VARIABLE IMPACTS OF DIFFERENT REMISSION STATES ON HEALTH RELATED QUALITY OF LIFE IN RHEUMATOID ARTHRITIS

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ABSTRACT

Objective

Targetting remission in rheumatoid arthritis (RA) improves health related quality of life (HRQoL) and disability. However, the impacts of different remission criteria and durations and their frequencies are uncertain. Our observational study assessed these factors.

Methods

We recruited RA patients with disease durations <10 years, stable suppressive therapies and stable disease activity scores for 28 joints using ESR (DAS28-ESR) ≤3.2. Intermittent and sustained remisisons were classified using DAS28ESR, simple disease activity index (SDAI) and ACR/EULAR Boolean criteria. HRQoL, measured using SF-36, fatigue, EuroQol and health assessment questionnaire (HAQ) was compared using time-integrated areas under the curve (AUC).

Results

104 patients were enrolled and followed for 12 months. DAS28-ESR remissions were intermittent in 42%, sustained in 47% and absent in 11%. Boolean remissions were intermittent in 38%, sustained in 10% and absent in 52%. Baseline remissions by all criteria significantly improved HAQ, Euroqol, SF36 and fatigue scores compared with low disease activity (LDAS); AUCs showed significant benefits for all HRQoLs persisted over 12-months. Boolean remissions achieved most benefits. Over time all remisison states gave significantly better HRQoL scores than LDAS. Sustained DAS28ESR and SDAI remisisons improved HRQoL more than intermittent remissions. Sustained and intermittent Boolean remissions gave similar improvements. Analysis of SF-36 domains showed even sustained Boolean remissions failed to optimise pain and fatigue.

Conclusions

All remissions improve HRQoL but different criteria have variable impacts. Boolean remission had most impact but occurred least. There are trade-off between otpimising individual impacts (Boolean remissions) and achieving maximal overall impacts (DAS28-ESR remissions).

INTRODUCTION

Rheumatoid arthritis (RA) is characterised by both inflammatory synovitis and long term disability and impaired health-related quality of life (HRQoL) [1,2]. Patients focus on their impaired HRQoL, which can be assessed by a variety of validated instruments including generic measures such as Medical outcomes study 36-Item Health Survey forms (SF-36), EuroQol and Functional Assessment of Chronic Illness Therapy (FACIT-F) and disease-specific measures like the Health Assessment Questionnaire (HAQ) [3].

Targeting remission when treating RA, encapsulated in treat-to-target management [4,5], is considered to maximise HRQoL and minimise disability [6,7]. There is strong evidence that effective treatment of active RA decreases disability [8,9]. There is also considerable evidence treatment improves HRQoL [10-13]. Radner et al [14,15] have provided observational evidence and an analysis of clinical trial data that shows remission in general and sustained remission in particular benefit HRQoL. Other observational study data supports the concept that sustained remission most benefits disability [16]. However, many chanllenges remain when targeting remission. One issue is that some patients have histological evidence of persisting inflammation despite achieving clinical remission [17]. Another complexity is the varying perspectives of patients about what they want from treatment [18].

The key factors influencing how RA remission benefits HRQoL are their type, duration and frequency and considerable uncertainty remains about their relative importance in assessing treatment benefits. The use of less arduous remission criteria has been the subject of critical comment [19]. We examined all three factors in a prospective cohort of treated RA patients with stable low disease activity states. We evaluated three questions about how remission affects HRQoL. Firstly do different definitions of RA remission have different impacts on HRQoL? Secondly how important are sustained as opposed to intermittent remissions? Finally what is the relative frequency of different forms of remission?

PATIENTS AND METHODS

Patients

We recruited consecutive consenting adult RA patients who had been diagnosed using the 1987 revised ACR criteria and were currently attending three rheumatology centres in south London who met the following criteria. Recruitment period was from 2009 – 2011. Firstly,

they had disease durations of less than 10 years from the date of diagnosis. Secondly they had received stable doses of disease modifying anti-rheumatic (DMARD) or biologic therapies for over 6 months. Thirdly their disease activity scores for 28 joints assessed using the erythrocyte sedimenatation rate (DAS28-ESR) had been ≤3.2 for one month or longer.

Assessments

Initial data was collected about demographics, disease duration and current treatment. Disease activity assessments were made initially and every three months for one year to assess the following remission criteria: DAS28-ESR (erythrocyte sedimentation rate), DAS28-CRP (C-reactive protein), simple disease activity index (SDAI), clinical disease activity index (CDAI) and American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean remission criteria [20, 21].

Health Assessment Questionnaire Disability Index (HAQ-DI) [22]. The Medical Outcomes Study 36-Item Short-Form Health Survey (SF36) [23] including its eight domains and two sub-scales. The EQ-5D, which is also known as EuroQol [24], recorded as a single score, and the Functional Assessment of Chronic Illness Therapy (FACIT-F) [25] for recording self-reported fatigue. These outcomes were all measured every 3 months over the 12 month period of follow up.

Definitions Of Remission

Internationally agreed criteria were used [19,20]. Point remission at baseline was DAS28-ESR <2.6, DAS28-CRP <2.32, SDAI ≤ 3.3 and CDAI ≤ 2.8. ACR/EULAR Boolean remission was defined as TJC, SJC, CRP (mg/dl) and patient VAS (0-10cm) all ≤1. Low disease activity State (LDAS) at baseline was defined as patients not in remission by any definition with DAS28-ESR ≤3.2. Sustained remission (SR) was defined as achieving remission at all visit time-points, intermittent remission (IR) defined as achieving remission in at least 1 visit time-point, but not all. No remission (NR) was defined as never achieving remission by any clinical definition at any visit time-point over the 12 month period of follow-up.

Statistical Analysis

STATA 11.2 (StataCorp, College Station, TX, USA) was used for statistical analysis. Individual variables were assessed descriptively as median values and interquartile ranges

(IQR). To assess the impact of remission on HRQoL over 1 year, time-integrated values were calculated using area under the curve (AUC). These were computed using GraphPad Prism software using the trapezoidal method. Last observations carried forward (LOCF) method was used to handle missing data. Comparisons of these HRQoL measures between remission vs non- remission at baseline and between NR vs IR, IR vs SR and NR vs IR were performed using Mann-Whitney test.

Ethics Approval

The study was approved by the local ethics committee and conducted according to the guidelines of the Declaration of Helsinki (REC:09/H0803/154, Wandsworth Research Ethics Committee). Written informed consent was obtained from all participants.

RESULTS

Patient Cohort And Remission Rates

104 patients were enrolled of median age 56 years and median disease duration 45 months. Their baseline characteristics are shown in Table 1.

At baseline 67/102 (66%) were in DAS28-ESR remission and 35/102 (34%) were in LDAS states. Other remission criteria at baseline were met by 58 (59%) for DAS28-CRP remission, 45 (46%) for SDAI remission, 47 (46%) for CDAI remission and 30 (30%) for Boolean remission.

During 12 months follow up intermittent DAS28-ESR remissions occurred in 42% and sustained remission in 47% patients; only 11% of patients never achieved a DAS28-ESR remission. In contrast intermittent Boolean remissions occurred in 38% and sustained remission in only 10%; 52% of patients never achieved a Boolean remission. Other remission criteria were achieved by intermediate numbers of patients; the findings are summarised in Figure 1.

Baseline Remission Status

Comparing patients in baseline remission by DAS28ESR, SDAI or Boolean remission criteria with patients in low disease activity states (LDAS) showed patients in initial remission by all three criteria had significantly better baseline HAQ, Euroqol, FACIT F and SF36 scores than LDAS patients (Table 2). Those patients in remission at baseline also had

better AUC assessments of all HRQoL outcomes over the ensuing 12 months compared to LDAS patients.

The different remission criteria had variable effects on different HRQoL outcomes. The impacts on HRQoL were greatest with Boolean remission and least with DAS28-ESR remissions.

Intermittent And Sustained Remissions

Both intermittent and sustained remission states using DAS28-ESR, SDAI and Boolean criteria gave significantly better HRQoL scores than LDAS (Figure 2). With both DAS28ESR and SDAI, HRQoL was significantly better with sustained remissions than with intermittent remissions. With Boolean criteria both sustained and intermittent remissions gave similar improvements; Boolean remissions also gave the best overall benefits in improving HRQoL.

SF36 components

The improvements for each of the eight SF-36 domains with different remssion criteria is shown using spidergrams in Figure 3. The AUCs were better for all domains when patients achieved remission. DAS28-ESR and SDAI sustained remissions gave greater improvements than intermittent remissions. The improvements across the different SF-36 domains were greatest with Boolean remissions; and intermittent and sustained Boolean remissions achieved similar improvmemnts. However, even with Boolean remissions vitality, general health and bodily pain domains were not optimised.

DISCUSSION

We have confirmed that RA patients who achieve remissions at both single time points or sustained remissions have better HRQoL than patients who only achieve low disease activity states, in keeping with previous reports [6-16, 26-28]. However, we have also shown that not all remission criteria are equivalent. Achieving Boolean remissions has the greatest impact on HRQoL, DAS28-ESR remissions have the least impact and SDAI remissions have an intermediate impact. We found that with Boolean remissions most aspect of HRQoL are normalized; fatigue, pain and general health are the main exceptions and are not completely controlled. Sustained and intermittent remission had similar benefits with Boolean remissions, but only 38% of patients achieved any Boolean remission. The situation was

different with DAS2-ESR remissions. Although they improved most aspects of HRQoL compared to low disease activity, their but impacts were relatively modest, and there were substantial differences between sustained and unsustained remission. Nevertheless 89% of patients had some periods in DAS28 remission.

The inter-relationships between HAQ scores and remissions are complex. Firstly, there is some evidence that initial HAQ scores predict subsequent remissions, with patients having low HAQ scores being more likely to achieve remissions after treatment [29,30]. Secondly, we have found that HAQ scores are significantly lower when patients achieve remission by any criteria than when they are in low disease activity states. This finding replicates several other published studies. [31,32]. Thirdly, there is debate about the optimal target for HAQ scores. Molenaar et al [33] suggested HAQ scores <0.5 were optimal targets. However, we found median HAQ scores with SDAI and Boolean remissions were zero, suggesting there may be floor effects with low disease activity states and that HAQ scores of 0.5 may be suboptimal as a target. Finally the relationship of HAQ to remission may be influenced by the type of patients studied. Analysis of HAQ scores in patients from the DREAM cohort who all received biologic therapy, had somewhat higher HAQ scores when in remission [34] than the patients we studied. However, they are all likely to have overall worse severities than the more heterogenous patient group we studied. Interestingly the median HAQ value in our patients was also lower than the original cut-off for predictive validity of the ACR/EULAR Boolean criteria [20].

The assessment of HRQoL using SF36 and EQ5D is more complex. Both assessments have been used in RA and are able to detect changes in health status [35,36]. They both improve with effective treatments and have been most often studied in patients receiving biologics. Although deeper remissions, particularly Boolean remissions, gave the greates improvements in these measures, we found vitality, general health and bodily pain SF-36 domains were not optimised in any patient group. This reflects previously reported failure to minimise pain levels in RA patients in DAS28 remission reported by Lee et al [37]. FACIT-F assessments, which focuss on fatigue showed a similar pattern of incomplete control, which has also recently been reported in patients treated with biologics who have achieved remissions [38]. These findings imply that achieving remission by intensive drug treatment may not always normalise HRQoL in RA. One explanation for this finding is the impact of comorbidities [39-41], which we did not assess in detail. It is also likely that in established RA it may be

impossible to reverse the impact of the disease; as a consequence there is greatest emphasis on achieving remission by early intensive treatment.

The strengths of our study include its relatively large size and its complete 12 months regular follow up in a homogenous clinical population receiving similar treatment approaches. The observations were made by a small number of trained collaborating clinicians with good inter and intra-observer reproducibility in their assessments and a range of HRQoL instruments were used. It also has several limitations. Firstly, relatively few achieved sustained Boolean remissions, limiting an assessment of intense remissions. Secondly, as different remission criteria describe overlapping patient groups, the analytical approaches available are limited. Thirdly, we studied patients seen in specialist centres; community-based patients might show different inter-relationships between disease activity and HRQoL. Finally, due to the observational design of this study, as well as the small sample size, we were unable to address treatment effects on HRQoL within the remission groups.

There remains a paradox in setting the target for treating RA intensively. How low and how sustained should the target be set [42]? The benefits of Boolean remission, which improves HRQoL and disability greatest but still has incomplete effects on fatigue and pain, must be set against its relative rarity [43,44]. It is possible that not all patients can ever achieve Boolean remission; and there is evidence that different remission criteria have different predictive factors [45]. It is also likely that complete remission is an appropriate target in early RA [46] and less intense remissions reasonable in established disease. Our study design did not focus on a comparison of early and established disease, but there is strong evidence remission rates are higher when patients with early disease receive intensive treatments. [47]. Current expert opinion continues to have doubts about the relative benefits of aiming for LDAS or different remission criteria [48]. Our findings highlight the nature of this uncertainty, which reflects the benefits for groups of patients versus individual patients. Future prognostic markers may allow a resolution of doubts by identifying individual targets for patients in which bespoke targets replace global aims. Although this is currently a future aspiration, it might be sensible to start using it in different disease durations and to mainly focus on obtaining Boolean remission in early RA patients beginning intensive treatment strategies.

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Table 1: Baseline Characteristics Of Patients

Patient Characteristics		
Age, Median (IQR) years		56 (47, 69)
Disease Duration, Median (IQR) months		45 (23, 75)
Female (Percent)		63%
IgM RF Positive (Percent)		88%
ACPA Positive (Percent)		72%
Ethnicity	*Caucasian*	74%
	Asian	7%
	Afro-carribean	19%
TJC28, Median (IQR)		0 (0,1)
SJC28, Median (IQR)		0 (0,1)
ESR, Median (IQR)		8 (4, 16)
Patient Global, Median (IQR) (0-100mm)		18 (10, 35)
DAS28ESR, Median (IQR)		2.10 (1.40, 2.78)
DAS28CRP, Median (IQR)		2.15 (1.79, 2.72)
SDAI, Median (IQR)		3.60 (1.70, 7.56)
CDAI, Median (IQR)		3.20 (1.20, 7.20)
HAQ, Median (IQR)		0.13 (0, 0.75)
EQ5D, Median (IQR)		0.80 (0.69, 0.88)
EQ5D VAS, Median (IQR)		80 (70,90)
FACIT-F, Median (IQR)		42 (35, 47)
SF36 MCS, Median (IQR)		52 (44, 58)
SF36 PCS, Median (IQR)		44 (38, 52)
Erosive Disease (Percent)		52%
Erosive Progression (Percent)		14%
Treatments	*Methotrexate*	87%
	Sulphasalazine	27%
	Hydroxychloroquine	31%
	Leflunomide	4%
	Prednisolone	3%
	Combination disease modifying therapy	43%
	Tumour Necrosis Factor Inhibitors	16%

Table 2: Impact Of Baseline LDAS and Remission Status On Baseline And AUC HRQoL

HRQoL	**LDAS**	**DAS28 Remission**		**SDAI Remission**		**Boolean Remission**	
	Level	*Level*	*Significance*	*Level*	*Significance*	*Level*	*Significance*
Baseline							
HAQ	0.75 (0.5,1.38)	0 (0, 0.5)	<0.001	0 (0, 0.125)	<0.001	0 (0, 0.125)	<0.001
Euroquol	0.69 (0.59,0.76)	0.80 (0.69, 1.00)	0.024	1.00 (0.80, 1.00)	<0.001	1.00 (0.80, 1.00)	<0.001
FACIT-F	35 (31, 38)	43 (38, 47)	<0.001	46 (42, 50)	<0.001	46 (43, 50)	<0.001
SF36 PCS	39 (34, 43)	48 (40, 53)	<0.001	51 (46, 55)	0.001	52 (48, 55)	<0.001
SF36 MCS	49 (41, 53)	54 (47, 58)	0.021	57 (51, 58)	<0.001	57 (51, 58)	0.002
Area Under Curve							
HAQ AUC	10.3 (4.0,14.1)	1.2 (0, 6.6)	<0.001	0.28 (0, 1.8)	<0.001	0.43 (0, 188)	<0.001
Euroquol AUC	8.7 (7.7, 9.3)	9.9 (8.7, 11.4)	<0.001	10.6 (9.5,11.7)	<0.001	11.1 (9.6, 12.0)	<0.001
FACIT-F AUC	414 (349, 488)	537 (455 575)	<0.001	553 (492, 589)	<0.001	569 (488, 594)	0.001
SF36 PCS AUC	467 (430, 512)	588 (513 638)	<0.001	622 (554, 695)	<0.001	622 (585, 655)	0.007
SF36 MCS AUC	552 (500, 648)	618(557, 674)	0.005	649 (583, 691)	0.001	663 (597, 689)	<0.001

Comparing low disease activity state at baseline (LDAS) with baseline DAS28ESR, SDAI and Boolean remission
All values are reported as median (IQR). HRQoL = Health related quality of life, SF36 = short form 36, PCS = physical component score, MCS = mental component score, HAQ = health assessment questionnaire, AUC = area under the curve.

Figure 1. Frequency Of Intermittent Remission And Sustained Remission Using Different Criteria

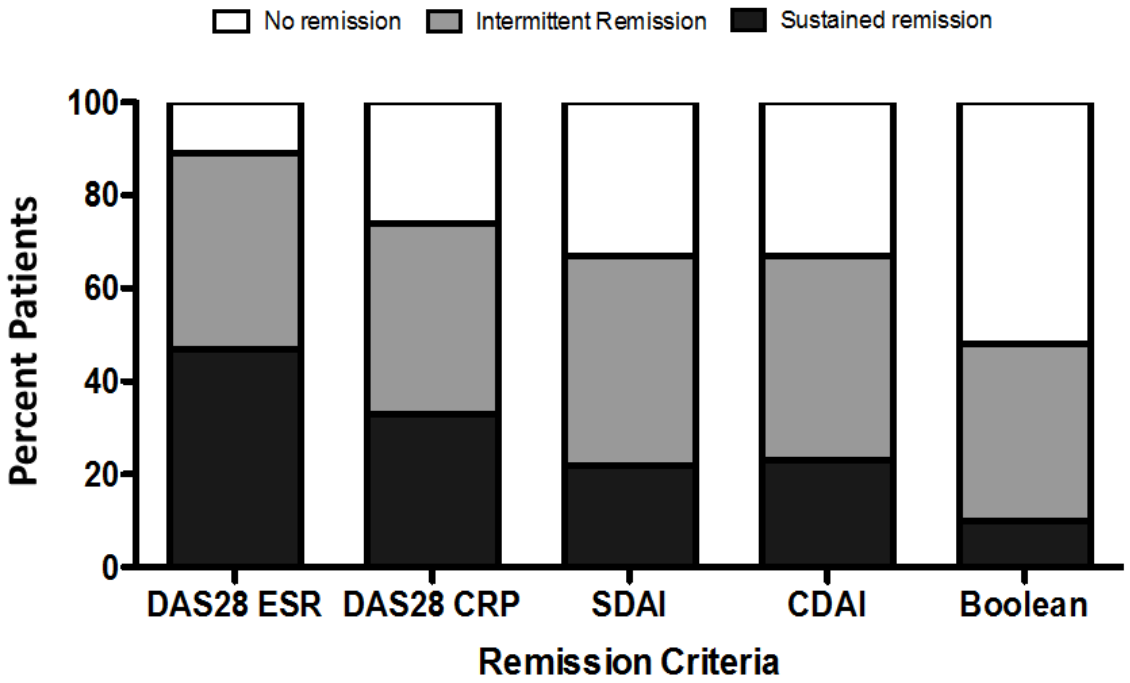
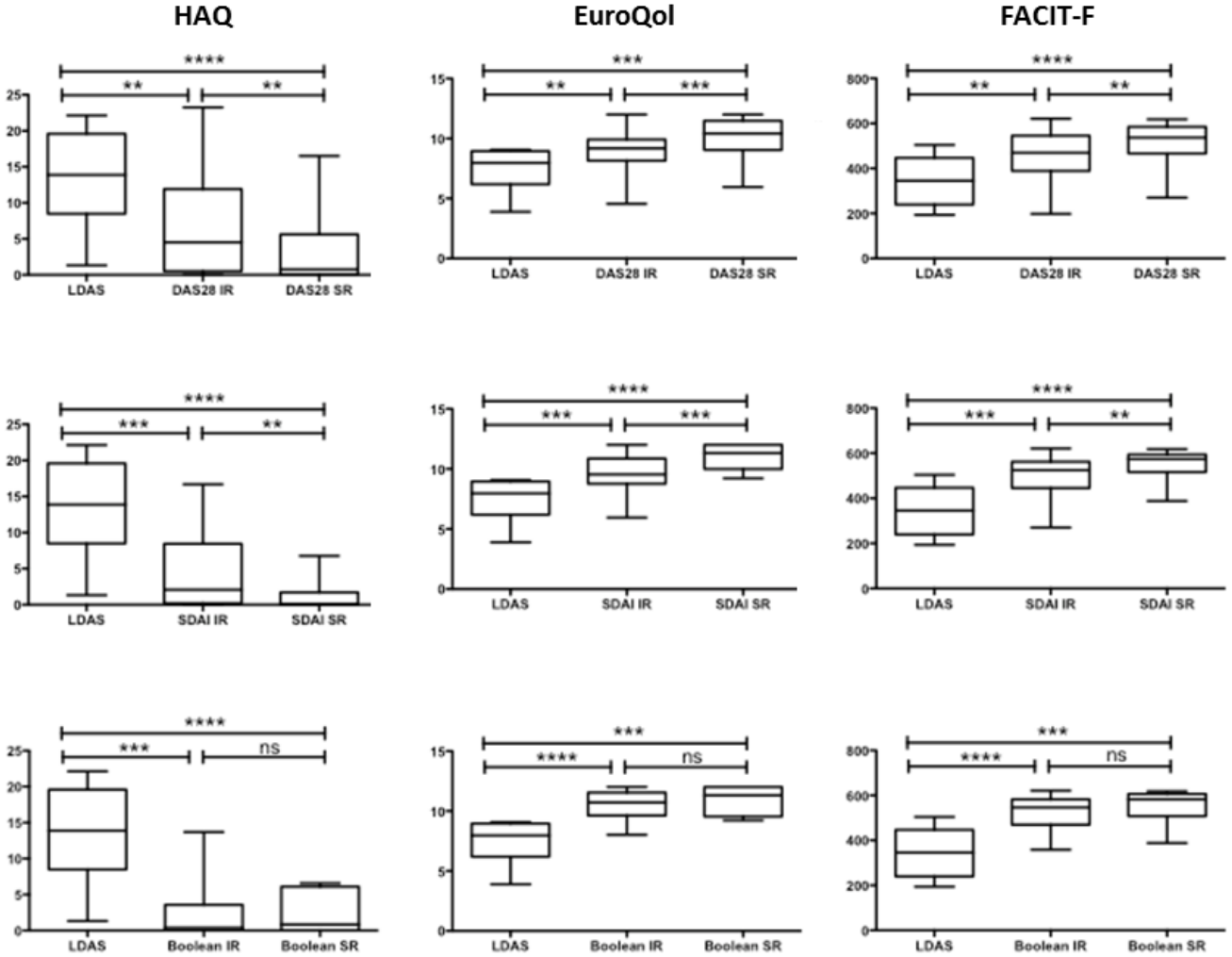
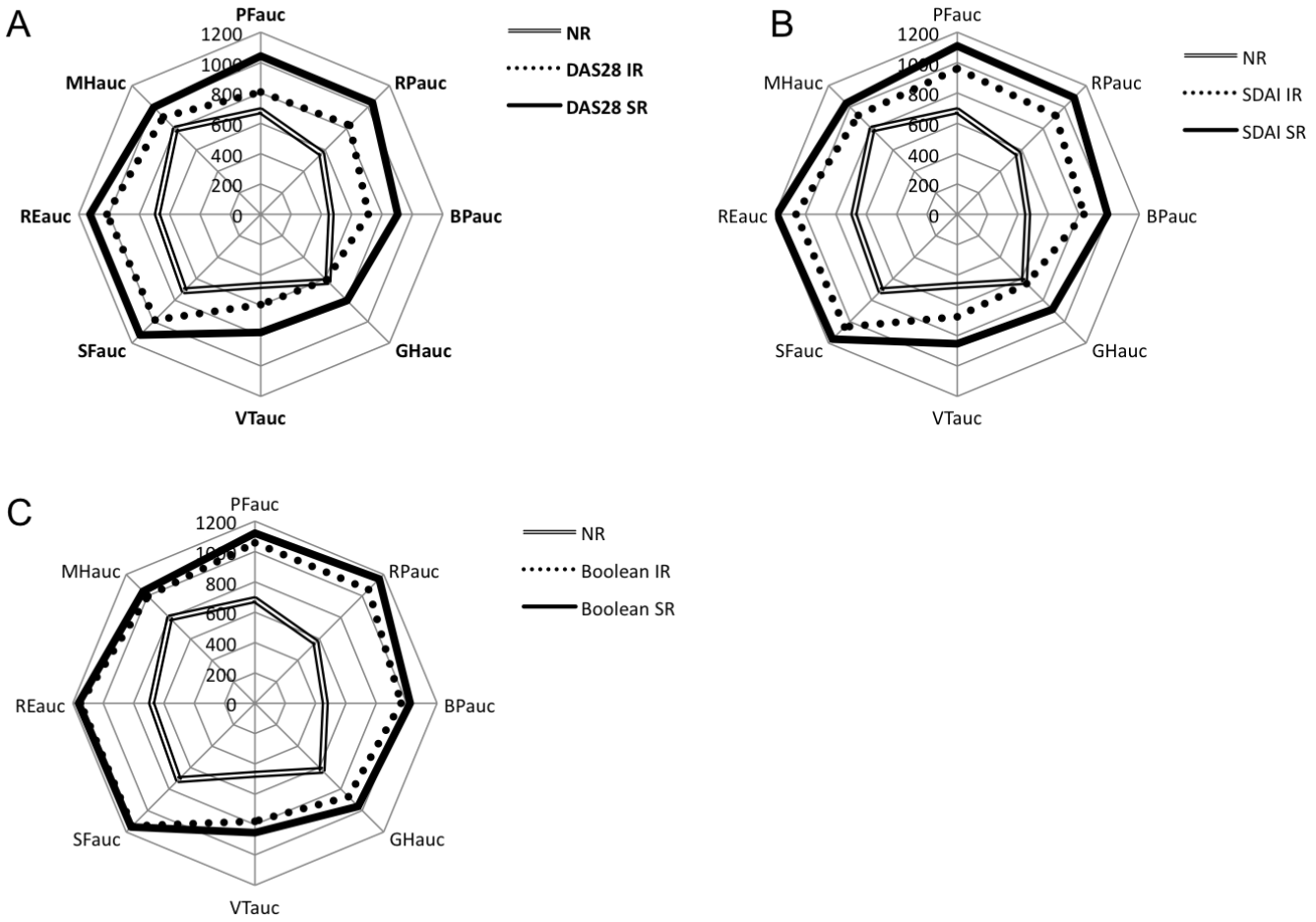


Figure 2. Impact Of Intermittent And Sustained Remission By DAS28, SDAI and Boolean Criteria On HRQoL Area Under Curve



Medians with interquartile and minimum and maximum ranges. IR = intermittent remission, SR = sustained remission
NS = Non-Significant, * = $P \leq 0.05$, ** = $P \leq 0.01$, *** = $P \leq 0.001$, **** = $P \leq 0.0001$ using Mann-Whitney test

Figure 3. Spidergrams Of SF-36 Domains In Patients Without Remissions And With Intermittent And Sustained Remissions



A=DAS28 remission, B=SDAI remission, C=Boolean remission. Values expressed as median AUC values
PR = physical functioning, RP = Role-physical, BP = bodily pain, GH = general health, VT = vitality, SF = social functioning, RE = Role-emotional, MH = mental health