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Long-term sustained remission in a cohort study of patients with rheumatoid arthritis – choice of remission criteria.

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Abstract

Objectives: Remission is a widely accepted goal for treatment of rheumatoid arthritis (RA) but has to be sustained to arrest joint damage and disability. However, appropriate criteria for the assessment of sustained remission in long-term studies are not established. Therefore, we have compared the DAS28 remission criterion, the SDAI Cr criteria and the new Boolean-based set of criteria, Boolean Cr, and assessed the association of these criteria with radiographic and functional outcome.

Design: Prospective, long-term observational study of patients with early RA.

Setting: Secondary level of care; six participating centres from southern Sweden; both urban and rural populations;.

Participants: 698 patients were consecutively included in the study and 527 remained at the 8 year follow-up visit. Almost all patients were Caucasians, 64% were women.

To be included, a patient, 18 years or older, should fulfill the 1987 ACR criteria for RA and have a disease duration of no more than one year.

Results: Sustained remission was most common by the DAS28 Cr, 14% while 3% met the Boolean Cr and 5% the SDAI Cr, which latter figures increased to 9 and 8%, respectively, when the patient´s global assessment was excluded. Radiographic joint damage was common but least pronounced in patients in sustained remission by all criteria. Sustained remission was associated with rapid and lasting improvement in function assessed by the Health Assessment questionnaire (HAQ), irrespective of criteria.

Conclusions: The DAS28 Cr acquired more patients in sustained remission compared with the other criteria. In spite of that, radiographic damage and disability were not worse than was seen by other criteria and the patients´ perspective was preserved. The DAS28 Cr may therefore still be used in long-term observational studies until more accurate criteria are available.

Key words: Rheumatoid arthritis, remission criteria, sustained remission, radiographic joint damage, HAQ.

Article summary

Article focus

- To assess the prevalence of sustained remission in early RA during the first 8 years after inclusion into the study.
- To study the feasibility in long-term studies of the most frequently used remission criteria, the DAS28 remission criterion and the new ACR/EU criteria.
- To assess the association of these criteria with radiographic and functional outcome.

Key messages

- Sustained remission was infrequent by all criteria used but most frequent by the DAS28 criterion.
- Patients in sustained remission by the DAS28 criterion did not have worse function nor more evidence of joint destruction compared with the more stringent criteria.
- The DAS28 criterion may be used in long-term studies until more accurate criteria become available.

Strength and limitations of this study

+ Data are derived from a cohort of patients with early RA followed in a structured way for up to eight years.
+ In addition to clinical data, radiographs are available for the evaluation of the progression of joint damage.
– One hundred and sixty-nine patients were lost to follow-up after 8 years. For 40 of these the reason is unknown.
– Flares of disease activity may have been missed due to the scarcity of follow-up visits during the eight year follow-up.

Introduction

The principal aim in the treatment of rheumatoid arthritis (RA) is to suppress the inflammatory process (the disease activity) and achieve remission. Remission may be defined as a state with no or little disease activity. However, remission must be sustained in order to eliminate or arrest joint damage.[1]

Several sets of criteria for remission have been proposed and applied in a number of studies of RA. The original American Rheumatism Association (ARA) remission criteria are infrequently used today since all components of the criteria are not included in the current core set of variables.[2] A Disease Activity Score (DAS) less than 1.6 was found to correspond well to the ARA remission criteria and was proposed as a remission criterion.[3, 4] Later, the DAS remission criterion was modified by a 28 joint count to the DAS28 remission criterion, DAS28 less than 2.6 (DAS28 Cr), which has been widely used. Since then, more stringent criteria have been developed, e.g. the Simplified Disease Activity Index less than 3.3 remission criterion (SDAI Cr).[5] Recently, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in collaboration proposed that remission in RA may be defined either according to the SDAI Cr or to the new Boolean-based set of criteria (Boolean Cr).[6] The Boolean Cr have been shown to perform well in clinical trials but their utility in long-term observational studies remains to be demonstrated.[6] The most frequently used criterion, the DAS28 Cr, has been questioned since patients may be in remission by this criterion in spite of several swollen and tender joints.

On the basis of these considerations, long-term sustained remission by different criteria has been studied in the BARFOT (Better AntiRheumatic PharmacOTherapy) observational study of patients with early RA and related to disability and radiographic joint damage.[7]

Patients and methods

Patients

In all, 698 patients with RA were consecutively included in the BARFOT observational study [7] from September 1995 to September 1999 and 527 of these have completed eight years.

171 patients were lost to follow-up, of these 119 had died, 9 had moved, 2 rejected further follow-up visits and in 41 cases the cause is unknown.

The group of patients lost to follow-up were older (mean age 67 vs 54 years, p=0.001), had higher HAQ (mean 1.09 vs 0.97, p=0.043) and were somewhat less frequently positive for antibodies to citrullinated proteins (ACPA) (49% vs 58%, p=0.044).

All patients should fulfill the ACR criteria for classification of RA and should have a disease duration of 12 months or less. The patients were checked by a structured protocol at baseline and after 6 months and 1, 2, 5 and 8 years. A few patients had been treated before inclusion with disease modifying drugs (DMARDs) or glucocorticoids (GCs) but treatment was in most patients initiated at inclusion (baseline). The patients were treated by the rheumatologists´ preferences.

Methods

Clinical assessments

Disease activity was measured by number of swollen and tender joints calculated on 28 joints, patient global assessment of disease activity (PatGA) on a visual analogue scale (VAS) of 10 cm, and the physician´s global assessment of the disease activity (PhGA) measured on a 5 stage Likert scale, which was transformed to a VAS of 10 cm.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (mg/dl) were measured, CRP by a standard non-high sensitive method. Patient experienced pain was assessed on a VAS. Disability was assessed by the Swedish version of the Stanford Health Assessment Questionnaire (HAQ).[8] Antibodies to cyclic citrullinated peptides (ACPA) were detected using the ELISA CCP2 test (anti-CCP, Euro-Diagnostica, Malmö, Sweden).

Remission was defined according to the following criteria:

- The DAS28 remission criterion (DAS28 Cr): Disease Activity Score (DAS) calculated on 28 joints (DAS28) is a combined index which includes number of swollen joints, number of tender joints, the patient's global assessment and

ESR.[9] Remission is defined as DAS28<2.6. [10] This was the criterion used in clinical practice when deciding treatment in the present population.

- The recently proposed Boolean-based ACR/EULAR remission criteria (Boolean Cr): Tender joint and swollen joint counts ≤1, patient global assessment (PatGA) ≤1 cm on a VAS of 10 cm and CRP ≤1 mg/dl.[6, 10].
- The SDAI remission criterion (SDAI Cr): Sum of number of swollen and tender joints, CRP (mg/dl), PatGA and physician global assessment (PhGA) ≤ 3.3.[5]
- "DAS28-3 Cr", "Boolean-3 Cr" and "SDAI-4 Cr": The only difference from the original criteria is that VAS PatGA has been excluded from the original criteria.

Sustained remission was defined as remission at all four follow-up visits at 1, 2, 5 and 8 years, never remission as absence of remission at all visits, while intermittent remission was defined as remission at one, two or three of these four follow-up visits.

Radiographic assessment

Posterior-anterior radiographs of the hands and feet were obtained at study entry in 630 patients, at 1 year in 594, at 2 years in 613, at 5 years in 560 and at 8 years in 468 patients.Patients not having any radiographs did not differ significantly in baseline characteristics from patients with radiographs (data not shown).

Radiographic joint damage was assessed according to the van der Heijde modification of the Sharp score.[11] Total scores (SHS) are presented (range 0-448). The films were read by one of two experienced readers. Double readings of a fraction of films showed good agreement between the two readers (data not shown).

Radiographic progression was defined as a change in SHS of more than one unit per year, based on the assumption that a change of 1 unit per year is the lowest value of minor radiographic change.[12, 13]

Statistical analysis

Statistical analyses were performed using SPSS v. 21.0 statistical software. To test the differences between groups, the Mann-Whitney U test and the Kruskal-Wallis test were used for continuous variables, and the chi-square test for proportions. Pearson's correlation test was used to assess the relations between two continuous variables. Positive likelihood ratios for the ability of sustained remission to predict favorable radiographic outcome were

calculated by the formula *sensitivity/(1-specificity)*. All significance tests were two tailed and conducted at the 0.05 significance level.

Results

Demographic and clinical baseline characteristics

At baseline, the mean age of the patients was 57 years and 64% were women. The mean DAS28 was 5.23, the mean HAQ 1.0 and the median SHS was 1. Forty-two per cent of the patients were started on GC treatment and 87% on non-biologic DMARDs, table 1.

Table 1. Demographic and clinical characteristics of the 527 RA-patients

		Percent	Mean (SD)
Inclusion age, years			57 (15)
Disease duration, months			6.2 (3.2)
Gender	women	64	
Ever smokers		55	
anti-CCP	positive	56	
Rheumatoid factor	positive	60	
VAS Pain (0-10 cm)			4.5 (2.4)
DAS28			5.23 (1.2)
CRP (mg/L)			35 (37)
Tender joint count (28 joints)			8 (6)
Swollen joint count (28 joints)			11 (6)
VAS PatGA (0-10 cm)			4.4 (2.5)
VAS PhGA (0-10 cm)			4.8 (1.7)
HAQ (0-3)			1.0 (0.65)
SHS (median (IQR))			1 (0-4.5)
Glucocorticoids	yes	42	
DMARDS	no	13	
MTX		40	
SAL		34	
Other		12	
Combination		1	
Biologics		0	

VAS- visual analogue scale, anti-CCP- antibodies to citrullinated peptides, DAS28- disease activity score calculated on 28 joints, PatGA- patients global assessment, PhGA- physician´s global assessment, HAQ- Health Assessment Questionnaire, SHS- Sharp van der Heijde total score, MTX- methotrexate, SAL- sulfasalazine.

Proportion of patients in remission at the follow-up visits

The frequencies of remission increased from 6 months and onwards by all criteria used. Table II shows that the remission rates from one to 8 years were most frequent by the DAS28 based criteria, irrespective of whether PatGA was excluded or not. Remissions by the Boolean Cr and the SDAI Cr were less frequent but the frequencies increased when PatGA was excluded from the criteria.

Table II. Remission rates at the follow-up visits (number (%)) at 1, 2, 5 and 8 years according to the criteria used.

	One year	Two years	Five years	Eight years
DAS28 Cr	175(36.2)	189(39.1)	190(39.3)	202(41.8)
DAS28-3 Cr	166(33.1)	188(37.5)	178(35.5)	198(39.5)
Boolean Cr	88(17.3)	93(18.3)	84(16.5)	97(19.1)
Boolean-3 Cr	136(27.2)	145(29)	158(31.6)	189(37.8)
SDAI Cr	124(19)	153(22.6)	145(24.4)	115(23.6)
SDAI-4 Cr	173(26.3)	195(28.7)	210(34.9)	184(37.4)

Number of patients in remission at one, two, three or all of the 4 follow-up visits

Table III shows the number of patients in remission at the follow-up visits between one and eight years. By the Das28 Cr *sustained remission* was achieved by 14%, 3% by the Boolean Cr and 5% by the SDAI Cr. Thirty-five per cent of the patients had no episode of remission at all (*never remission*) by the DAS28 Cr, 62% by the Boolean Cr and 58% by the SDAI Cr. The remaining patients had one, two or three episodes of remission (*intermittent remission*). PatGA is included in all these remission criteria. With low cut-off values for PatGA, remission may be difficult to achieve. When PatGA was excluded from the criteria, the rates of sustained remission increased to 9% by the Boolean-3 Cr and to 8% by the SDAI-4 Cr but decreased to12% by the DAS28-3 Cr.

Table III. Patients in sustained, intermittent or never remission by the different criteria. .

	Number (%) of patients in remission at all four, three, two, one or no visits				
	Sustained remission	Intermittent remission			Never remission
	All four visits	Three	Two	One	No visit
DAS28 Cr	69 (14)	76 (16)	81 (17)	90 (19)	167 (35)
DAS28-3 Cr	60 (12)	75(15)	88 (17)	89 (18)	189 (38)
Boolean Cr	14 (3)	32 (6)	62 (11)	86 (17)	315 (62)
Boolean-3 Cr	45 (9)	51 (10)	90 (18)	115 (23)	199 (40)
SDAI Cr	22 (5)	34 (8)	67 (16)	56 (13)	245 (58)
SDAI-4 Cr	39 (8)	61 (13)	104 (22)	87 (18)	186 (39)

Influence of number of tender and swollen joints on sustained remission

The DAS28 formula allows classification of a patient as in remission even in the presence of several swollen or tender joints. To investigate whether this might be the case also in patients in sustained remission in this study, the number of tender and swollen joints, which were components of DAS28 in these patients, were counted. Table IV shows that more than one or two swollen or tender joint were infrequent.

Table IV. Number of patients in remission by DAS28 Cr with more than one tender or swollen joint. Results from 276 assessments of DAS28 in patients with sustained remission.

	2 joints	3 joints	4 joints	5 joints	6 joints
Tender joint count >1	12	1	2	1	0
Swollen joint count >1	22	7	6	2	1

Drug treatment

At baseline, one and 2 years, information on GC and DMARD treatment was available in all or almost all patients while no such information was available at 5 years in 11 and13% and at 8 years 27 and 28%, respectively. At baseline there were no statistically significant differences between remission groups in frequency and kind of DMARD treatment. At the follow-up visit at 8 years significantly more patients in the sustained remission groups (48-64%) had stopped DMARDs than was the case in the intermittent (26-35%) and never remission groups (19-23%). The differences were statistically significant, irrespective of criteria used, $p<0.002$ or less. Only 0-5% of the patients in the sustained remission groups were treated with biologics vs 9-15% and 16-18% of the patients in the intermittent and never remission groups, respectively. Post hoc analyses showed that this was significant when the DAS28- based criteria and the Boolean-3 Cr were used.

At baseline 42% of the patients in all remission groups were started on glucocorticoids (GCs). After 8 years fewer patients in sustained remission were treated with GCs (0-5%) than in the intermittent (16-20%) and the never remission groups (24-28%). The differences were statistically significant, irrespective of criteria used, $p <0.03$ or less).

Radiographic joint damage in the sustained remission groups

Radiographic joint damage as assessed by SHS increased significantly from year 1 to 8 in all remission groups, least in the sustained remission groups and most in the groups with no remissions at all (fig. 1 a-f). In the sustained remission groups, the mean (SD) increase in SHS between baseline and 8 years were similar: 7.4 (8.6) by the DAS28 Cr, 7.3 (9.3) by the

DAS28-3 Cr, 7.2 (9.2) by Boolean Cr; 7.8 (8.4) by the Boolean-3 Cr, 8.0 (15) by the SDAI Cr and 8.7 (13.1) by the SDAI-4.

Radiographic progression, defined as a change of more than 1 unit per year between baseline and 8 years, occurred in 38% of the patients in sustained remission by the DAS28 Cr. The corresponding figures for patients in sustained remission by the DAS28-3 Cr, Boolean Cr, Boolean-3 Cr, SDAI Cr and SDAI-4 Cr were similar: 37%, 31%, 45%, 26% and 40%, respectively.

Performance of the criteria

Table V displays the performance of the criteria. There was a general tendency for sustained remission to be associated with absence of radiographic progression. The association varied somewhat between criteria, the sensitivity was low and the likelihood ratios were small and not statistically significant for the Boolean- based and SDAI-4 criteria.

Table V. The performance of the different criteria in patients in sustained remission. Sensitivity, specificity, PPV, NPV and positive likelihood ratios, all with absence of radiographic progression from baseline to 8 years as outcome.

	Non progressors*							
	% in sustained remission	% not in sustained remission	Sens	Spec	PPV	NPV	p-value	Likelihood ratio (95% CI)
DAS28 Cr	62	45	0.19	0.90	0.62	0.55	0.015	1.82 (1.11-2.97)
DAS28-3 Cr	63	45	0.16	0.91	0.63	0.53	0.022	1.77 (1.04-3.02)
Boolean Cr	62	47	0.05	0.98	0.69	0.53	0.11	2.47 (0.77-7.91)
Boolean-3 Cr	55	47	0.12	0.91	0.55	0.53	0.32	1.33 (0.75-2.38)
SDAI	74	47	0.08	0.97	0.74	0.53	0.025	2.96 (1.09-8.05)
SDAI-4	60	47	0.11	0.93	0.60	0.53	0.14	1.62 (0.8-3.09)

*Non progressors – patients without radiographic progression from baseline to 8 years.

Disability in the sustained remission groups

Disability assessed by the HAQ decreased after 6 months in all remission groups by all criteria used, most pronounced in the sustained remission groups and least in the never remission groups(Fig. 2 a-f). Thereafter HAQ remained more or less on that lower level during the rest of the study. At baseline the sustained remission groups had lower HAQ and remained on a HAQ score of about 0.2 or less during the rest of the study while the groups of patients who never achieved remission remained on a HAQ score of 0.8 or higher.

Improvement in function was defined as a change in HAQ from baseline to 8 years of 0.22 or more.[14] Irrespective of criteria, sustained remission was associated with improvement. By the DAS28 Cr, 73% of the patients in sustained remission improved after 8 years vs 62% of the patients with intermittent remission and 40% of the patients who never achieved remission. The corresponding figures for the DAS28-3 Cr, the Boolean Cr, the Boolean Cr-3, the SDAI and the SDAI-4 were 80, 58 and 45%; 79, 57 and 48%; 73, 61 and 43%; 73, 67 and 45%; 69, 63 and 41%. All comparisons were statistically significant, overall p=0.001.

Sustained remission and gender

Irrespective of criteria used, the proportion of men in sustained remission was higher than that of women. Thus, by the DAS28 Cr 10% of the women vs 23% of the men achieved sustained remission, p=0.001 and by the DAS28-3 Cr 9% vs 19%, p=0.001. The respective rates were by the Boolean Cr 2% vs 5%, p=0.008; by the Boolean-3 Cr 7% vs 13%, p=0.001; by the SDAI Cr 4% vs 7%, p=0.001; and by the SDAI-4 Cr 7% vs 11%, p=0.001.

Discussion

Long-term sustained remission in RA is expected to be associated with a favorable outcome as regards disability and joint destruction. However, this may not be readily demonstrated since the validity of available remission criteria in long-term observational studies still is insufficiently known. Therefore, we have, in our long-term observational study of patients with early RA, used the DAS28 remission criterion (DAS28 Cr) as well as both the recently proposed ACR/EULAR remission criteria - the Boolean variant and the SDAI Cr. In addition, these criteria have also been modified by excluding the patient´s global assessment (PatGA).

In the present study, remission by the DAS28 Cr was about twice as frequent as that by the Boolean Cr. The frequencies found were similar to those in other studies. Thus, in one inception cohort 33.7% of the patients had, one year after enrollment, achieved remission by the DAS28 Cr, 13.8% by the Boolean Cr and 16.8% by the SDAI Cr.[15] Furthermore, in unselected patients with established RA, 28% were found to be in DAS28 Cr remission while only 7% had achieved remission by the Boolean Cr.[16] Cross-sectional data from two large registries of patients with established RA showed that only 5 - 6.2% of the patients had achieved remission by the Boolean Cr and 6.9 - 10.1% by the SDAI Cr.[17]

In this study, long-term sustained remission was considerably less frequent, 3% of the patients by the Boolean Cr, 5% by the SDAI Cr and 14% by the DAS28 Cr. In the study by Shahouri, the probability of having 2 or more visits in remission during 2 years was at most 2.8% for the Boolean Cr and 4.2% for the SDAI.[17] In the ERAS study remission by the DAS criterion ≤1.6 was achieved by 11% percent of the patients at all three follow-up visits at 3, 4 and 5 years, only slightly less than the 14% found in our study.[18] A study on patients with established RA treated in clinical practice reports that only a minority of those who achieved remission remained in remission during follow-up, irrespective of criteria used.[19] In an editorial to that article, Aletaha et al stresses the importance of considering sustained remission as “an outcome measure of successful treatment”, which is in line with the purpose of this study.[20]

Remission criteria should satisfy the requirements of absent or minimal disease activity and no or little future disability or joint damage. However, if the criteria are too stringent, overtreatment may follow. Conversely, if too permissive criteria are chosen, patients with

significant disease activity may be classified as being in remission and thus miss adequate treatment.

Sometimes it may be difficult to decide whether tenderness or swelling is related to the disease activity or not. During the long-term course of RA, tender or swollen joints may be unrelated to disease activity and lead to misclassification. Thus, as has also been pointed out by Thiele et al [16], tender and swollen joints may reflect some other co-existing rheumatic disorder or represent sequels of RA. Tenderness in non-swollen joints may also be due to painful disorders like fibromyalgia, which occurs in 12 -20 % of patients with RA.[21] All this may cause misinterpretations and missed remissions, conceivably more often by the more stringent criteria.

The required very low cut-off for VAS PatGA (≤1 cm) has been found to be a limiting factor for achieving remission by the Boolean Cr.[22] In most remission criteria a VAS PatGA is included representing the patient´s perspective. However, its disease specificity may be questioned since an elevated PatGA may be due to e.g. low back pain or other co-morbidities.[16] In agreement with others, we found that VAS PatGA correlated well with VAS pain (r=0.80, 0.81, 0.86 and 0.83 at the follow-up visits at 1, 2 5 and 8 years), a common symptom not only of current disease activity but also of various comorbidities.[23, 24] In the present study the phrasing (translated into English) was similar to that used by others: “How do you feel to-day with reference to your rheumatic disease?” The possibility that the questions, although seemingly clear, may cause misclassifications is supported by Thiele et al. who report that 91% of the patients in their study gave the same (77%) or almost the same (14%) rating to the questions “describe your health to-day” and “assess the activity of your disease”.[16] A way to overcome this bias would be to phrase the questions more distinctly.

The low frequency of sustained remission by the Boolean Cr criteria suggests that they may be too stringent to be suitable for long-term studies in clinical practice. In the present study, the exclusion of PatGA from the Boolean Cr and the SDAI Cr resulted in an increase in the rate of sustained remission from 3 to 9% and 5 to 8%, respectively. This effect was not seen with the DAS28 Cr. This may suggest that missed remissions due to non RA- related high VAS PatGA are less common when the DAS28 Cr were used. This could partly be explained by the fact that the contribution of PatGA to DAS28 is only 15%.[25] A VAS PatGA of 2-3 cm was not infrequent in patients in sustained remission by DAS28Cr (data not shown).

The formula for DAS28 allocates twice as much weight to the number of tender joints as to the number of swollen joints. This means for example that remission can be missed with one

swollen and 3 tender joints while remission can be achieved with one tender joint and five or even more swollen joints.[25] Consequently, the DAS28 Cr has been criticized for allowing classification of patients as being in remission in spite of having several swollen joints, not compatible with a state of remission.[6] However, in the group of patients who achieved sustained remission in the present study, only a minority had more than a few tender or swollen joints. So, it seems reasonable to use DAS28 Cr for the definition of sustained remission in this patient material. Furthermore, tender joints in absence of swelling have been shown to be unrelated to active synovitis diagnosed by ultrasound or power Doppler, which suggests that tender joints, which are not swollen, may be a source of misclassification.[26]

Gender may influence remission rates.[16] In the BARFOT study we have earlier reported that sustained remission from year 2 to 5, determined by the DAS28 <2.6 criterion, was significantly less frequent in women than in men.[27] Furthermore, women had higher DAS28 after five and eight years than men, but no gender difference was observed in radiographic progression.[28, 29] Similarly, in the present study, sustained remission by all criteria was significantly less frequent in women than in men, while radiographic joint damage was similar (data not shown). The explanation to this inconsistency is probably that non inflammatory pain confounds the measurement of disease activity in women.

Ideally, a state of sustained remission should indicate that disease activity is virtually absent and thus eliminate or minimize the risk of further joint damage. Even if no study has shown a complete arrest of joint damage over extended periods of timed, two studies lend support that this may be possible. In the Fin-RaCo study sustained remission by the DAS28 Cr over 2 years was associated with only modest radiographic joint damage and in the PREMIER study sustained remission during the second year was associated with arrest of joint damage, irrespective of therapy given.[30, 31] As a consequence, the authors proposed that sustained remission should be the ultimate goal of treatment of RA.

The validity of the Boolean Cr and SDAI Cr has been established in short or medium term studies by demonstrating satisfactory likelihood ratios for “good radiographic outcome” of being in remission. [6, 13] In this study, as in another long-term study [18], radiographic progression was common also in patients in sustained remission, regardless of criteria used, and consequently, the likelihood ratios were small. However, the degree of radiographic damage was minor in the groups of patients in sustained remission and often below the “the lowest value of minor radiological change”.[12] Similar results were obtained using different cut-off values for radiographic progression (data not shown). So, sustained remission by all criteria seems to be associated with slow long-term radiographic progression.

The progression of radiographic joint damage in patients in sustained remission may be explained by flares of disease activity between the four assessment points. Here we have the main limitation of this study, i.e. the scarcity of follow-up visits during the eight year follow-up. However, at the time this study was planned, it was not feasible to predetermine controls tight enough to be able to catch up flares. Another possible explanation is presence of subclinical inflammation, which may cause progressive joint damage in patients without clinical evidence of inflammation.[32] However, in the patients in sustained remission in this study, the radiographic joint damage over the eight years was very limited and similar between criteria. Furthermore, a state of sustained remission by all criteria was associated with lasting return to a functional level corresponding to that of an age and sex matched general population.[33]

Conclusion

The present study has focused on finding suitable criteria for identifying patients in long-term sustained remission to be used in the assessment of the disease course and outcome of RA. The data suggest that the Boolean Cr, although performing well in clinical trials, are very stringent and bring about risks for misclassifications mainly due to the requirement of a very low PatGA, and hence risk for over treatment. Similar objections may be made to the use of the SDAI Cr, which may make these criteria less appropriate for use in long-term studies in which PatGA frequently may be increased due to co-morbidities. Both these sets of criteria classified more patients in sustained remission when PatGA was excluded. However, using criteria without PatGA means that the much wanted patient perspective of the criteria is abandoned. [34] Furthermore, cut-offs for remissions have not been established for criteria without VAS PatGA. The DAS28 Cr performed reasonably well in this eight year study and presented very little of previously observed drawbacks. In spite of more patients in sustained remission by DAS28 Cr, radiographic damage and disability was apparently not worse than what was seen with the other criteria and the patients´ perspective was preserved. The DAS28 Cr may therefore still be used in long-term observational studies until more accurate criteria are available.

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Contributors

BS: Incited the study, designed it, analyzed data, performed statistics and led the writing of the manuscript.

MA: Responsible for sampling and data recovery.

VB: Participated in data analysis and discussion.

KF: Responsible for the radiographic assessments including scoring of radiographs, participated in manuscript preparation.

IH: Participated in design and interpretation of data as well as manuscript preparation.

All authors have critically revised and approved the final manuscript.

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Competing interests

The authors declare that they have no conflicts of interest.

Patient consent

Obtained.

Ethics approval

All patients gave their informed consent and the Ethics committees approved the study which was performed in accordance with the Declaration of Helsinki.

Provenance and peer review

Not commissioned; externally peered reviewed.

Data sharing statement

No additional data are available.

References

1. Smolen JS, Aletaha D, Bijlsma JW, et al: Treating rheumatoid arthritis to target: recommendations of an international task force. Annals of the rheumatic diseases 2010, **69:**631-637.
2. Pinals RS, Masi AT, Larsen RA: Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis and rheumatism 1981, **24:**1308-1315.
3. van der Heijde DM, van 't Hof M, van Riel PL, et al: Development of a disease activity score based on judgment in clinical practice by rheumatologists. The Journal of rheumatology 1993, **20:**579-581.
4. Prevoo ML, van Gestel AM, van THMA, et al: Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. British journal of rheumatology 1996, **35:**1101-1105.
5. Smolen JS, Breedveld FC, Schiff MH, et al: A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003, **42:**244-257.
6. Felson DT, Smolen JS, Wells G, et al: American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Annals of the rheumatic diseases 2011, **70:**404-413.
7. Svensson B, Schaufelberger C, Teleman A, et al: Remission and response to early treatment of RA assessed by the Disease Activity Score. BARFOT study group. Better Anti-rheumatic Farmacotherapy. Rheumatology (Oxford) 2000, **39:**1031-1036.

8. Ekdahl C, Eberhardt K, Andersson SI, et al: Assessing disability in patients with rheumatoid arthritis. Use of a Swedish version of the Stanford Health Assessment Questionnaire. Scandinavian journal of rheumatology 1988, **17:**263-271.

9. Prevoo ML, van 't Hof MA, Kuper HH, et al: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis and rheumatism 1995, **38:**44-48.

10. 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 (Oxford) 2004, **43:**1252-1255.

11. van der Heijde D: How to read radiographs according to the Sharp/van der Heijde method. The Journal of rheumatology 2000, **27:**261-263.

12. van der Heijde D, Landewe R, van Vollenhoven R, et al: Level of radiographic damage and radiographic progression are determinants of physical function: a longitudinal analysis of the TEMPO trial. Annals of the rheumatic diseases 2008, **67:**1267-1270.

13. Lillegraven S, Prince FH, Shadick NA, et al: Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. Annals of the rheumatic diseases 2012, **71:**681-686.

14. Bruce B, Fries JF: The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health and quality of life outcomes 2003, **1:**20.

15. Sakellariou G, Scire CA, Verstappen SM, et al: In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Annals of the rheumatic diseases 2013, **72:**245-249.

16. Thiele K, Huscher D, Bischoff S, et al: Performance of the 2011 ACR/EULAR preliminary remission criteria compared with DAS28 remission in unselected patients with rheumatoid arthritis. Annals of the rheumatic diseases 2012.

17. Shahouri SH, Michaud K, Mikuls TR, et al: Remission of rheumatoid arthritis in clinical practice: application of the American College of Rheumatology/European League Against Rheumatism 2011 remission criteria. Arthritis and rheumatism 2011, **63:**3204-3215.

18. Jayakumar K, Norton S, Dixey J, et al: Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. Rheumatology (Oxford) 2012, **51:**169-175.

19. Prince FH, Bykerk VP, Shadick NA, et al: Sustained rheumatoid arthritis remission is uncommon in clinical practice. Arthritis research & therapy 2012, **14:**R68.

20. Aletaha D: Nothing lasts forever - a critical look at sustained remission. Arthritis research & therapy 2012, **14:**116.

21. Yunus MB: The prevalence of fibromyalgia in other chronic pain conditions. Pain research and treatment 2012, **2012:**584573.

22. Studenic P, Smolen JS, Aletaha D: Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Annals of the rheumatic diseases 2012, **71:**1702-1705.

23. Masri KR, Shaver TS, Shahouri SH, et al: Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. The Journal of rheumatology 2012, **39:**1139-1145.

24. Studenic P, Radner H, Smolen JS, et al: Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis and rheumatism 2012, **64:**2814-2823.

25. Belmonte Serrano MA: [Is the DAS28 Score the Most Adequate Method to Estimate Activity in Rheumatoid Arthritis? Clinimetric Considerations and Simulations Scenarios]. Reumatologia clinica 2008, **4:**183-190.

26. Rees JD, Pilcher J, Heron C, et al: A comparison of clinical vs ultrasound determined synovitis in rheumatoid arthritis utilizing gray-scale, power Doppler and the intravenous microbubble contrast agent 'Sono-Vue'. Rheumatology (Oxford) 2007, **46:**454-459.

27. Forslind K, Hafstrom I, Ahlmen M, et al: Sex: a major predictor of remission in early rheumatoid arthritis? Annals of the rheumatic diseases 2007, **66:**46-52.

28. Hafstrom I, Bala V, Albertsson K, et al: Joint destruction in early rheumatoid arthritis over 8 years is similar in women and men despite apparently higher disease activity and poorer function in women. Annals of the rheumatic diseases 2011, **70:**709-710.

29. Ahlmén M, Svensson B, Albertsson K, et al: Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. Annals of the rheumatic diseases 2010, **69:**230-233.

30. Makinen H, Kautiainen H, Hannonen P, et al: Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. The Journal of rheumatology 2007, **34:**316-321.

31. Aletaha D, Funovits J, Breedveld FC, et al: Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. Arthritis and rheumatism 2009, **60:**1242-1249.

32. Brown AK, Conaghan PG, Karim Z, et al: An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis and rheumatism 2008, **58:**2958-2967.

33. Krishnan E, Sokka T, Hakkinen A, et al: Normative values for the Health Assessment Questionnaire disability index: benchmarking disability in the general population. Arthritis and rheumatism 2004, **50:**953-960.

34. Khan NA, Spencer HJ, Abda E, et al: Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis care & research 2012, **64:**206-214.

Legend to figure 1 a-f.

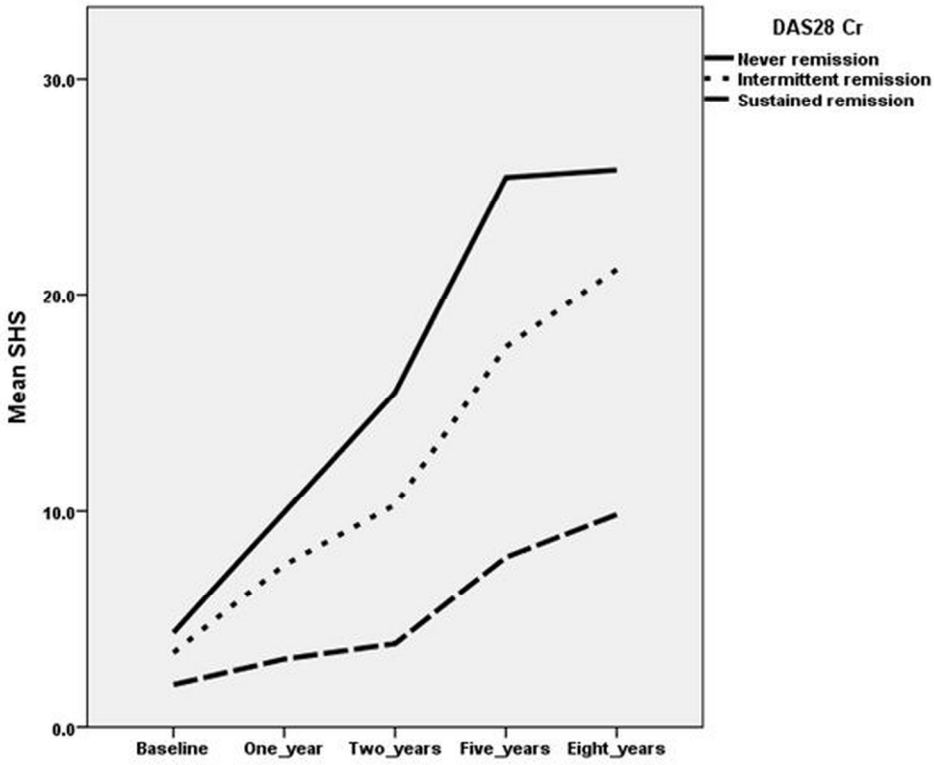
Fig. 1 a-f. Mean SHS from baseline to one, two, five and eight years in patients in sustained remission, intermittent remission or never in remission by the DAS28 Cr (a), DAS28-3 Cr (b), Boolean Cr (c), Boolean-3 Cr (d), SDAI (e), SDAI-4 (f).

At baseline, there was an overall statistically significant difference only for DAS28-3 Cr, p=0.002 (Kruskal-Wallis test). At the follow-up visits, there was an overall statistically significant difference with p <0.001 between remission groups except for the Boolean Cr at one year, p=0.046, at two years, p= 0.002 and at eight years, p=0.013 and for the SDAI Cr at one year, p= 0.011 and at eight years, p=0.008.

Legend to figure 2 a-f.

Fig. 2 a-f. Mean HAQ from baseline to 6 months, one, two, five and eight years in patients in sustained remission, intermittent remission or never in remission by the DAS28 Cr (a), DAS28-3 Cr (b), Boolean Cr (c), Boolean-3 Cr (d), SDAI (e), SDAI-4 (f). The differences between remission groups at baseline were significant for all criteria, overall p=0.013 (a), 0.018 (b), 0.001 (c), 0.048 (d), 0.009 (e) and 0.044 (f). At all follow-up visits, the overall p for the differences between remission groups was <0.001 by all criteria (Kruskal-Wallis test).

Fig 1 a



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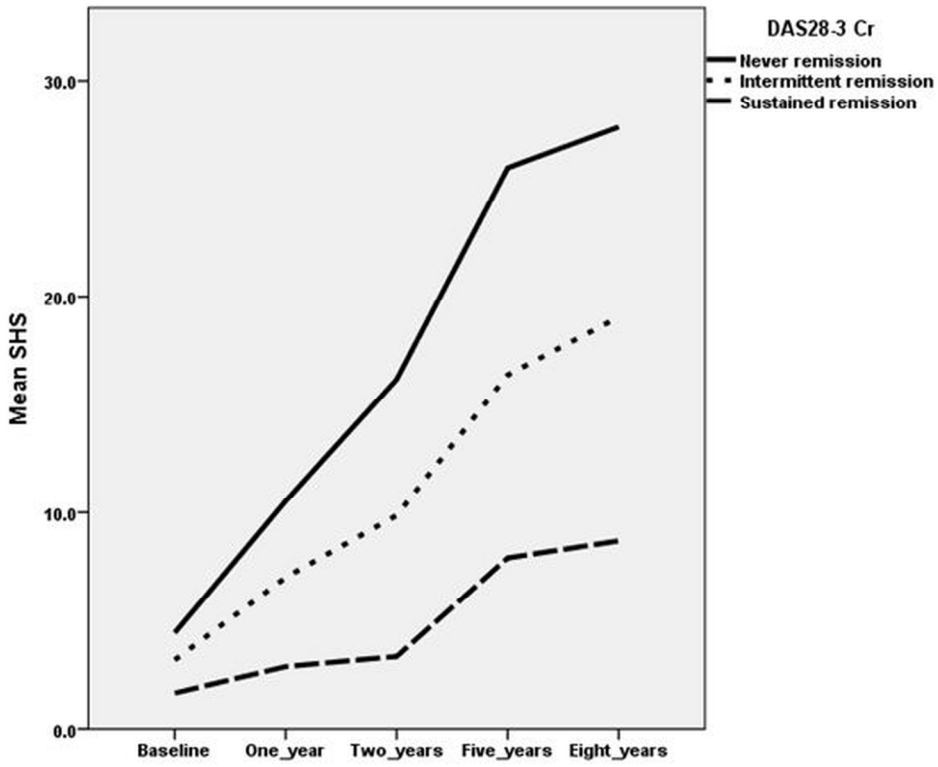

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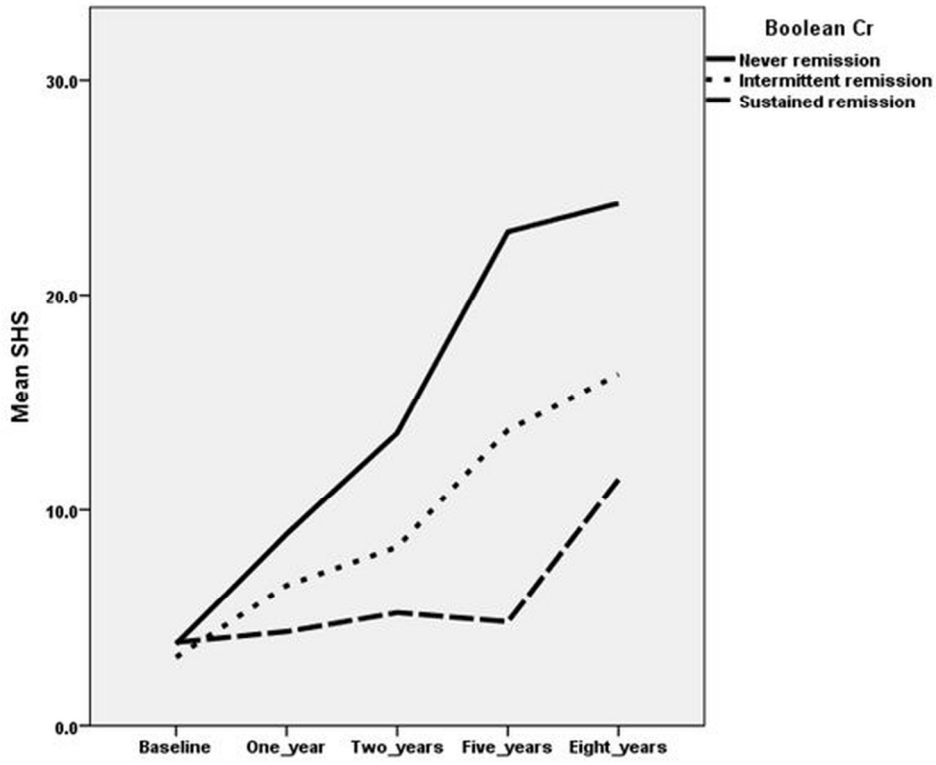

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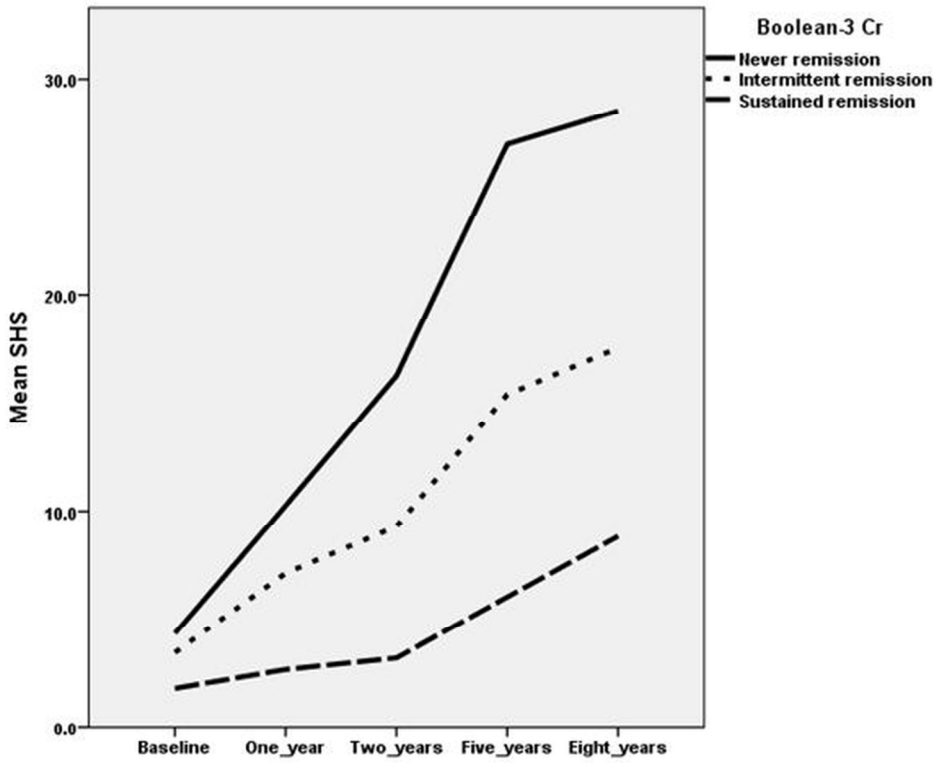

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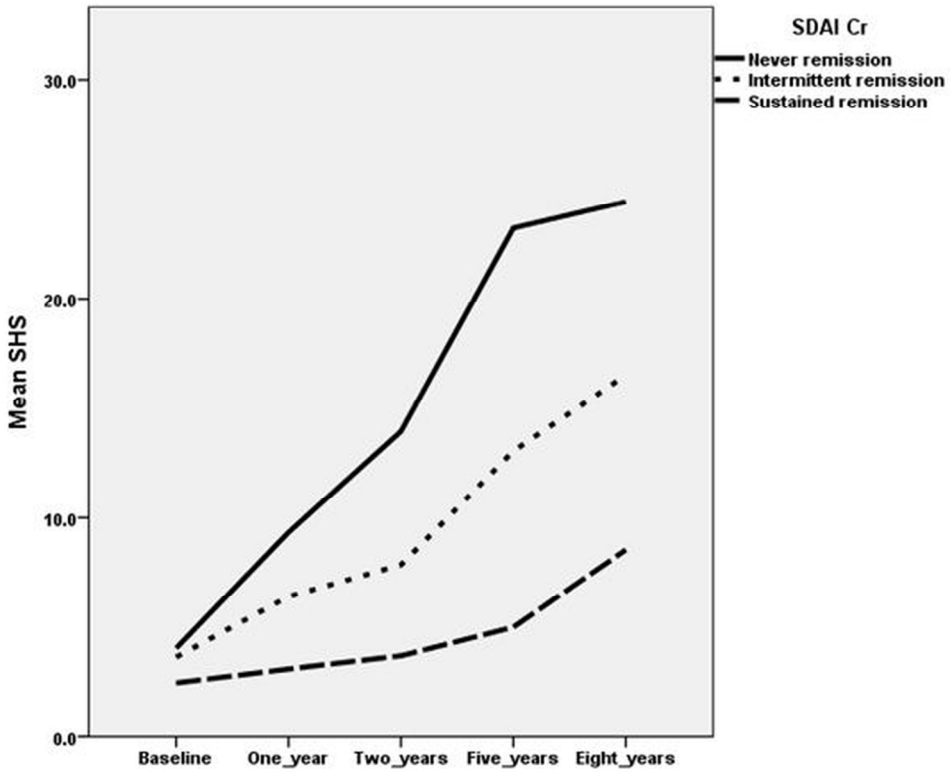

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Fig 1 f

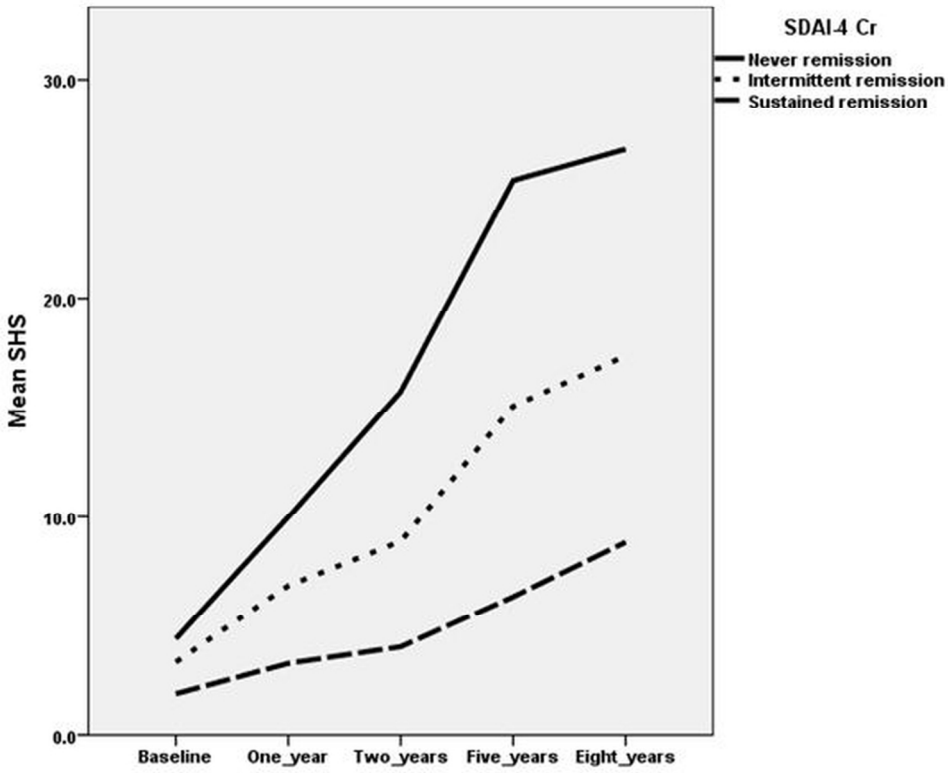

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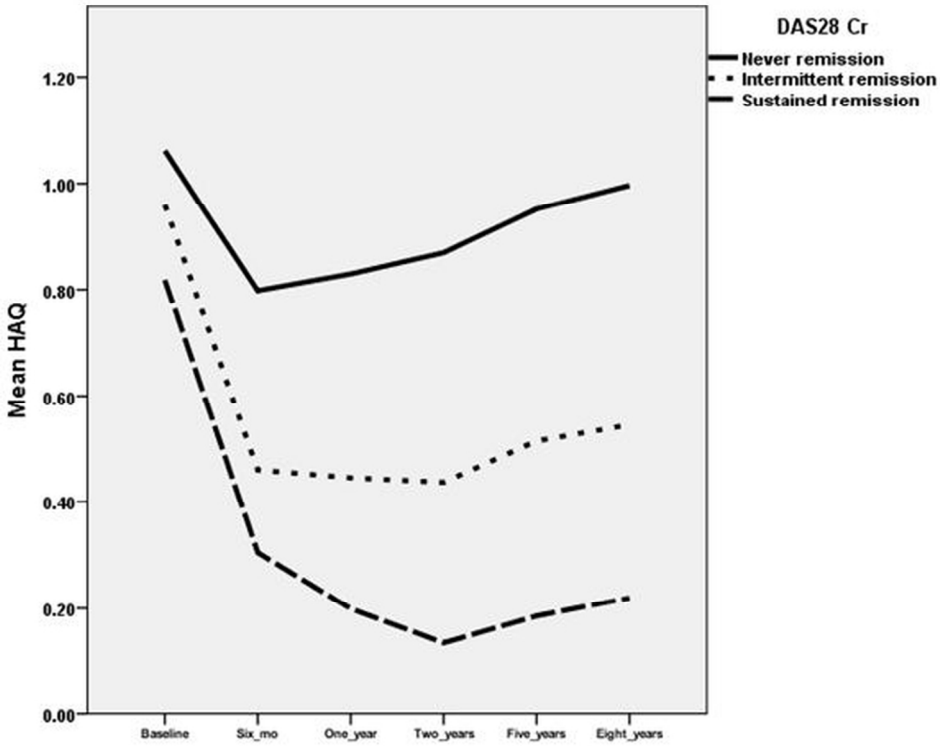
Fig 2 a.



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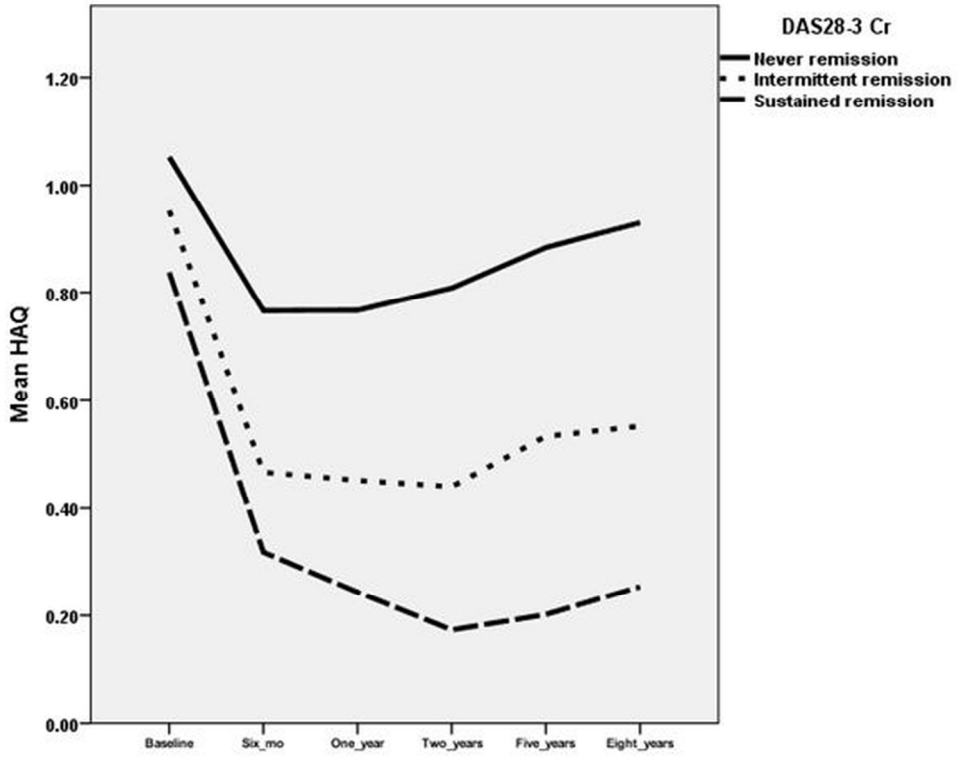

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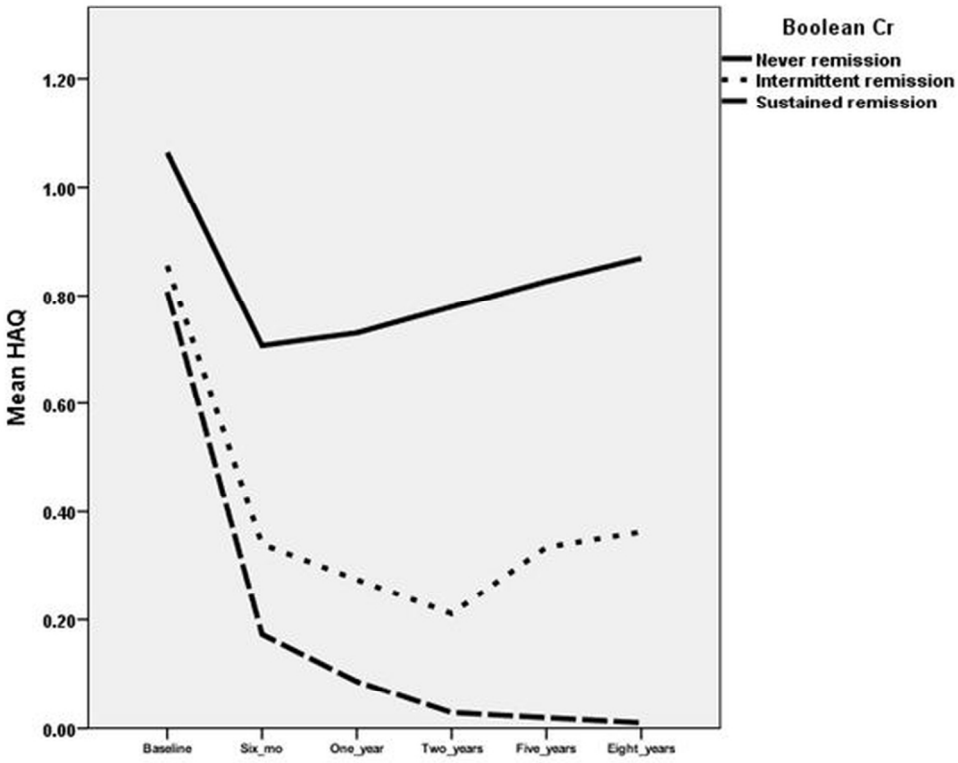

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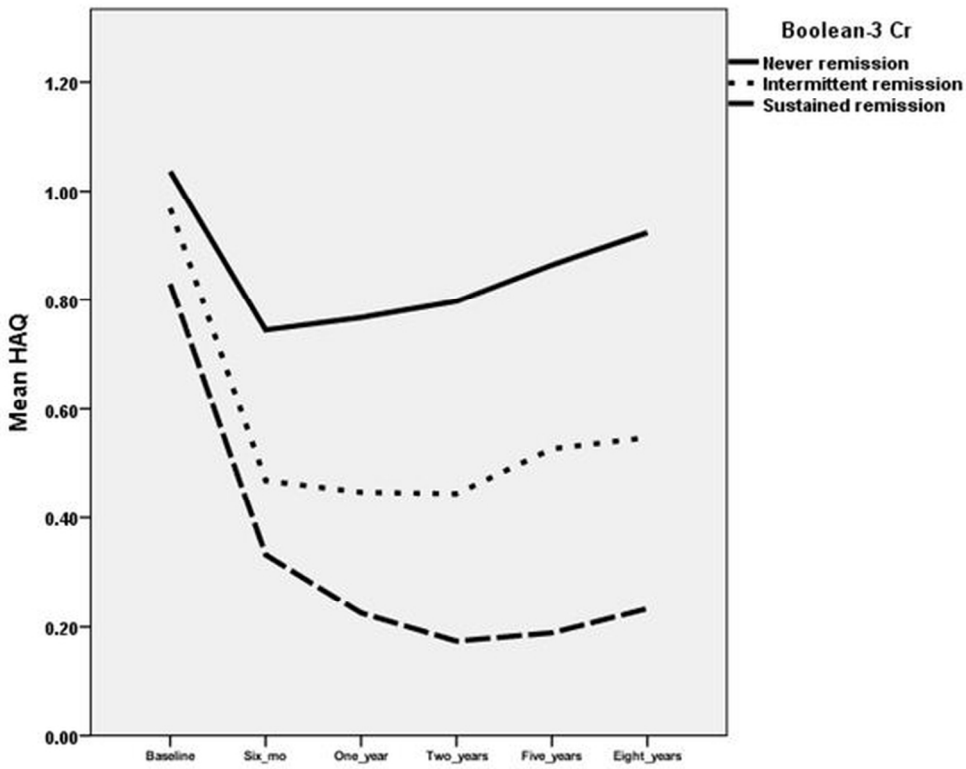

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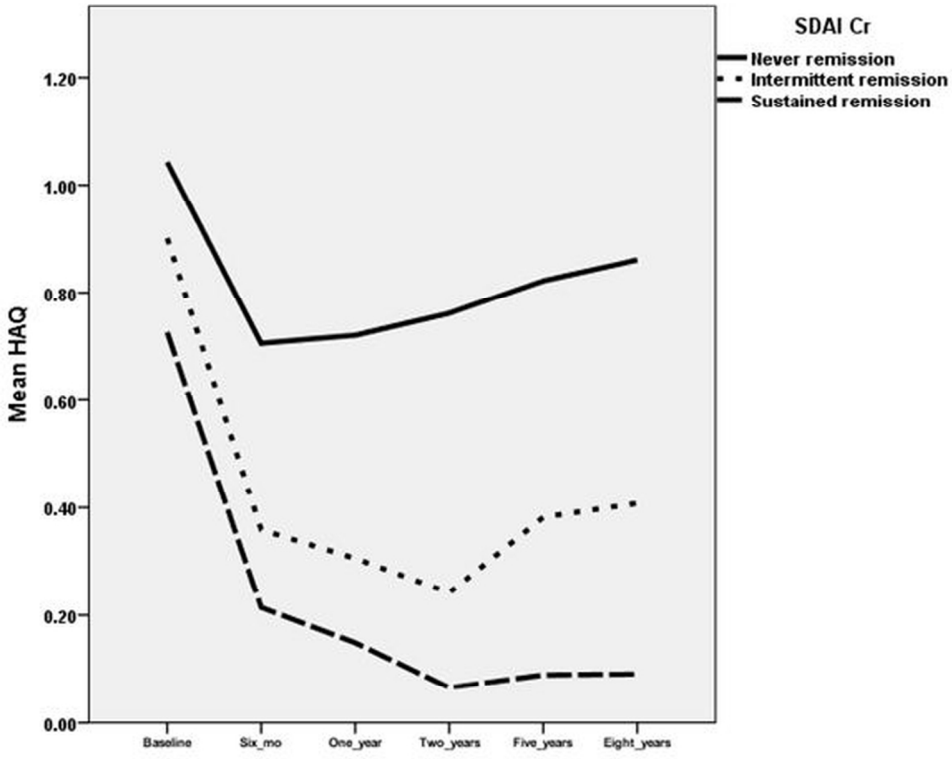

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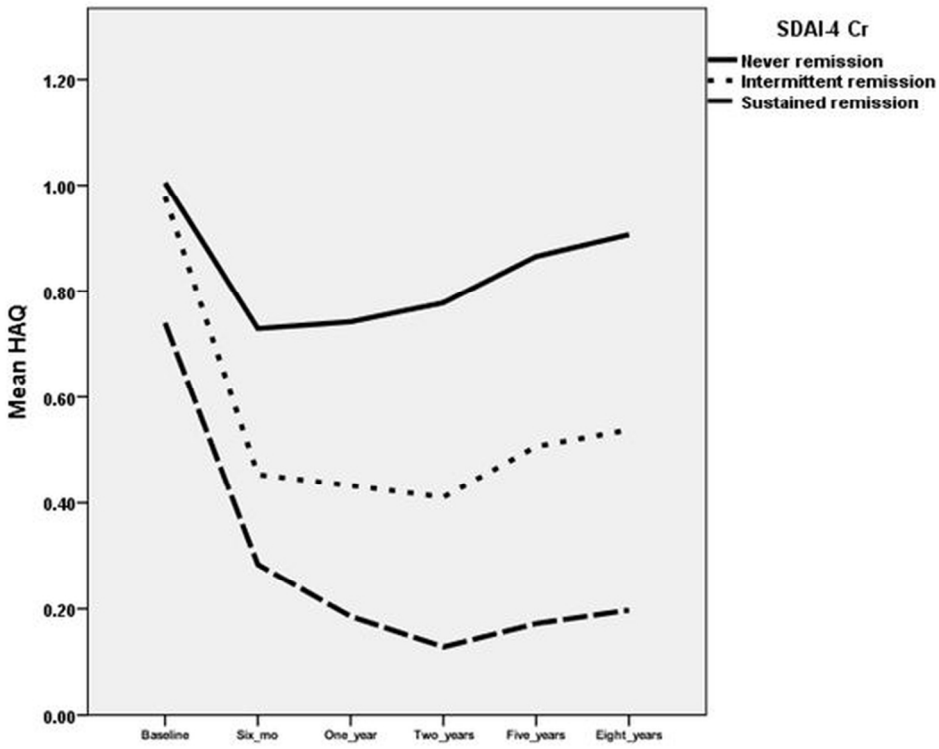

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