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Gul, HL, Eugenio, G, Rabin, T et al. (5 more authors) (2020) Defining remission in rheumatoid arthritis: does it matter to the patient? A comparison of multi-dimensional remission criteria and patient reported outcomes. Rheumatology, 59 (3). kez330. pp. 613-621. ISSN 1462-0324

https://doi.org/10.1093/rheumatology/kez330

Journal: Rheumatology

Article Type: Original Article

Title: Defining remission in rheumatoid arthritis: does it matter to the patient? A comparison of multi-dimensional remission criteria and patient reported outcomes.

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Word Count: 2999

Disclosure Statement

Paul Emery has undertaken clinical trials and provided expert advice to Pfizer, MSD ,Abbvie, BMS, UCB, Roche, Novartis, Samsung, Sandoz and Lilly. Paul Emery has received consultant fees from BMS, AbbVie, Pfizer, MSD, Novartis, Roche and UCB. Paul Emery has received research grants paid to his employer from AbbVie, BMS, Pfizer, MSD and Roche.

All other authors declare no conflicts of interest.

Funding

No external funding.

ABSTRACT

Objectives

In a cross-sectional study we evaluated the prevalence of 'multi-dimensional remission' (MDR) and its component parameters, assessed using objective measures in a cohort of rheumatoid arthritis (RA) patients in treatment-induced DAS28-remission, and and their relationship with patient-reported outcome measures (PROMs). We sought to confirm the feasibility and face validity of the MDR construct, providing a platform for future longitudinal studies in which its clinical utility might be further established.

Methods

605 Patients were selected from an inflammatory arthritis register using DAS28(CRP)<2.6. Demographic, clinical and PRO data were collected. Ultrasound power doppler (PD) synovitis (n=364) and T-cell subsets (n=297) were also measured. Remission using clinical parameters (CR) was defined as: TJC28/SJC28/CRP all ≤1; ultrasound remission (UsR): total PD=0 and T-cell remission (TcR): positive normalised naïve T-cell frequency. MDR was defined as the achievement of all three dimensions.

Results

Overall, only 53% (321/605) patients achieved CR, failures being mainly due to raised CRP (52%), TJC(28)>1 (37%) or SJC(28)>1 (16%). 211/364 (58%) of patients achieved USR and 193/297 (65%) patients showed TcR. Complete data were available for 231 patients. MDR was observed in only 35% and was associated with the best (lower) PRO scores (all p≤0.05 vs non-MDR) when compared to the other definitions of remission assessed. The MDR rate was similar in early and established RA patients on b-DMARDs, however it was lower in established RA patients who received multiple cs-DMARDs (p=0.011).

Conclusions

In this study, MDR, which may represent a state closer to normality, was found to occur in about a third of DAS28-remission patients and was associated with better PROMs. MDR could be a novel optimal treatment target, notably from a patients perspective. The relevance of these findings needs further assessment.

Key messages

1. Clinical remission, as defined by DAS28 does not reflect absence of inflammation.

2. Multi-dimensional remission (MDR), using objective measures (imaging and immunological) is associated with better patient-reported outcomes.

3. Achieving MDR may be useful if aiming for a state closer to normality (true remission).

Keywords: Rheumatoid Arthritis, Disease Activity, Ultrasound, T-cells, Patient-Reported Outcomes

INTRODUCTION

Treat-to-target (T2T) strategies for rheumatoid arthritis (RA) aiming for remission have led to significantly improved outcomes however, despite achieving this target, patients may still progress/deteriorate. This is thought to be due to the subjective nature of remission definitions[1, 2].

Several clinical defintions (composite scores) exist, which vary greatly in terms of stringency[3]. DAS28-remission is the standard measure in clinical practice[4, 5], which uses a cut-off of the disease activity score (DAS28<2.6). It includes a score reflecting patient global perception of general health (GH)[4], which may be influenced by physical comorbidities (e.g. osteoarthritis and fibromyalgia) or psychosocial factors. Swollen joint counts can be inaccurate in remission[6], whilst objective markers of inflammation (erythrocyte sedimentation rate, ESR and C-reactive protein, CRP) are non-specific[7]. Thus, patients who achieve DAS28-remission are a heterogeneous population, with some patients still displaying clinical signs and symptoms of inflammation (tender and swollen joints) and sub-clinical synovitis on ultrasound (US)[8-11]. Radiographic progression has also been demonstrated in a proportion of patients[10]. Therefore, DAS28-remission may in fact reflect a spectrum of 'minimal' disease activity[12] rather than a distinct state of 'no disease'.

New attempts to define clinical remission more stringently include the ACR/EULAR 2011 Boolean remission criteria (TJC28, SCJ28, CRP & GH all ≤1[13]), however this still includes subjective measures and potentially inaccurate joint counts. Boolean remission is frequently used in clinical studies and has been shown to be effective at group level, however not representing the absence of inflammation. The concept of 'deep' clinical remission has been reported (DAS28<1.98), which is suggested to reflect the absence of biological inflammation however, longitudinal outcome data relating to this target have not yet been studied prospectively[14].

To circumvent these issues, objective measures that can define the absence of inflammation more accurately and can be translated into clinical practice have been proposed. It is probable that joint damage in patients with no clinically swollen joints is a consequence of sub-clinical synovitis[11]. US can detect synovitis with greater sensitivity than clinical examination and predicts progressive joint damage in patients in clinical remission[10, 11], hence its potential use as a biomarker of remission. The concept of 'multi-dimensional' remission using objectice measures[12] has recently been introduced, which involves the achievement of different depths of remission, using clinical (normal inflammatory markers), imaging (US and/or MRI) and additional serological parameters (negative autoantibodies), although not yet used prospectively. RA is a systemic disorder with many immunological features[15, 16]. Abnormalities in the frequency of certain T-cell subsets have been reported, notably a reduction in normalised naïve $CD4^+$ T-cells, the presence of inflammation-related cells (IRC) and the loss of regulatory T-cells (Treg)[17, 18], for which potential value as biomarkers of immune dysregulation at various critical points in the continuum of RA has been established[17, 19-21].

There is growing emphasis on patient-centred care in rheumatology, with increased importance placed on integrating PROMs as endpoints in clinical trials and standard care[22-25]. Although some PROMs are included in existing composite scores, these only provide a global assessment of disease and do not encompass the spectrum of symptoms and burden of disease experienced by patients[26]. Their current use in this context is therefore limited. However, realising the importance of patient-perceived health status, the optimum tools to define remission should ideally be directly associated

with better PROMs, including disability and quality of life (QoL) assessments such as the RA Quality of Life Questionnaire (RAQoL) and Health Assessment Questionnaire Disability Index (HAQ-DI). Nonetheless, it should also reflect a true state of biological remission to be achieved.

We hypothethised that multi-dimensional remission (MDR), using the combination of clinical, US and T-cell subsets may help to define a more complete state of remission by assessing inflammation directly at structural and immunological levels, which would also reflect better patient health status. This could therefore represent a novel optimal treatment target. The aims of this work are, for the first time to phenotype remission in RA, first by evaluating the prevalence of objective measures of remission, in particular MDR, second to assess associated factors and last to evaluate which definition of remission tested correlates with better PROMs, arguably an important feature.

PATIENTS AND METHODS

Patient population

Patients were identified from an 'inflammatory arthritis continuum' (IACON) register (REC: 09/H1307/98, 15/01/2010) when fulfilling two inclusion criteria: (i) RA diagnosis (ACR/EULAR 2010 classification criteria) and (ii) DAS28(CRP)<2.6 (3-variables) at a single study visit. Patient global health (GH) assessment score was omitted due to missing data (missing rate: 14.7%). DAS28(CRP) (3-variables) was used because all patients could be included and the mean values of DAS28(CRP) (3-variables) and DAS28(CRP) (4 variables) agrees well[27]. Written consent was obtained upon inclusion. The first DAS28-remission visit was given priority for cross-sectional data collection. In the case of missing data, subsequent visits were reviewed chronologically until a visit with sufficient data was identified for each patient.

Assessments

Clinical: Standard demographic and clinical data were collected: age, gender, autoantibody status, smoking status, disease duration, tender and swollen joint counts (TJC28 & SJC28) and CRP.

PRO: Patient questionnaires were collected, including measures of visual analaogue scores (VAS) for GH, disease activity (DA), fatigue and pain, HAQ-DI and RAQoL however, not avalible for all patients at all visits.

Imaging: US assessments recorded grey scale (GS) synovial hypertrophy and power doppler (PD) abnormalities as presence/absence per joint and total score, graded according to the OMERACT standardised consensus based scoring system[28]. The joints chosen represented a pragmatic and feasible core set, which from our previous observations were most commonly affected in patients with RA (bilateral wrists, MCPJ's 2-3, PIPJ's 2-3, elbows, knees, ankles and MTPJ's 1-5).

Immunological: T-cell subsets (naïve $CD4^+$ cells, T-regulatory cells (Treg) and inflammatory related cells (IRC) were measured by flow-cytometry and normalisation was performed as detailed in supplementary material, and as previously described[16, 20].

Statistics

Data are described using non-parametric tests (median, interquartile range (IQR) or number and proportion (%). Continuous measures were compared between groups using Mann-Whitney-U and ANOVA tests and nominal measures with Chi-square tests. Post hoc analysis (Dunn's method) was performed following the ANOVA with correction for multiple testing. Analyses were conducted using SPSS 21.1. Venn diagrams were constructed with assistance from the BioVenn© web application[29].

RESULTS

Patient characteristics

605 patients fulfilled the inclusion criteria. Patient characteristics are described in Table 1 and clinical and PRO characteristics are displayed using dot-plots in Figure 1. Treatment used to achieve/induce remission was variable. Three main categories were used to classify patients (i) only cs-DMARDs (71%) (ii) 1st-line b-DMARD as part of a clinical study, discontinued at the time of recruitment (9%) or (iii) b-DMARD following cs-DMARD failure (20%).

The median 3v-DAS28(CRP) was 1.77 (n=605). US data was available for 364 patients. PD synovitis was detected in 42% patients with a median total score of 0 however, with a wide range of values (0-33). The median total GS score was 14 (range 0-60). T-cell phenotyping was performed in 297 patients. Normalised naïve CD4$^+$ T-cells had variable frequencies (median +7.59%) with a large proportion of patients having positive values (73%), suggesting recapitulation of thymic activity in remission, as previously observed[30]. IRC's were still detected (median +1.9%) but only in a small proportion of patients (15%), in agreement with inflammation being well-controlled. Treg (normalised) were also heterogeneous (median -2.5%) and only a small proportion of patients (19%) had recovered positive levels, which as per previous studies suggests a poor ability to restore Treg frequencies in remission.

Following this cross-sectional evaluation of characteristics of patients achieving DAS28-remission, we aimed to evaluate whether different remission dimensions provided additional information to help define remission more precisely.

Defining remission dimensions

Clinical Remission (CR): A Boolean remission definition was adapted for this study (by omitting GH from the definition due to missing data) as this represents the most stringent of definitions used in clinical studies. 321/605 (53%) patients in DAS28-remission were in CR (Table 1). The failure to achive CR (n=284, 47%) was mainly due to raised CRP≥5g/dl (148/284, 52%), followed by TJC(28)>1 (107/284, 38%) and more occasionally SJC(28)>1 (45/284, 16%).

For patients in CR who had imaging data, 61/181 (34%) had evidence of PD synovitis (median total score=0) and GS signal (median total score=14). T-cell subset abnormalities also persisted in CR, with negative naïve T-cell values in 58/165 (35%) patients. 35/192 (18%) also had IRC values above normal and 154/185 (83%) had negative Treg values.

CR (vs. non-CR) was associated with anti-CCP antibody positivity (p=0.012), longer disease duration (p=0.022) and better scores for all PROMs (all p<0.0001).

Ultrasound Remission (UsR): Defined as total PD=0, reflecting the complete absence of inflammation at the structural level was present in 211/364 (58%) of the cohort. Individually, UsR (vs. non-UsR) was associated with achievement of CR (p=0.001), reflected by lower levels of CRP (p=0.027), fewer swollen joints (p=0.005); younger age (p<0.0001) and lower scores for certain PROMs (VAS GH, pain and disease activity, all p<0.05).

T-cell Remission (TcR): T-cell subset phenotyping has not yet been used as a remission criterion, although positive normalised naïve CD4$^+$ frequency predicts the induction of remission in early RA with

1st-line cs-DMARDs while other subsets were not predictive[16]. At this stage, we chose the naïve subset as a basis for classification for TcR, although analysis of other outcome (i.e. flare for example) may require IRC or Treg as previously reported[8, 21]. In this group, 193/297 (65%) patients presented a positive value. There was no difference in IRC or Treg values between patients in TcR or not. Individually, TcR (vs. non-TcR) was more frequently observed with older age (p=<0.0001) and anti-CCP antibody positivity (p=0.015), however it was not associated with the achievement of the other two remission dimensions. There was no difference in the frequencies of naïve cells between drug groups for cs-DNARDs and b-DMARDs (supplementary material).

Multi-dimensional Remission (MDR): When the three remission dimensions were investigated together in patients with a complete dataset (n=231), only 80 (35%) patients satisfied all three. MDR was associated with disease duration (p=0.004) and male gender (p=0.012) and lower PROMs (all p≤0.05) (Table 2). No significant association was found between MDR and method of remission induction.

PROMs according to different dimensions of remission (n=191)

To address whether patients felt any better in one type of remission compared to another, we compared PROMs between different remission definitions.

We first compared MDR (n=68) with (CR: (n=120), then with CR+UsR: (n=88), and CR +TcR: (n=84) and MDR=68). MDR demonstrated lower median PROM scores for all variables assessed compared to the achievement of CR (data not shown), while the combination of either UsR or TcR with CR demonstrated lower scores compared to CR alone as well as MDR, however slightly higher than MDR. This comparison however, cannot be performed due to the overlap of patients between groups.

To assess this strictly, we compared PROMs for single remission dimensions versus the combination of two dimensions or MDR (Figure 2). Median PROM scores were lower in MDR compared to CR alone, UsR alone, or TcR alone. Similarly, when dual remission dimensions were assessed, MDR was associated with lower PROMs median compared to any dual combinations. Using an ANOVA test, all PROMs were significantly different between the 7 groups (p<0.05) except for GH and fatigue (p<0.10). Using post-hoc comparision, MDR was individually significantly different to one or other group for each PROM (i.e. indicative line on Figure 2, p<0.05) with the exception of CR+USR. Therefore, despite very small numbers in some groups, median PROMs for MDR were altogether lower compared to the achievement of single or dual remission dimensions, thus confirming the potential value of MDR as a novel optimum treatment target.

Early vs. longer disease duration (n=231)

Since longer disease duration was associated with MDR (Table 2), we explored whether drug regimen used to induce remission yielded different proportions of patients in remission between early and established disease. We used venn diagrams (Figure 3), separating patients who received a 1st-line biologic in early RA (n=18) compared to the other 2 drug groups in established RA (n=52 for biologics and n=161 for cs-DMARDs). In the early RA group, only 6/18 (33%) achieved MDR. The proportion in late disease was 34% for cs-DMARDs and 38% for b-DMARDs. There was therefore no significant

difference in MDR rates between groups (p=0.805) suggesting it could be used for early as well as established disease.

In early RA treated with b-DMARDs (n=18), CR was observed in all but 1 patients (94%) while MDR was only achieved in 33%. USR (72%) was almost equaly observed as TcR (67%) but not in the same patients. MDR in this group therefore offers a deeper evaluation of remission and both imaging and immunology seems important in assessing a state of deep remission.

In established RA treated with b-DMARDs (n=52), CR is observed in 76% of patients while MDR in 38%. USR is achieved in 67% of patients and TcR in 75%. There is no dimension most frequently associated with MDR, suggesting that all 3 may also be highly relevant in this group.

In established RA treated with cs-DMARDs (n=161), CR is observed in 62% of patients but only 34% were in MDR. 67% of patients achieved USR and 78% TcR. TcR appears more independently achieved (44%) than USR (33%) or CR (28%).

DISCUSSION

Clinical remission is the current optimum treatment target for RA, however current evidence suggests that a proportion of patients continue to have signs and symptoms of disease and may continue to progress structurally despite achieving this target[1, 2].

To develop a tool reflecting a 'true' state of remission, which better reflects a patients health status, we tested the potential of defining remission multi-dimensionally using objective measures. We first demonstrated that RA patients in DAS28-remission display evidence of continued abnormalities, clinically (tender and swollen joints, CRP>5mg/l) or with US (presence of sub-clinical synovitis), as well as not normalising T-cell subsets. We also demonstrated that such patients display a wide range of PROMs. DAS28-remission is therefore heterogeneous and unlikely to accurately represent a state of 'no disease'[12]. We then compared composite definitions of remission, establishing the best association with PROMs and showed that MDR represents the best state. .

Patients who met CR criteria demonstrated more homogeneity as a group compared to those not meeting CR (Table 1). This is to be expected, being a more stringent remission definition compared to DAS28-remission[13]. CR was associated with anti-CCP positivity, longer disease duration and better scores for all PROMs. Current literature suggests that remission can be achieved equally in antibody positive and negative patients, although the quality of remission is less stringent, as anti-CCP antibody positive patients tend to have more residual tender and swollen joints[31].

UsR was associated with the achievement of CR, lower median CRP values and fewer swollen joints (Table 1). In-line with current evidence[11], we have further validated the presence of residual synovitis in remssion as measured by US. In addition, it was associated with lower scores for several PROMs including GH, pain and disease activity.

We demonstrated some heterogeneity in the frequencies of the different T-cell subsets (Table 1). The achievement of TcR appears to be independent of both CR and UsR. Unlike these, it was not associated with PROM scores. Instead, it was associated with anti-CCP positivity, suggesting that TcR may reflect the implication of T-cells in seropositive disease notably as the genetic risk in anti-CCP positive RA is

clearly associated with T-cell genes[32]. TcR was also associated with older age. There are contradictory data about the relationship between anti-CCP positivity and age[33, 34]. Furthermore, age when achieving remission may be confounded by many other factors, notably age at onset, disease duration and remission induction regimen. In active RA, we previously observed positive and negative values irrespective of age [16, 20], which suggests that recovery of naïve T-cells in remission, is more frequently seen in older individuals (as also previously reported [35]).This therefore requires more complex analysis with a larger group to control for all parameters. Altogether, MDR was significantly different for PROMs compared to all other remission definition tested, with medians in MDR for each PROMS being lower. Importantly, the PROMs included HAQ-DI and RAQoL, which both more appropriately reflect the impact/burden of disease (compared to VAS scores), as such patients in MDR had more optimal QoL scores (median=1) compared to patients who achieved single or combination of two remission dimensions (median ranged from 3 to 7). MDR was however not individually significantly superior to CR+USR for any PROMs tested despite the lower medians. In this exploration of the individual parameters composing MDR. Defining remission multi-dimensionally may therefore offer a novel optimum treatment target from a patient's perspective.

MDR was also associated with longer disease duration. The overall cohort was biased towards established RA (only 53 treatment-naïve early RA patients versus 552 patients with longer-lasting disease), probably contributing to this association. Drugs used to induce remission may therefore be more relevant. This may be the group of patients where objective assessment of remission may have the most value, potentially facilitating informed tapering of b-DMARDs for patients only when in a true state of remission.

In early RA patients receiving a 1st-line biologic, UsR was more frequently observed (20/24, 83%, acounting for all available data for US). This may reflect the fact that the range of a PD signal is potentially less well established than in later disease and therefore more easily reversible. In late disease, reducing PD to 0 is more difficult. In contrast, in early disease, TcR was less frequently achieved (15/31, 48%) (also compared to CR (32/53, 61%)) suggesting that TcR may be a limiting factor in achieving true remission. These patients all stopped their b-DMARDs after 12 months (as per trial protocol) but the remission baseline was at anytime, therefore, this needs to be further explored. In established RA on cs-DMARDS, no dimension was preferentially achieved. Previous work has demonstrated that b-DMARDs correct T-cell abnormalities longitudinaly better than cs-DMARDs[16]. Normalised naïve T-cells were more frequently positive in patients with long-lasting disease on b-DMARDs (43/59, 72%) compare to cs-DMARDs (135/206, 65%), possibly reflecting this known mode of action[16]. TcR may prove useful as a more objective measure of remission, not being associated with residual pain, inflammation or damage.

Limitations of the study include the heterogeneity of the cohort with respect to method of remission-induction, disease and remission duration and the use of retrospective register data. Missing GH also prevented the use of classic Boolean remission. USR using PD=0 may also have been overly strict. Our data will therefore need to be validated in a subsequent cohort. Future studies will also require correlations with other clinical outcomes such as the sustainability of remission and flare prediction, notably with respect to tapering treatment. The use of regression analyses assessing the weight of each remission dimension should help develop predictive tools for these outcomes.

In conclusion, clinically defined remission is heterogeneous and does not reflect the absence of inflammation and disease-related abnormalities. Achieving MDR was associated with better PROMs,

including QoL assessments, therefore a better outcome from a patients perspective. Our findings suggest that imaging and immunological characteristics, added to clinical data, may be useful if aiming for a target of true remission (MDR). The potential for using MDR in future studies is therefore will help the managment of patients in remission and may provide rationale for tapering therapties, notably b-DMARDs providng quality of life of patients is maintained.

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Table 1: Baseline characteristics

	Total Cohort (DAS-28 remission)	CR	UsR	TcR
n (over total cohort)	605	321/605 (53%)	211/364 (58%)	193/297 (65%)
Demographic Variables				
Age (years)*	58 (46-67)	59 (47-68)	57.5 (45.5-68)	63 (51-70.5)
Gender (F)	411/605 (68%)	208/321 (65%)	130/211 (62%)	120/193 (62%)
RF+	427/605 (71%)	119/321 (37%)	121/211 (57%)	104/193 (54%)
ACPA+	355/605 (59%)	241/321 (75%)	146/211 (69%)	132/193 (68%)
Smoking status (%): **Current** **Previous** **Never**	 121/582 (20%) 214/582 (35.4%) 247/582 (40.8%)	 54/309 (53%) 119/309 (39%) 136/309 (44%)	 37/199 (19%) 76/199 (38%) 86/199 (43%)	 25/178 (14%) 76/178 (43%) 78/178 (44%)
Disease duration (months)*	34 (15-59) (n=530)	28 (12-61)	36 (16.25-58.75)	20 (9-55.5)
Remission induction with (%): **cs-DMARD** **1st line Biologic** **Biologic after failed csDMARD**	 429/605 (71%) 53/605 (9%) 123/605 (20%)	 213/321 (71%) 32/321 (10%) 76/321 (24%)	 153/211 (73%) 20/211 (9%) 38/211 (18%)	 135/193 (70%) 15/193 (8%) 43/193 (22%)
Clinical Variables*				

TJC(28)	0 (0-1)	0 (0)	0 (0-1.75)	0 (0-1)
SJC(28)	0 (0-5)	0 (0)	0 (0-1)	0 (0-1)
CRP (mg/L)	0 (0)	0 (0-8)	0 (0)	0 (0-5)
3v-DAS28(CRP)	1.77 (1.15-2.2)	1.15 (1.15-1.46)	1.8 (1.15-2.22)	1.9 (1.15-2.3)
Imaging Variables*				
Total PD	0 (0-2)	0 (0-2)	2.5 (1.25-5)	0 (0-3)
Total GS	14 (8-19)	13.5 (17-19.25)	11 (6.25-19.75)	16 (0.5-20)
Immunological ($CD4^+$ T-cell variables)*				
Normalised naïve T-cell (%)	+7.59 (-3.23 to +20.54)	+3.88 (-2.71 to +11.30)	3.8 (-4.5 to +14.55)	11.17 (5.27 to +22.54)
IRC (%)	+1.90 (+1 to +4)	+1.80 (+0.90 to +4)	+2.10 (+0.95 to +4.50)	+1.80 (+0.9 to +4)
Normalised Treg (%)	-2.51 (-3.7 to -0.99)	- 2.39 (-3.67 to-0.77)	-3.0 (-4.28 to -1.85)	-2.39 (-3.70 to -0.77)
Patient Reported Outcomes* (n=525/605)				
Global Health (GH) VAS	16 (6-31)	15 (5-43)	15.5 (5-28)	15 (7-33)
Fatigue VAS	24 (3-43)	24 (5-36)	26 (2.25-42)	24 (3-42)
Disease Activity VAS	10 (3-29)	9 (3-24)	11.5 (3-28.5)	15 (3-30.5)
Pain VAS	10 (4-27)	10 (3-25)	10.5 (4-24)	10 (4-23.5)
HAQ-DI	0.38 (0-1)	0.2 (0-0.75)	0.5 (0-1)	0.63 (0-1.06)
RAQoL	3 (0-10)	2 (0-5.3)	3 (0-9)	3 (0-9.5)

***Median (IQR)**

Table 2: Multi-dimensional remission vs. not multi-dimensional remission: associated baseline characteristics (n=231)

Multi-dimensional remission	Achieved (n=80/231)	Not achieved (n=151/231)	P value
Age*	52 (25-80)	59 (19-87)	0.437
Gender (F)	40/80 (50%)	101/150 (67%)	0.012
RF+	43/80 (54%)	89/150 (63%)	0.448
ACPA+	56/80 (70%)	112/150 (74%)	0.498
Smoking status: Current **Never** **Previous**	7/73 (10%) 32/73 (44%) 34/73(47%)	24/140 (17%) 62/140 (44%) 54/140 (39%)	0.269
Disease duration (months)*	58 (5-192)	33 (5-242)	0.004
Remission induction with: **1st line Biologic (n=18)** **Biologic after failed csDMARD (n=52)** **csDMARD (n=161)**	6 (33%) 20 (38%) 54 (34%)	12(67%) 32 (62%) 107(66%)	0.805
Global Health VAS*	10 (0-59)	16 (0-84)	0.050
Fatigue VAS*	7 (0-83)	24 (0-59)	0.006
Disease Activity VAS*	6 (0-65)	10 (0-90)	0.003
Pain VAS*	6 (0-69)	10 (0-99)	0.003
HAQ-DI*	0 (0-1.38)	0.5 (0-2.14)	0.004
RAQoL*	2 (0-16)	4.5 (0-20)	0.009

***Median (IQR)**

Legends For Figures:

Figure 1: Clinical, Imaging and Immunological characteristics of total cohort (DAS28-remission, n=605).

TJC/SJC tender/swollen joint counts n=605; CRP (mg/L) C-reactive protein n=605, values plotted at 0 are those deemed below detection (<5mg/L); DD disease duration (months) n= 434; PD power dopler; GS grey scale n=364; T-cell subsets (% of CD4+T-cells) n=291, patient reported outcomes n=525, GH (global health); DA (disease activity); HAQ-DI (health assessment questionnaire –disability index; RAQoL (RA quality of life).

Figure 2: **Number (%) of patients in different states of remission according to treatment**
We used a venn diagram to show how MDR was achieved with respect of ClinR, USR and TcR. Patients were segregated according to the treatment regime used to induce remission, with cs-DMARDs or b-DMARDs (the latter being further separated between 1st line or not).

Figure 3: Association of baseline PROMs with depth of remission achieved

PROMs are reported in relation with achieving different definitions of remission. Altogether there are significantly differences between all groups (ANOVA, $p<0.05$) furthermore, lines indicate significant difference following the ANOVA combined with post hoc individual tests ($p<0.05$). MDR (n=68), CR only (n=11), USR only (n=9), TcR only (n=20) CR+TcR (n=20) and UsR+TcR (n=32), CR+UsR (n=28).