Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomised clinical trials for the rate of remission

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ABSTRACT

Various definitions of remission in rheumatoid arthritis (RA) have been proposed. The ACR (American College of Rheumatology — formerly ARA, American Rheumatism Association) remission criteria are strict and include nonspecific symptoms such as fatigue. More recently remission according to the Disease Activity Index (DAS) and DAS28 has been described. However, patients who meet the DAS28 remission cut point of < 2.6 may nonetheless have tender and/or swollen joints. The ACR remission criteria are more rigorous than the requirement of DAS28 <2.6. Newer tools for evaluation of RA activity include the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI), and cut points for remission according to these new indices have been defined. However, all available remission criteria may ignore important aspects of RA, including physical function and radiographic damage.

Introduction

Early diagnosis and prompt initiation of disease-modifying antirheumatic drugs (DMARDs) are needed to reduce or prevent long-term structural damage in rheumatoid arthritis (RA). Treatment of RA should be targeted to remission (1, 2). However, remission remains an ambitious aim, which is achieved only in a minority of patients in standard clinical care (3). Furthermore, a single measure for remission does not exist and several criteria for remission have been developed.

The American Rheumatism Association (ARA) (now, the American College of Rheumatology [ACR]) remission criteria provided the first effort to define remission in RA (4). These criteria are rigorous, and modifications have included omission of elements such as fatigue (5). Other definitions of remission have included " full recovery" (6), "no joint swelling" (7), "absence of swollen joints or tender joints" (8), "inactive disease" (9), "complete control of synovitis and normal erythrocyte sedimentation rate (ESR)" (10), and "being symptom free" (11, 12). In some studies remission has been used as an outcome without any definition (13-15).

The Disease Activity Score (DAS) (16), and its modified version including 28 joints (DAS28) (17), were developed to assess disease activity in RA patients. Prevoo *et al*. compared ACR remission criteria with DAS and observed that DAS <1.6 best corresponds with remission according to the ACR remission criteria (18). Later, a corresponding cut point of <2.6 for DAS28 was derived from a formula

Table I. The ACR criteria for clinical remission in rheumatoid arthritis (4).

Five or more of the following requirements must be fulfilled for at least 2 consecutive months

1. Duration of morning stiffness not exceeding 15 minutes
2. No fatigue
3. No joint pain (by history)
4. No joint tenderness or pain in motion
5. No soft tissue swelling in joints or tendon sheaths
6. Erythrocyte sedimentation rate (Westergren method) < 30 mm/h for a female or 20 mm/h for a male

developed to convert DAS to DAS28 (19).

The Simplified Disease Activity Index (SDAI) (20) and Clinical Disease Activity Index (CDAI) (21) are new tools for the evaluation of disease activity in RA. Recently, cut points for remission have been defined for the both of these new indices (22, 23).

Remission rates range from 3% to 54% (5, 11, 13, 14, 24-38) in RA studies depending on selection of remission criteria, patient selection, duration of the follow-up period, and therapies. This article reviews different definitions of remission in RA and rates of remission in selected RA clinical cohorts and randomised clinical trials.

Definitions of remission criteria in rheumatoid arthritis

ACR remission criteria

Preliminary remission criteria for RA were proposed by a committee of the ARA (now, ACR) in 1981 (4) (Table I). To develop the criteria, 35 rheumatologists were asked to collect information from patients concerning symptoms, laboratory data, and results of a joint examination. These rheumatologists classified patients into four categories: complete remission without drugs, complete remission with drugs, partial remission, or active disease. Each variable was analysed with the objective to select variables that best discriminate patients who were described as being in remission from those with active disease. Of the criteria sets tested in 175 RA patients in complete remission and in 169 patients in partial remission or with active disease, six criteria were chosen (Table I). If four of the criteria were met, sensitivity was 90% and specificity 69% for complete remission. If five of the criteria were met, the corresponding figures were 72% and 92%. A duration requirement of 2 months was chosen, as 90% of the patients in remission fulfilled this criterion.

The sensitivity and specificity of the ACR remission criteria performed well in a study that compared gold and penicillamine in the treatment of RA (31). In a study by Alarcon *et al*., specificity of the criteria was high while sensitivity was low in some patient groups (39). Fatigue is a nonspecific symptom, and a requirement of "no fatigue" is sometimes omitted when ACR criteria are applied to identify patients in remission (5, 24, 26, 27, 30). In fact, clinically important levels of fatigue on a visual analog scale (VAS ≥ 2 on a scale 0-10) were present in more than 41% of patients who had RA or osteoarthritis, and in 76% of patients with fibromyalgia (40). Furthermore, no significant association was found between fatigue and inflammation (40). Pollard *et al*. (41) found that a high level of fatigue in RA patients is associated primarily with pain and depression.

In addition to fatigue, morning stiffness and pain appear to be common and nonspecific symptoms. Yazici *et al*. (42) reported that duration of morning stiffness did not differ among patients with RA and osteoarthritis. Widespread musculoskeletal pain was reported by 24% of the 1002 community-dwelling elderly women in the United States (43), while chronic pain was reported by 35% of the Finnish population aged from 15 to 74 years (44). Furthermore, the majority of people over age 50 in the general population do not meet ACR remission criteria for RA (45).

Remission assessed by DAS and DAS28

DAS (16, 46) and its modified version DAS28 (17) including 28 joints were developed to assess disease activity in RA. The original DAS published in the early 1990s includes four variables: Ritchie articular index (RAI) of tender joints (47), a 44 swollen joint count (SJC), ESR, and general health on VAS. Prevoo *et al*. (18) made a comparison between ACR remission criteria and DAS with an observation that DAS <1.6 corresponds to ACR remission criteria. DAS28 includes four components: tender joint count (TJC), SJC, ESR, and patient's global health. Prevoo *et al*. (17) showed that DAS28 is as valid as original DAS. A remission cut point of DAS28 < 2.6 was found to correspond to DAS < 1.6 based on a formula developed to convert DAS to DAS28 (19), and therefore DAS28 < 2.6 has been used to define remission in RA.

A slightly higher cut point for DAS28 remission of 2.66 was shown by Fransen *et al*. (48), and 2.81 by Balsa *et al*. (49). In other studies, lower cut points of DAS28 remission were observed, including 2.32 by Aletaha *et al*. (22), and 2.4 by Mäkinen *et al*. (22, 50). It was found that among patients with DAS28 < 2.32, 19% had tender joints and 11% had swollen joints (22), and that a cut point of 2.4 allowed the presence of up to 12 swollen joints (22). Therefore, a definition of remission according to DAS28 of 2.4 or higher includes a considerable number of patients with joint swelling or tenderness.

The original DAS remission criterion of 1.6 appears more conservative than DAS28 remission (51). Activity in the joints not included in DAS28 accounts for most of the discrepancy between DAS and DAS28 remission. Landewe *et al*. (51) concluded that DAS28 remission at a cutoff level of 2.6 has insufficient construct validity and should be used with caution in clinical practice and clinical trials.

Remission assessed by SDAI and CDAI

DAS is calculated according to a complex mathematical formula, which, however, is easily performed using a DAS calculator or at the DAS web site. Two less complex composite indices that are derived from the DAS but do not require a calculator or computer have been constructed. The SDAI index includes five components: SJC (28 joints included), tender joint count (28 joints included), C-reactive protein (CRP) in mg/dL (with a range of 0.1-10), patient's global disease activity on a 10-cm VAS, and physician's global assessment on a 10-cm VAS. The index constitutes a simple numerical summation of the values of the individual components of SDAI, and ranges from 0.1 to 86. Four of these components are included in CDAI, which excludes the CRP. CDAI scores may range from 0 to 76. CDAI is the only composite index constructed to measure clinical remission in RA that does not include a laboratory test.

Aletaha *et al*. analysed ratings of RA patients by expert rheumatologists for disease activity to define a cut point for SDAI and CDAI remission (23). The

Table II. Rate of remission in selected clinical cohorts and randomised clinical trials.

A. ACR remission criteria, clinical remission

Study	Study medication	No. of patients	Disease duration at baseline	Follow-up time, years	Definition of remission	Rate of patients in remission
Wolfe *et al*. 1993 (11)	Clinical cohort	503	Mean 0.81 y	7	Symptom free (Clinical remission)	7.6%
Suarez-Almazor *et al*. 1994 (24)	Clinical cohort	233	N.A. Inception cohort	6.5	1) ACR remission criteria, fatigue omitted, 4/5 criteria had to be fulfilled 2) 5 criteria had to be fulfilled	1) 12% 2) 3%
Eberhardt and Fex 1998 (26)	Clinical cohort	183	Mean 11 months	5	1) ACR remission criteria, fatigue omitted, 4/5 criteria had to be fulfilled 2) No arthritis	1) Remission periods constituted 7% of follow-up time 2) 36%
Lindqvist *et al*. 2002 (30)	Clinical cohort	183	Mean 11.1 months	10	ACR remission criteria, fatigue omitted, 4/5 criteria had to be fulfilled	18%
Möttönen *et al*. 1996 (28)	Clinical cohort "Saw tooth strategy"	142	Median 7 months	6.2	ACR remission criteria	32%
Pease *et al*. 1999 (25)	Clinical cohort	1) 186 pts Disease onset < 65 y 2) 214 pts Disease onset ≥ 65 y	1) Median disease duration 7.2 months 2) Median disease duration 4.2 months	3.6	RAI = 0 plus absence of soft tissue swelling in joints and soft tissue sheets	1) 20.4% 2) 45.8%
ERAS study Young *et al*. 2000 (29)	Clinical cohort	746	Mean 8.9 months	5	ACR remission criteria	13%
Mäkinen *et al*. 2005 (5)	Clinical cohort	127	Median 5 months	5	1) ACR remission criteria, fatigue omitted, all remaining 5 criteria had to be fulfilled 2) Clinical remission (no tender and swollen joints and normal ESR) 3) Radiographic remission*	1) 17% 2) 37% 3) 55%
Wolfe et Hawley 1985 (31)	1) Gold 2) Penicillamine	458	8 y	2.5	ACR remission criteria	18.1% all pts 1) 18.6% 2) 16.7%
FIN-RACo trial Möttönen *et al*. 1999 (27)	1) SSZ 2) SSZ, MTX, HCQ, and prednisolone	1) 98 2) 97	1) Mean 8.6 months 2) Mean 7.3 months	2	ACR remission criteria, fatigue omitted all remaining 5 criteria had to be fulfilled	1) 18% 2) 37%
FIN-RACo trial Korpela *et al*. 2004 (32)	From 2 years treatment was not restricted	1) 82 2) 78		5		1) 22% 2) 28%

Study	Study medication	No. of patients	Disease duration at baseline	Follow-up time, years	Definition of remission	Rate of patients in remission
Ferraccioli *et al*. 2002 (33)	1) MTX 2) CsA 3) SSZ	1) 42 2) 42 3) 42	1) 1.2 y 2) 1 y 3) 2 y	3	ACR remission criteria	1) 9% 2) 9% 3) 7%
Gerards *et al*. 2003 (34)	1) CsA 2) CsA and MTX	1) 60 2) 60	1) Mean 2.7 months 2) Mean 2.9 months	1	ACR remission criteria	1) 7% 2) 10%
B. DAS remission						
FIN-RACo trial Mäkinen *et al*. 2006 (56)	1) SSZ 2) SSZ, MTX, HCQ, and prednisolone	1) 79 2) 90	Median 6 months	2	DAS28 < 2.6	1) 41% 2) 68%
TICORA study Grigor *et al*. 2004 (57)	Traditional DMARDs 1) Intensive care 2) Routine care		1) Mean 19 months 2) Mean 20 months	1.5	DAS < 1.6	1) 65% 2) 16%
RELIEF trial Dougados *et al*. 2003 (35)	Leflunomide	969	Mean 7.3 y	0.5	DAS28 < 2.6	12.7%
APIRE study St Clair *et al*. 2004 (36)	1) MTX 2) MTX plus 3 mg/kg infliximab 3) MTX plus 6 mg/kg infliximab	1) 240 2) 302 3) 300	Mean 0.7 y	1	DAS28 < 2.6	1) 15% 2) 21.2% 3) 31%
PREMIER study Breedveldt *et al*. 2006 (37)	1) Adalimumab plus MTX 2) Adalimumab 3) MTX	1) 268 2) 274 3) 257	Mean 0.7 y	2	DAS28 < 2.6	1) 49% 2) 25% 3) 25%
TEMPO study van der Hejde *et al*. 2006 (38)	1) MTX 2) Etanercept 3) Etanercept plus MTX	1) 228 2) 223 3) 231	Range 0.5–20 y	2	DAS < 1.6 DAS28 < 2.6	1) 24.8% 2) 31.1% 3) 51.2% 1) 25.6% 2) 29.6% 3) 53.7%

ACR: American College of Rheumatology; CsA: cyclosporine A; ESR: erythrocyte sedimentation rate; HCQ: hydroxychloroquine; MTX: methotrexate; RAI: Ritchie articular index; SSZ: sulfasalazine; *Radiographic remission = no worsening of erosions and no new erosions from baseline to 5 years.

cut points for remission for SDAI and CDAI were defined as 3.3 and 2.8, respectively. SDAI was preliminarily validated in leflunomide trials (20), but further studies are needed to test the validity of SDAI and CDAI remission cut points.

Radiographic remission

Radiographic imagining may be regarded as the "gold standard" of assessing disease progression in RA (52). The Food and Drug Administration (FDA) has formulated the most rigorous definition of remission: ACR remission criteria must be met in addition to radiologic arrest of joint damage progression (Sharp/van der Heijde or Larsen method). These criteria include a time period requirement of 6 months (53, 54).

Jäntti *et al*. (55). assessed radiographs of hands and feet over 20 years according to Larsen score (scale 1-100). If the score did not increase more than 1 point compared to radiographs taken 5 to 19 years earlier, a patient was considered to be in radiographic remission; the radiographic remission rate was 26% at 20 years. In another study, a clinical cohort of 127 patients with early RA was followed for 5 years. Radiographic remission was defined as: 1) no extension of existing erosions, and 2) no development of new erosions from baseline to 5 years. More than half of the patients fulfilled these criteria for radiographic remission at 5 years (5).

Rate of remission in selected clinical cohorts and randomised clinical trials

ACR remission criteria have been used in randomised clinical trials concerning traditional DMARDs, with remission rates of 7% to 37% (27, 31-34), and in clinical cohorts with remission rates of 3% to 32% (5, 24, 26, 28-30) (Table II). ACR remission criteria have not been used to date in clinical trials of biologic agents (Table II).

The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) trial used a rigorous modification of the ACR remission criteria, requiring that all five criteria other than fatigue, which was omitted, be met. Nonetheless, after 2 years, 37% of patients who received a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone were in remission (27). According to the same set of criteria, only 17% of patients in a clinical cohort were in remission at 5 years (5) (Table II).

DAS28 remission levels of 21% to 53% (36-38) were found in several clinical trials of biologic agents, and were highest in patients treated with a combination of methotrexate and a biologic agent (infliximab, etanercept, or adalimumab) (Table II). In the PREMIER study (37), the remission rate at 2 years was 25% when adalimumab was used alone and 49% when it was used in combination with methotrexate. In the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) trial (38) remission rates were 29.6% (etanercept as a single agent) and 53.7% (etanercept in combination with methotrexate). The remission rate was 31% at 1 year in the study of St Clair *et al*. (36) in RA patients who were treated with a combination of methotrexate and infliximab (dose 6 mg/kg) (Table II).

DAS28 remission criteria have been used in studies concerning traditional DMARDs. In the FIN-RACo patients treated with a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone DAS28 remission rate was 68% at 2 years (56). DAS28 remission was also used in a leflunomide study, and 12.7% of the patients receiving leflunomide were in remission at 6 months (35). In the TICORA (Tight Control of Rheumatoid Arthritis) trial, the DAS remission rate was 65% in patients who received traditional DMARDs according to an intensive strategy and 16% in patients who were treated in routine care (57).

To our knowledge, SDAI and CDAI indices have not been used to assess remission in clinical trials.

Conclusion

Various definitions of remission in patients with RA have been proposed. The use of the ACR remission criteria has been heterogeneous concerning fatigue and the number of criteria required for remission. Furthermore, fatigue and morning stiffness are commonly seen in individuals with common conditions such as osteoarthritis or fibromyalgia, and even many normal elderly individuals. The ACR remission criteria have not been used in clinical trials to study the efficacy of biologic agents.

The DAS and DAS28 have been major advances in evaluation of disease activity in RA. However, patients in remission according to DAS28 of < 2.6 or even < 2.4 may include many patients with a considerable number of tender and/or swollen joints (22, 50).

The ultimate goal of treatment of the RA patient is to prevent serious long-term consequences of RA, such as joint damage, loss of functional and work capacity, increased comorbidity and preterm mortality. Thus, future remission criteria for RA might include not only inflammatory activity but also radiographic progression and physical function (58).

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