19]. Also, the presence of the HLA alleles that encode the amino acids DERAA, which are associated with a lower odds ratio to develop RA and a milder disease course, did not induce a higher risk to achieve remission [20]. The shared epitope that includes HLA alleles was significantly less often present in the patients that achieved remission compared to the patients with persistent RA [20]; however, after

Table 1

Definition of remission as treatment outcome/disease state in RA

Remission criteria	Definition

ACR criteria	For clinical remission, a minimum of five of the following items must be present for at least two subsequent months:
	    Morning stiffness <15 minutes
	    No fatigue
	    No joint pain by history
	    No joint tenderness or pain on motion
	    No soft-tissue swelling in joints or tender sheats
	    ESR <30 mm/1st hour in women or <20 mm/1st hour in men

Disease activity score criteria	DAS remission defined as a score <1.6 using a compound index of the following measures:
	    Ritchie articular index of tender joints
	    44 swollen joint count
	    ESR
	    Patient's assessment of general health (measured on a 100 mm visual analogue scale)
	
	DAS28 remission defined as a score <2.6 using a compound index of the following measures:
	    28-joint count for tender and swollen joints
	    ESR
	    Patient's assessment of general health

FDA criteria	Remission
	    Requires achieving ACR clinical remission and absence of radiological progression (Larsen or Sharp-van der Heijde method) over a continuous 6 month period in the absence of DMARDs
	
	Complete clinical remission
	    Same as remission, but while continuing DMARD therapy
	
	Major clinical response
	    Requires achieving ACR70 response for at least 6 subsequent months (ACR70 response means 70% improvement of tender and swollen joint count coupled with improvement in 3 of 5 of the following: patient's assessment, physician's assessment, ESR or CRP, pain scale, Health Assessment Questionnaire)

The formula to calculate the DAS is: $0.54 \times \sqrt{\text{Ritchie articular index}} + 0.065 \times 44\text{swollen joint count} + 0.33 \times \ln\text{ESR} + 0.0072 \times \text{general health}$. The formula to calculate the DAS28 score is: $0.56 \times \sqrt{28\text{tender joint count}} + 0.28 \times \sqrt{28\text{swollen joint count}} + 0.7 \times \ln\text{ESR} = 0.014 \times \text{general health}$.

correction for the presence of anti-CCP antibodies, there was no association between HLA and remission, and only the absence of anti-CCP antibodies was independently correlated with the chance to remit spontaneously.

Remission used to indicate a state of low disease activity

To guide clinicians in evaluating treatment responses in daily practice and to define remission in clinical trials, standardized measures for remission have been formulated by the American College of Rheumatology (ACR), the European League against Rheumatism (EULAR) and the US Food and Drug Administration (FDA). The ACR criteria for remission include six core variables, of which five must be fulfilled for at least two consecutive months. These include fatigue, joint pain, joint tenderness, joint swelling, duration of morning stiffness, joint swelling, and ESR [21]. The EULAR response criteria use an index of disease activity (the disease activity score (DAS)), which is determined by a mathematical formula [22] (Table 1). The initial DAS counted 44 joints on swelling and included the Ritchie articular index for tender joints. The DAS28 uses an abbreviated 28-joint count for tender and swollen joints, omitting, among others, the feet [22]. Using the original DAS (44 joints), low disease activity is defined by

a score between 1.6 and 2.4, and remission is defined by a score below 1.6. When the DAS28 is applied, a score between 2.6 and 3.2 indicates low disease activity, and a score lower than 2.6 points to remission. In a Spanish random sample of 788 RA patients, the positive predictive value of each of the DAS28 indices was assessed: the positive predictive value for remission of a normal ESR was 7%, of morning stiffness <15 minutes 8%, of the absence of fatigue 9%, of the absence of joint tenderness 13%, of the absence of joint swelling 16% and of the absence of joint pain by anamnesis 28% [23]. The FDA has formulated the most rigorous definition for remission. These guidelines require that the ACR criteria for remission are met in addition to a radiological arrest (Sharp-van der Heijde or Larsen method) over a period of six following months in the absence of DMARDs [24]. Two less stringent response criteria were also formulated, complete clinical response and major clinical response [24]; according to this classification, complete clinical response is similar to remission while continuing antirheumatic therapy (Table 1).

It has been argued that the ACR criteria for remission are difficult to apply for clinical trials, as patients do not easily fulfill these criteria due to the time requirement of two months

and the inclusion of fatigue. Therefore, most recent trials currently use a DAS-based definition of remission or use the ACR70 response criteria. However, the ACR70 response criteria are not an adequate measure for remission as the concordance between ACR70 and DAS remission is low and ACR70 responders have a higher number of tender or swollen joints or ESR than patients in DAS remission [25]. Several studies have compared the DAS-defined remissions with the ACR criteria for remission or the DAS remission with remission according to the DAS28. Although it is reported that a DAS28 <2.6 corresponds to the ACR remission criteria [26], a recent report showed that DAS remission is more conservative than DAS28 remission and concludes that a DAS28 cutoff of 2.6 has insufficient validity to use in clinical trials [27]. A Finish comparison of remission according to the DAS28 and ACR criteria showed that a DAS cutoff value of 2.3 corresponds to the ACR criteria and that, even among patients with a DAS <2.3, tender joints were present in 19%, swollen joints in 11% and both swollen and tender joints in 7% [28]. The FDA clinical response criteria include a time requirement of six months; the percentage of patients achieving remission according to this definition is lower than the percentages when remission was assessed at one time point [25]. This time requirement seems relevant given data that show that when remission is based on a single time measurement disease progression can occur [29]. The most likely explanation for this observation is that either subclinical disease is present or the waxing and waning disease activity of a low disease activity state is measured at the lowest level thereby creating 'false-positive remissions'.

In conclusion, the DAS and ACR criteria are both an important outcome measure for treatment response in clinical trials. The ACR and FDA criteria contain a time constraint that results in a lower percentage of remissions in comparison with the assessment of remission at one time point. Obviously, a time constraint in the definition of remission leads to less 'false-positive' findings of remission in patient management. Therefore, in our opinion, the presence of a time condition in the definition of remission enhances the significance of the remission for use as an outcome measure in clinical trials, and when a DAS-based definition of remission is used, the study should consider repeating it over time in order to calculate the mean and standard deviation of the disease activity.

Remission used to indicate a state of low disease activity in rheumatoid arthritis

A number of studies have used the ACR criteria for remission or a DAS-based definition. In a study with a 3 year follow-up, ACR remission while using methotrexate was observed in 7% of patients and in 9% while treated with the combination of methotrexate, cyclosporine A and sulfasalazine [30]. After treatment for 48 weeks with cycosporin A monotherapy, ACR remission was achieved in 7% of patients and in 10% after the combined treatment with cyclosporine A and metho-

trexate [31]. Also, the COBRA trial used the ACR definition for remission (modified, with the fatigue criterion excluded) and observed a remission rate of 28% after 28 weeks of combined treatment with methotrexate, sulfasalazine and prednisone. However, almost all remissions ended after prednisone was stopped [32]. Investigating the disease outcome in RA patients treated with leflunomide showed a DAS28 remission in 13% after 6 months [33].

It is interesting to note that the remission rates while being treated with DMARDs are comparable with the reported natural remission rates in RA; both clinical states are described to occur in about 10% of the RA patients. However, the remissions under antirheumatic treatment are generally more rapidly achieved and, with the currently available data, the cumulative level of joint destruction can not be easily compared. As an alternative wording for 'state of low disease activity', one may consider the wording 'drug-requiring remission'. Given the fact that it is not known whether the patients with drug-induced remission differ from the patients with 'drug-requiring low disease activity', we propose the wording 'disease state with low disease activity' for this patient group.

Risk factors for a state of low disease activity in rheumatoid arthritis

The clinical or serological risk factors for achieving an ACR- or DAS-defined remission while being treated with DMARDs are not well defined. Intriguingly, while the presence of anti-CCP antibodies is unambiguously associated with persistency of joint inflammation, the absence or presence of autoantibodies in RA is not reported to be a powerful factor in predicting treatment responses. In a trial in which subanalysis has been reported, the presence of anti-CCP antibodies was associated with a higher chance to achieve a low disease activity state [34].

Can early and aggressive treatment increase the rate of (drug-induced) remission in RA?

An intriguing question is whether the now available anti-rheumatic treatment strategies can increase the percentage of RA patients that achieve a remission with the absence of both clinical signs of arthritis and progression of joint destruction that persists after the treatment has been stopped (drug-induced remission). A disease state formulated like this closely resembles the FDA definition of remission and might be regarded as 'cure' of the disease. In other words, since a small amount of RA patients (about 10%) remits naturally in the absence of treatment, the query now is whether current antirheumatic therapies are able to increase this number of patients, are capable of shortening the time period to achieve this remission and can reduce the level of joint destruction at the moment of remission.

The most effective treatment strategies at present are most likely the combination of TNF inhibitors with other DMARDs. For the combination of etanercept with methotrexate, a

remission rate of 41% (DAS remission) has been reported at the 2-year time point [35]. While using the combination of infliximab (6 mg/kg) with methotrexate, 31% of patients remitted (DAS28) after a follow-up of 54 weeks in the study of St Clair and colleagues [36]. In addition, in the BeSt study, treatment with infliximab and methotrexate combined with a tight control of treatment efficacy (DAS-based treatment adjustments every 3 months), resulted in a DAS remission in 56% of patients after 13 months of treatment; these patients continued with methotrexate monotherapy without the need to restart infliximab in the subsequent months. The use of adalimumab together with methotrexate induced a remission rate (DAS28) of 49% after 2 years of treatment [37]. Although the combined use of TNF inhibitors with methotrexate is evidently more effective in achieving minimal disease activity compared to DMARD monotherapy, the question whether these patients remain in remission after the cessation of therapy still needs to be determined.

Conclusion

Remission as an outcome measure of an observational study or clinical trial can have different meanings. It may concern a clinical state with persistent absence of clinical and radiological signs of disease activity without being treated for a specific time period. This remission might be drug induced, but can, in a small percentage of RA patients, also be achieved naturally. The RA patients that remit spontaneously are extremely interesting, as studying these patients in relation with risk factors might increase the understanding of the processes that are involved in remission/disease persistency. Remission may also point to a disease state with (very) low disease activity during treatment with DMARDS; this state of minimal disease activity is generally measured using the ACR criteria or the DAS. For reasons of clarity, we propose that these meanings of remission are not mixed and that the term remission is reserved for patients that are not being treated with DMARDs. In contrast, the patients with a low disease activity during antirheumatic therapy should be denoted as having minimal disease activity. The fact that these two states should not be mixed is further illustrated by the different risk factors for each state. Absence of anti-CCP antibodies is the best risk factor for achieving natural remission in both UA and early RA, whereas the risk factors for treatment responses and a state of low disease activity are not yet clear. Whether the currently available treatment strategies for RA are able to increase the percentage of remissions in RA will become evident in the next decade.

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Competing interests

The authors declare that they have no competing interests.

References
1. Storey GD: **Alfred Baring Garrod (1819-1907).** *Rheumatology* 2001, **40:**1189-1190.
2. Venkovski, Huizinga: **Rheumatoid arthritis: the goal rather than the health-care provider is key.** *Lancet* 2006, **367:**450-452 .
3. Huizinga TW, Machold KP, Breedveld FC, Lipsky PE, Smolen JS: **Criteria for early rheumatoid arthritis: from Bayes' law revisited to new thoughts on pathogenesis.** *Arthritis Rheum* 2002, **46:**1155-1159.
4. van Aken J, van Bilsen JH, Allaart CF, Huizinga TW, Breedveld FC: **The Leiden Early Arthritis Clinic.** *Clin Exp Rheumatol* 2003, **21(Suppl 31):**S100-105.
5. Lichtenstein MJ, Pincus T: **Rheumatoid arthritis identified in population based cross sectional studies: low prevalence of rheumatoid factor.** *J Rheumatol* 1991, **18:**989-993.
6. Harrison BJ, Symmons DP, Brennan P, Barrett EM, Silman AJ: **Natural remission in inflammatory polyarthritis: issues of definition and prediction.** *Br J Rheumatol* 1996, **35:**1096-1100.
7. Tunn EJ, Bacon PA: **Differentiating persistent from self-limiting symmetrical synovitis in an early arthritis clinic.** *Br J Rheumatol* 1993, **32:**97-103.
8. van Aken J, Van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW: **Long-term outcome of rheumatoid arthritis that presented with undifferentiated arthritis compared to rheumatoid arthritis at presentation - an observational cohort study.** *Ann Rheum Dis* 2006, **65:**20-25.
9. Quinn MA, Green MJ, Marzo-Ortega H, Proudman S, Karim Z, Wakefield RJ, Conaghan PG, Emery P: **Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application of a structured management protocol.** *Arthritis Rheum* 2003, **48:**3039-3045.
10. Salmon M, Wordsworth P, Emery P, Tunn E, Bacon PA, Bell JI: **The association of HLA DR beta alleles with self-limiting and persistent forms of early symmetrical polyarthritis.** *Br J Rheumatol* 1993, **32:**628-630.
11. Huizinga TW, Amos CI, van der Helm-van Mil AH, Chen W, van Gaalen FA, Jawaheer D, Schreuder GM, Wener M, Breedveld FC, Ahmad N, *et al.*: **Refining the complex rheumatoid arthritis phenotype based on specificity of the HLA-DRB1 shared epitope for antibodies to citrullinated proteins.** *Arthritis Rheum* 2005, **52:**3433-3438.
12. van der Helm-van Mil AHM, Verpoort KN, Breedveld FC, Huizinga TWJ, Toes REM, de Vries RRP: **The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-CCP antibodies and are not an independent risk factor to develop rheumatoid arthritis.** *Arthritis Rheum*, in press.
13. Wolfe F, Hawley DJ: **Remission in rheumatoid arthritis.** *J Rheumatol* 1985, **12:**245-252.
14. Prevoo ML, van Gestel AM, van T Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL: **Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score.** *Br J Rheumatol* 1996, **35:**1101-1105.
15. Eberhardt K, Fex E: **Clinical course and remission rate in patients with early rheumatoid arthritis: relationship to outcome after 5 years.** *Br J Rheumatol* 1998, **37:**1324-1329.
16. Linn-Rasker SP, Allaart CF, Kloppenburg M, Breedveld FC, Huizinga TWJ: **Sustained remission in a cohort of patients with RA: association with absence of IgM-rheumatoid factor and absence of anti-CCP antibodies.** *Int J Adv Rheumatol* 2004, **2:**4-6.
17. Jantti J, Kaarela K, Kautiainen H, Isomaki H, Aho K: **Radiographic remission in seropositive rheumatoid arthritis. A 20-year follow-up study.** *Clin Exp Rheumatol* 2001, **19:**573-576.
18. ten Wolde S, Breedveld FC, Hermans J, Vandenbroucke JP, van de Laar MA, Markusse HM, Janssen M, van den Brink HR, Dijkmans BA: **Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis.** *Lancet* 1996, **347:**347-352.
19. Wesoly J, van der Helm-van Mil AHM, Toes REM, Chokkalingam AP, Carlton VEH, Begovich AB, Huizinga TWJ: **Association of the PTPN22 C1858T single nucleotide polymorphism with rheumatoid arthritis phenotypes in an inception cohort.** *Arthritis Rheum* 2005, **52:**2948-2950.

20. van der Helm-van Mil AHM, Huizinga TWJ, Schreuder GMTh, Breedveld FC, de Vries RRP, Toes REM: **An independent role for protective HLA Class II alleles in rheumatoid arthritis severity and susceptibility.** *Arthritis Rheum* 2005, **52:**2637-2644.

21. Pinals RS, Masi AT, Larsen RA: **Preliminary criteria for clinical remission in rheumatoid arthritis.** *Arthritis Rheum* 1981, **24:**1308-1315.

22. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL: **Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria.** *Arthritis Rheum* 1996, **39:**34-40.

23. Balsa A, Carmona L, Gonzalez-Alvaro I, Belmonte MA, Tena X, Sanmarti R, EMECAR Study Group: **Value of disease activity score 28 (DAS28) and DAS28-3 compared to American College of Rheumatology-defined remission in rheumatoid arthritis.** *J Rheumatol* 2004, **31:**40-46.

24. Sesin CA, Bingham CO: **Remission in rheumatoid arthritis: wishful thinking or clinical reality?** *Semin Arthritis Rheum* 2005, **35:**185-196.

25. van der Heijde D, Klareskog L, Boers M, Landewe R, Codreanu C, Bolosiu HD, Pedersen R, Fatenejad S, TEMPO Investigators: **Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results.** *Ann Rheum Dis* 2005, **64:**1582-1587.

26. Fransen J, Creemers MC, Van Riel PL: **Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria.** *Rheumatology* 2004, **43:**1252-1255.

27. Landewé R, van der Heijde DM, van der Linden S, Boers M: **28-joint counts invalidate the das28-remission definition due to the omission of the lower extremity joints: A comparison with the original das-remission.** *Ann Rheum Dis* 2006, **65:**637-641.

28. Makinen H, Kautiainen H, Hannonen P, Sokka T: **Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis?** *Ann Rheum Dis* 2005, **64:**1410-1413.

29. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA: **Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission.** *Arthritis Rheum* 2004, **50:**36-42.

30. Ferraccioli GF, Gremese E, Tomietto P, Favret G, Damato R, Di Poi E: **Analysis of improvements, full responses, remission and toxicity in rheumatoid patients treated with step-up combination therapy (methotrexate, cyclosporin A, sulphasalazine) or monotherapy for three years.** *Rheumatology* 2002, **41:**892-898.

31. Gerards AH, Landewe RB, Prins AP, Bruyn GA, Goei The HS, Laan RF, Dijkmans BA: **Cyclosporin A monotherapy versus cyclosporin A and methotrexate combination therapy in patients with early rheumatoid arthritis: a double blind randomised placebo controlled trial.** *Ann Rheum Dis* 2003, **62:**291-296.

32. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, *et al.*: **Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis.** *Lancet* 1997, **350:**309-318.

33. Dougados M, Emery P, Lemmel EM, de la Serna R, Zerbini CA, Brin S, van Riel P: **Efficacy and safety of leflunomide and predisposing factors for treatment response in patients with active rheumatoid arthritis: RELIEF 6-month data.** *J Rheumatol* 2003, **30:**2572-2579.

34. Huizinga TWJ, McKay J, Chwalkinska-Sadowska H, Freimuth W, Weiser S, Zhong J, Verpoort KN, Van der Helm-van Mil AHM, Toes REM: **Distinct genetic and environmental risk factors, distinct disease outcome and distinct responses to anti-B cell therapy Belimumab indicate that anti-CCP positive RA is a distinct disease entity.** OP0019, Eular abstract 2006.

35. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martin Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators: **Therapeutic effect of the combination of etaner-cept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial.** *Lancet* 2004, **363:**675-681.

36. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, *et al.*: **Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial.** *Arthritis Rheum* 2004, **50:**3432-3443.

37. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT: **The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment.** *Arthritis Rheum* 2006, **54:**26-37.