Suppressing Inflammation in Rheumatoid Arthritis: Does Patient Global Assessment Blur the Target? A Practice-Based Call for a Paradigm Change

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Running title: PGA in RA

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Abstract:

Objectives: In current management paradigms of Rheumatoid Arthritis (RA), patient global assessment (PGA) is crucial to decide whether a patient has attained remission (target) or needs reinforced therapy. We investigated whether the clinical and psychological determinants of PGA are appropriate to support this important role.

Methods: This was a cross-sectional, single centre study including consecutive ambulatory RA patients. Data collection comprised swollen (SJC28) and tender joint counts (TJC28), C-Reactive protein (CRP), PGA, pain, fatigue, function, anxiety, depression, happiness, personality traits, and comorbidities. Remission was categorised using ACR/EULAR Boolean-based criteria: remission, near-remission (only PGA>1) and non-remission. A binary definition without PGA (3v-Remission**)** was also studied. Univariable and multivariable analyses were used to identify explanatory variables of PGA in each remission state.

Results: 309 patients were included (remission: 9.4%; near-remission: 37.2%; non-remission: 53.4%). Patients in near-remission were indistinguishable from remission regarding disease activity, but described a disease impact similar to those in non-remission. In multivariable analyses, PGA in near-remission was explained ($R^2_{adjusted}$=.50) by fatigue, pain, anxiety and function. Fatigue and pain had no relationship with disease activity measures.

Conclusion: In RA, a consensually acceptable level of disease activity (SJC28, TJC28, and CRP≤1) does not equate to low disease impact: a large proportion of these patients are considered in non-remission solely due to PGA. PGA mainly reflects fatigue, pain, function, and psychological domains, which are inadequate to define the target for immunosuppressive therapy. This suggests that clinical practice should be guided by two separate remission targets: inflammation (3v-Remission) and disease impact.

Significance and Innovations

- In Rheumatoid Arthritis, Patient Global Assessment (PGA) is frequently the sole criterion impeding patients from achieving the target of remission as defined by the ACR/EULAR Boolean-based criteria ("4v-Remission").
- A large proportion of patients with tight control of inflammation maintain a high PGA and this cannot be improved by further disease control.
- We, therefore, propose that an alternative definition of remission, based solely on joint counts and C-reactive protein ("3v-Remission"), is more appropriate to define the target for immunosuppressive therapy.
- Patients' perspective should remain core to disease assessment and management, but this will be better served by more discriminative instruments than PGA.

The outlook of RA has improved remarkably over recent years, due to not only the development of new therapies but also novel treatment strategies (1). Among these, the Treat-to-Target (T2T) recommendation (2, 3) epitomizes the consensual concept that disease treatment should aim at achieving, as early and consistently as possible, a target of level of remission, or at least low disease activity (3, 4).

The provisional definition of remission in rheumatoid arthritis proposed conjunctly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)(5), has been recommended for use in daily care of RA patients (3). This definition takes into consideration, in a Boolean format, swollen and tender joint counts (SJC28, TJC28), CRP and patient global assessment (PGA). PGA weights the same as the other components, which are more closely related to disease activity (inflammation). The ethical and clinical imperative of incorporating patient reported outcomes (PROs) in the decision process is indisputable, but reflection is needed on the best way to achieve this (6). PGA's inclusion was mainly justified because it represents the patient's perspective and is responsive to treatment in clinical trials, discriminating between active and control intervention (5). However, considering stopping progression of joint damage is one of the most important objectives of treatment in RA, a recent systematic review (7) concluded that only SJC and acute phase reactants, but not PGA, were independent predictors of radiographic progression. Another point against PGA is its difficult interpretation (8-10). Until now, most studies suggest that PGA essentially reflects pain, function and fatigue (10-15), which in turn have shown a variable correlation with inflammatory markers, in studies that did include psychosocial dimensions or perform multivariable analyses. Considerable percentages of PGA remain unexplained (>22%)(11) and few studies have explored its relationship with the underlying level of disease activity (10), or with the patient's psychological profile (10, 16, 17).

PGA has been identified as the main single factor impeding patients from reaching the state of remission (9, 18-20). These patients represent 61% to 80% of all those who do not reach the

ACR/EULAR Boolean remission due to one single parameter being >1, a state that has been designated as "near-remission" (18). Similar to patients in remission, they have a maximum of 1 SJC, 1 TJC and 1 mg/dl PCR. However, according to the ACR/EULAR definition they will be considered in non-remission, because of PGA>1, thus becoming candidates for reinforced immunosuppressive therapy, following the current treatment guidelines (3, 4).

The key clinical question we want to address is whether such patients require an increase in immunosuppressive therapy or would be best treated with alternative interventions directed at the causes of high-perceived disease impact. In order to answer this crucial clinical question it is essential to understand whether PGA conveys dimensions of the disease that are amenable to change by immunosuppressive therapy, especially in patients in near-remission.

The objectives of the present study were to: (i) understand how PGA correlates with a broad array of variables, from disease activity, comorbidities, psychological dimensions, and other measures of disease impact in people with RA; (ii) determine whether these components of PGA variability change in different remission state categories, especially in near-remission thus impacting upon T2T driven decisions; (iii) understand the explanatory variables for pain and fatigue, and (iv) explore the adequacy of a remission definition without PGA (3v-remission) as a basis to define the target for immunosuppressive therapy, separating it from disease impact.

Participants and Methods

Study design & Setting

This was an observational, cross-sectional study, performed in a single rheumatology outpatient department, in Portugal between September and December 2015.

Participants

Consecutive adult patients satisfying current RA criteria (21, 22) were invited to participate. Patients were excluded only if they were unable to respond to the questionnaires unaided. Patients

are followed, monitored and treated according to standard Department's guidelines. Ethical approval was granted by the University of Coimbra's Faculty of Medicine Ethics Committee (CE-037/2015) and all patients signed an informed consent form before start of study procedures.

Patient global assessment

PGA was assessed using two different formulations: (a) as stated in the ACR/EULAR definition of remission (5) - "Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?", and (b) as stated in the Disease Activity Score using 28 joints (DAS28) definition (23) - "How active was your arthritis during the past week?". Both were presented as a 0-100 mm visual analogue scale (VAS) as recommended, with their respective anchors: "very well" and "very poor" for the former and "not active at all" and "extremely active" for the latter. Each formulation of PGA was presented in a single page of the questionnaire, interspersed with other PROs. The first formulation was used to define the ACR/EULAR remission status and was also taken as the dependent variable in all analyses.

Other Variables

Patients responded to questionnaires including demographic data and the following PROs: pain [Numerical Rating Scale (NRS), range 0–10], fatigue (NRS, range 0–10), function (Health Assessment Questionnaire (24)), anxiety and depression (Hospital Anxiety and Depression Scale (25)), happiness, through the Subjective Happiness Scale (26), a 4-item measure (7-point Likert scale). Personality was assessed with the Ten Item Personality Inventory (27), a brief measure of the Big-Five personality dimensions, each being scored as the mean of 2 items (7-point Likert scale). For both the latter measures, higher means correspond to more intense expression of the respective conditions.

The attending physician collected the following: year of diagnosis, rheumatoid factor and ACPA status, presence/absence of erosions, TJC28, JC28, CRP, physician global assessment of

disease activity (0-100mm VAS), and current medications. Concomitant diagnoses were registered (fibromyalgia, depression, low back pain, osteoporotic fractures, osteoarthritis, and stroke) and the total number of comorbidities was computed.

Patients completed the questionnaires unaided and before clinical consultation in order to minimise the influence of physician's assessment. Both patients with experience of using VAS/NRS (54.7%) and those with no previous experience were included.

Remission definitions

Patient's remission state was classified in three categories derived from the ACR/EULAR 2011 Boolean-based definition(5): i) **Remission** (TJC28, SJC28, CRP mg/dl, and PGA, all ≤1), ii) **Near-remission** (18) (TJC28, SJC28, and CRP mg/dl ≤1; PGA>1), iii) **Non-remission** (TJC28 or SJC28 or CRP mg/dl >1). In addition, we explored the binary definition **3v Remission** (28) (TJC28, SJC28, and CRP mg/dl ≤1; where PGA is excluded from consideration).

The DAS28-CRP(3v) considers TJC, SJC and CRP. The 3v version excludes the consideration of PGA, as required for the purposes of this study. We used the variant with CRP as this is more readily available in this medical centre than the erythrocyte sedimentation rate.

Statistical methods

Quantitative data were expressed as means (SD) and categorical data as frequencies and percentages. There was no imputation of missing data.

Pearson's correlation coefficients between PGA, and pain, fatigue and all potentially explanatory continuous variables were calculated. Correlations were categorized as very good, r≥.60; moderate, r=.40-.59 and poor r<.40 (29). Differences in variables between remission state categories were tested in pairs using Independent Student's *t*-test, with adjustment for relevant cofactors (ANCOVA) where appropriate. Variables with p<.10 in the overall sample, and patients with full sets of data were included in stepwise multivariable linear regression models (backward method) with PGA as dependent variable. Two methods were used to prevent multicollinearity

between explanatory variables in the multivariable models: i) assessment of bivariate correlations of possible explanatory variables prior to inclusion, defining r<.80 as the threshold for inclusion (30); ii) assessment of the variance inflation factor, assuming values <4 as acceptable (30). None of the variables was excluded based on these criteria. These multivariable linear regression analyses were performed for the overall sample. They were then repeated, using the same variables, for subsamples defined by the different disease remission states. Regarding sample size, we established that a minimum of 10-15 patients per each explanatory variable should be recruited (total 200-300 patients) as recommended by Austin and Steyerberg (31).

IBM® SPSS® Statistics, version 20.0 software was used for all analyses.

Results

Patient characteristics

In total, 309 RA patients were included. Reasons for exclusion are presented in Supplementary Figure 1.

Demographic and clinical characteristics of patients are presented in Table 1. A total of 79 (25.6%) patients had no comorbidities and 5 accumulated a maximum of five comorbidities (data not shown). The mean (SD) DAS28-CRP(3v) was 2.5 (0.9) and the mean PGA was 43.7 (26.7). Regarding remission state, only 29 (9.4%) patients satisfied the ACR/EULAR criteria for remission. All remaining patients, in non-remission, were split according to the criteria described above, into near-remission 115 (37.2%) and non-remission 165 (53.4%). If PGA was not considered in the definition (3v-Remission), the rate of patients classified in remission would increase from 9.4% to 46.6%.

Disease activity and disease impact across remission state categories

The comparison between remission state categories (Table 2) shows that near-remission is almost indistinguishable from remission in terms of disease activity measures, except for a slightly

higher TJC28. Conversely, in terms of disease impact (PROs), near-remission is clearly distinct from remission but quite similar to non-remission. For instance, PGA in near-remission and non-remission is 10 and 11 fold, respectively, of the PGA reported by patients in remission.

When comparing all patients with TJC28, SJC28, and CRP (mg/dl) ≤1 (3v-Remission) versus those with at least one of these parameters >1 (3v-Non-remission) the differences were equally clear-cut in terms of disease activity (Supplementary Table S1). Conversely, the disease impact measures largely overlap between these two categories (see also Table 2).

Anxiety and depression were present at similar levels in near-remission and non-remission, but were significantly lower in remission. Happiness followed a similar pattern but did not reach statistical significance (Table 2).

PGA correlates across remission state categories - univariable analyses

Overall, there were significant correlations between PGA and all continuous variables included, except for the personality domains “agreeableness” and "conscientiousness" (Table 3). These correlations were classifiable as "good" for pain, fatigue, and function and “moderate” for depression and anxiety. The remaining correlations were "poor", including not only personality traits but also all variables representing disease activity. Looking at the correlations between PGA and explanatory variables by disease states, near-remission was similar to non-remission in showing significant correlation between PGA and all PROs, including subjective happiness. In remission however, only fatigue and anxiety were significantly correlated with PGA. In both non-remission and in remission, PGA was significantly correlated with CRP and DAS28-CRP(3v) but this was not the case in near-remission (Table 3).

The correlation between personality traits and PGA was largely absent or poor, except in the remission group were "openness to experience" had moderate correlation with PGA. Overall, age, disease duration and number of comorbidities were all significantly correlated with PGA in univariable analyses and, variably, in the remission state categories. Years of formal education were

inversely correlated with PGA in all groups (Table 3).

In the overall sample, a significantly higher PGA was observed in association with the presence of erosions and of each of the comorbidities considered, except osteoporotic fractures (p=.055). There were no significant differences in PGA by gender, RF and ACPA status or familiarity with VAS/NRS (Supplementary Table S2).

Correlates of PGA across remission states - multivariable analyses

The explanatory variables of PGA differed between the three remission state categories. The best-fit model for near-remission ($R^2_{adjusted}$=.50), included fatigue, pain, anxiety and function. None of the objective measures of disease activity was retained (Table 4). In non-remission, the model ($R^2_{adjusted}$=.62) retained function, pain, anxiety, SJC28 and years of formal education. Age, disease duration, depression, happiness, personality traits, number of comorbidities, and CRP were not retained in the multivariable models for any of the remission state categories.

The correlates of pain and fatigue

The origins of pain and fatigue, the most important correlates of PGA in near-remission patients were statistically explored through univariable (Supplementary Table S3) and multivariable analyses. Patients in non-remission were also studied, for comparison. In the multivariable analyses (Table 5), pain was poorly explained in both near-remission ($R^2_{adjusted}$=.51) and in non-remission ($R^2_{adjusted}$=.54). The best-fit models are different in the two remission states, including fatigue, anxiety, years of formal education and extraversion for patient in near-remission while for those in non-remission, the latter two are substituted by function and happiness. The correlates of fatigue in best-fit models include pain and function for both remission state categories. In near-remission, two personality traits are also retained in the model, having a significant correlation with fatigue, whereas in non-remission, personality traits are dropped and anxiety is retained, increasing fatigue.

None of the disease activity measures have a significant relationship with either pain or

fatigue irrespective of the remission state category.

Discussion

This is one of very few studies assessing PGA correlates across remission state categories and the first using the Boolean-based definition for this purpose. The results confirm previous observations (9, 18-20) that a large percentage of RA patients in routine clinical practice miss the target of remission solely because of PGA. The percentage of near-remission observed (37.2%) was higher than reported before: 14.4% to 34.1% (9, 15, 17, 18, 20). These differences may be related to cultural issues (32, 33) but the level of education and prevalence of emotional distress may also play a role. Whatever the reason, none of these percentages is negligible, as they could lead to different and potentially hazardous therapeutic decisions according to the current RA management recommendations. In this study it represents a five-fold increase (from 9.4% to 46.6%) in the rate of remission.

PGA from patients in near-remission is not associated with disease activity but rather with fatigue, pain, anxiety and function. Pain and fatigue, in turn, were correlated among them, and were influenced by anxiety, personality traits and happiness, but bear no relationship with SJC28 or CRP (Table 5). These observations are in close agreement with the findings reported by Ward et al. (10).

In other studies (9-15, 19) pain has been shown to be the best "predictor" of PGA, regardless of remission state. In the current study, pain was second to fatigue in explaining PGA in near-remission. Using a similar near-remission definition to ours, Studenic et al. (18) demonstrated that higher pain levels lead to patients failing the ACR/EULAR Boolean-based definition only due to PGA. Ward, Guthrie and Dasgupta (10) concluded that pain severity is the strongest determinant of PGA, not only directly, but also indirectly via deteriorated function, DAS28, and health distress (10).

In essence, the results of our study confirm and expand previous observations, and conjunctly they underline that, in near-remission, PGA seems to convey and be driven by

dimensions that are not obviously related to the inflammatory process therefore, cannot be expected to change because of reinforced immunosuppressive therapy.

This does not imply that PGA is not correlated with disease activity, as argued to support the inclusion of this parameter in the ACR/EULAR definition of remission (5). In fact, PGA was also correlated, although just moderately, with DAS28-CRP(3v) in this study (Table 3). Interestingly, this was true for the overall population (r=.36), for patients in non-remission (r=.30) and even for patients in remission (r=.47), despite the very low level of disease activity and PGA (≤1) in the latter group. However, this was not the case in near-remission. PGA seems, therefore, to be in accordance with disease activity in both the remission and the non-remission group, but there is a clear mismatch between these dimensions in the near-remission group. These weak correlations between PGA and disease activity parameters reflect that there is no meaningful relationship on the individual level. This does not mean, in any way, that the patient's perspective is not important. On the contrary! It is essential to care, as we discuss below.

The conclusions of this study need to be considered in the light of potential limitations. First, our population was recruited in a single centre in Portugal, which may limit generalizability as PGA and other PROs have been shown to vary across countries (33-35). The similarity of our findings with other studies is however rather reassuring in this respect. Second, the mean DAS28 in this sample was very low (mean=2.5, SD=0.9), reflecting a well-controlled disease cohort. Samples with higher mean DAS28 may have a lower percentage of near-remission patients. However, our analyses were performed by disease activity subgroups and these conclusions are probably applicable to other similar disease activity strata. Pharmacological treatment used in our sample may also differ from other countries (36), but we believe that this does not affect the main results or the conclusions of this study. Third, its cross-sectional nature limits the ability to assess causality and progress over time. Fourth, the overall model explained only 62% of PGA. This may be due to an inherent characteristic of the outcome or some relevant variables not being assessed, such as stiffness (13) work disability (37) or joints of the feet, although these were not a significant factor in

the study by Studenic's et al. (18). Finally, analyses within the remission group are weakened by the small size of the group and the limited range of disease activity parameters and PGA allowed by the definition (all ≤1).

Conversely, the study presents a very robust and complete set of data, including domains that most physicians consider highly relevant but are seldom studied, like personality traits and emotional states. The sample included a wide diversity of age, disease activity, years of formal education and previous experience with questionnaires and VAS, all of these being potentially relevant dimensions, rarely represented with a range that allows proper statistical evaluation. Additionally, contrary to previous studies, we used the different formulations of PGA approved for each instrument, as this may affect the results (38, 39). Finally, our sample was also powered to allow strong statistical evaluation and was composed of unselected ambulatory patients.

The clinical implications of these observations are far-reaching. This study demonstrates that non-remission state as defined by the ACR/EULAR 4v-Boolean concept brings together, due to a similar PGA, two different groups of patients in terms of disease activity: near-remission and non-remission (Table 2). This strongly supports the view that the target chosen to drive immunosuppressive therapy should not include PGA. In near-remission, the only targets that are appropriate for immunosuppressive therapy (SJC, TJC, and CRP, i.e. 3v-Remission) have already been achieved, but including PGA in the definition obscures that fact and puts the patient at risk of excessive treatment. A sharp target for any therapy should be defined by parameters amenable to change by that same therapy. This is not the case for PGA regarding immunosuppression.

These observations call for a clear separation of the concepts of remission according to the objective of their use: control of inflammation (physicians' remission, as a target for immunosuppressive therapy) and control of disease impact (patients' remission, as target for overall management of the disease). The former offers a strong contribution but not a guarantee for the latter.

The concept of 3v-remission provides the most appropriate definition for "physician's remission" as it results in two clearly separate and homogeneous groups of patients in terms of disease activity. For clarity, these concepts are presented in Figure 1.

The importance of "patient's remission" cannot and should not be overlooked as controlling the impact of disease upon patients' lives is the core objective of disease management. Given the relationship between disease activity and PGA described above, rheumatologists can be reassured that they will reduce disease impact in most patients, while controlling the disease process into remission. However, once TJC28, SJC28 and CRP are close to or below 1 but PGA remains high, it is obviously not the time to increase immunosuppressive therapy but rather to consider adjuvant therapies. Some adjuvant therapies have shown to improve several PGA-related variables. This is the case for non-pharmacological interventions, such as cognitive-behavioural therapy (40, 41) and relaxation or biofeedback interventions (42) that address pain, functional disability, fatigue, sleep, depressive symptoms, anxiety, coping, self-efficacy, and even tender joints. Other non-pharmacological interventions that have been shown to be effective are physical activity (43, 44), occupational therapy (45) and patient education (46, 47). These studies highlight the importance of a team approach to disease management as well as the importance of incorporating patient's perspective in the overall treatment plan. PGA is not an appropriate instrument at this stage either, because it does not discriminate between the reasons for continued impact, which is essential to guide the selection of adjuvant therapy but can only provided by discriminating instruments, such as the RAID in its seven domains (48).

Further investigation is needed to fully clarify these issues, including assessment of possible persistence of minimal inflammatory activity in patients in near remission and studies to determine whether a persistently high PGA in patients who are otherwise in remission has any impact upon long-term structural damage. The TJC may also be affected by concomitant diseases (e.g. fibromyalgia) and other factors such as psychological status. Factors associated to a high TJC when SJC and CRP are ≤1 also deserve investigation in future studies. Additional evidence and guidance

is needed on the origins and best management strategies for pain, fatigue and other relevant domains of disease impact in RA.

In conclusion, this study demonstrates that in RA, control of inflammation does not equate to low disease impact. The impact of disease upon patients' lives is predominantly independent from the degree of inflammation, especially in near-remission. The results of this study suggest that the concepts of disease activity and disease impact should be addressed as separate domains. A definition of remission focused on inflammatory activity (physician's perspective, 3v-Remission) is the most appropriate to serve as target for immunosuppressive therapy. The patient's perspective, i.e., disease impact should be examined separately with more analytical measures than PGA, in order to guide efforts to alleviate impact beyond what is achieved through disease control.

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Table 1 – Demographic and clinical characteristics of RA patients (n=309)

Demographic	
Age, years, mean (SD)	59.5 (12.3)
Female gender, n (%)	253 (81.9)
Formal education, years, mean (SD)[a]	7.4 (4.5)
Disease characteristics	
Disease duration, years, mean (SD)	12.0 (9.0)
RF positive, n (%)[a]	224 (74.2)
ACPA positive, n (%)[a]	148 (69.8)
Erosions, present, n (%)[a]	174 (69.6)
Comorbidities, yes, n (%)	
Fibromyalgia	52 (16.8)
Depression	66 (21.4)
Low Back Pain	79 (25.6)
Osteoporotic fractures	29 (9.4)
Osteoarthritis	181 (58.8)
Stroke	6 (1.9)
Current Pharmacological Treatment, n (%) [a]	
Synthetic disease modifying drug	275 (89.3)
Biologic agents	95 (30.8)
Glucocorticoids	212 (68.8)
Disease activity measure, mean (SD)	
TJC28 (0–28)	1.4 (2.9)
SJC28 (0–28)	1.4 (2.5)
CRP (mg/dl)	0.8 (1.4)
DAS28-CRP(3v) (0–9.4)	2.5 (0.9)
PhGA (VAS, 0-100)	13.4 (15.2)
Disease activity status, n (%)	
Remission#, n (%)	29 (9.4)
Near-remission##	115 (37.2)
Non-Remission###	165 (53.4)

3v-Remission####	144 (46.6)
Disease impact measures, mean (SD)¶	
PGA (VAS, 0–100)	43.7 (26.7)
Pain (NRS, 0–10)	4.9 (2.5)
Fatigue (NRS, 0–10)	5.1 (2.7)
HAQ (0–3)	1.1 (0.7)
HADS-Anxiety (0–21)[a]	8.4 (4.3)
HADS-Depression (0–21)[a]	7.3 (4.2)
SHS (1–7)([a]	4.8 (1.3)
TIPI (1-7) [a]	
Extraversion	4.2 (1.5)
Agreeableness	5.7 (1.2)
Conscientiousness	5.7 (1.3)
Emotional Stability	3.6 (1.5)
Openness to Experience	4.5 (1.4)

ACPA= anti-citrullinated antibody; CRP= C-reactive protein; DAS28= Disease Activity Score using 28 joints; HADS= Hospital Anxiety and Depression Scale; HAQ= Health Assessment Questionnaire; PGA= patient global assessment; PhGA= physician global assessment; RF= rheumatoid factor; SHS= Subjective Happiness Scale; SJC28= swollen joint counts using 28 joints; TIPI= Ten Item Personality Inventory; TJC2 = tender joint counts using 28 joints.

[a] Percentages of patients with missing data were < 2.5%, except for ACPA (31.4%) and erosions (19.1%).

Remission = TJC28, SJC28, CRP mg/dl, and PGA all ≤1

Near-remission = TJC28, SJC28, and CRP mg/dl all ≤1; PGA>1

Non-remission (TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value)

3v-Remission = TJC28, SJC28, and CRP mg/dl all ≤1; PGA not considered. It equates to merge " Remission" and " Near-remission" disease states.

¶ For all, except SHS and TIPI, higher scores correspond to worse outcomes.

Table 2 – Adjusted comparison of disease activity measures and disease impact measures between remission state categories in RA patients (n=309)

	A) Remission n=29	B) Near-remission n=115	C) Non-Remission n=165	Adjusted# p-values A vs B	A vs C	B vs C
Disease activity measures, mean (SD)						
TJC28 (0–28)	0.1 (0.3)	0.3 (0.4)	2.5 (3.7)	**.028**	**.005**	**<.001**
SJC28 (0–28)	0.2 (0.4)	0.2 (0.4)	2.5 (3.0)	.449	**<.001**	**<.001**
CRP (mg/dl)	0.2 (0.2)	0.3 (0.2)	1.3 (1.8)	.133	**.008**	**<.001**
DAS28-CRP(3v) (0–9.4)	1.7 (0.3)	1.8 (0.4)	3.0 (0.8)	.165	**<.001**	**<.001**
PhGA (VAS, 0-100)	6.0 (10.2)	6.0 (8.5)	19.8 (16.6)	.770	**<.001**	**<.001**
Disease impact measures¶, mean (SD)						
PGA (VAS, 0–100)	4.5 (3.2)	44.4 (22.3)	50.0 (26.2)	**<.001**	**<.001**	.273
Pain (NRS, 0–10)	2.0 (2.1)	4.7 (2.3)	5.5 (2.3)	**<.001**	**<.001**	**.019**
Fatigue (NRS, 0–10)	1.8 (2.1)	5.1 (2.3)	5.7 (2.6)	**<.001**	**<.001**	.208
HAQ (0–3)	0.3 (0.5)	1.0 (0.7)	1.3 (0.7)	**<.001**	**<.001**	**<.001**
HADS-Anxiety (0–21)	5.3 (4.9)	8.5 (3.9)	8.9 (4.4)	**.004**	**.009**	.924
HADS-Depression (0–21)	3.3 (3.4)	7.0 (3.7)	8.2 (4.3)	**<.001**	**<.001**	.091
SHS (1–7)	5.4 (1.2)	4.9 (1.0)	4.6 (1.4)	.154	.065	.072

CRP = C-reactive protein; DAS28 = Disease Activity Score using 28 joints; HADS = Hospital Anxiety and Depression Scale; HAQ = Health Assessment Questionnaire; PGA = patient global assessment; PhGA = Physician global assessment; SHS = Subjective Happiness Scale; SJC28 = swollen joint counts using 28 joints; TJC28 = tender joint counts using 28 joints.

One-way ANCOVA test adjusted for: Age, gender, disease duration, years of formal education, and number of comorbidities.

¶ For all, except for SHS, higher scores correspond to worse outcomes.

Table 3 – Pearson's correlation coefficients between PGA and other outcome measures according to remission state categories in RA patients (n=309)

	All patients (n=309) r (p-value)	Remission# (n=29) r (p-value)	Near-Remission## (n=115) r (p-value)	Non-Remission### (n=165) r (p-value)
Demographic				
Age (years)	.26**	.03	.19*	.26*
Disease duration (years)	.16*	-.02	.24*	.10
Formal Education (years)	-.34**	-.40*	-.24*	-.36**
Nr of comorbidities (0-6)	.36**	.19	.34**	.32**
Disease activity measures				
TJC28 (0–28)	.32**	.39*	.12	.32**
SJC28 (0–28)	.16*	.12	.02	.07
CRP (mg/dl)	.15*	.20	.09	.08
DAS28-CRP(3v) (0–9.4)	.36**	.47*	.16	.30**
PhGA (VAS, 0-100)	.22**	.04	.12	.13
Disease impact measures¶				
Pain (NRS: 0–10)	**.67****	.10	.59 **	**.64****
Fatigue (NRS: 0–10)	**.67****	**.65****	**.62 ****	**.61****
HAQ (0–3)	**.65****	.22	.49 **	**.67****
HADS-Anxiety (0–21)	.53**	.43*	.42 **	.58**
HADS-Depression (0–21)	.54**	.33	.36 **	.53**
HSS (1–7)	-.29**	-.05	-.30*	-.21*
TIPI (1-7)				
Extraversion	-.17*	.17	-.09	-.15
Agreeableness	-.22	-.27	.08	-.06
Conscientiousness	-.11	-.37	-.04	-.08
Emotional Stability	-.25**	-.13	-.16	-.24*
Openness to Experience	-.18*	-.53*	-.09	-.16*

CRP = C-reactive protein DAS28 = Disease Activity Score using 28 joints; HADS = Hospital Anxiety and

Depression Scale; HAQ = Health Assessment Questionnaire; PGA = patient global assessment; PhGA = Physician global assessment; SHS = Subjective Happiness Scale; SJC28 = swollen joint counts using 28 joints; TIPI = Ten Item Personality Inventory; TJC28 = tender joint counts using 28 joints. r_p = Pearson's correlation coefficient, where, ≥.60, .40-.59 and <.40 represent good, moderate and poor correlations respectively.

¶ For all, except SHS and TIPI, higher values correspond to worse status.

Remission = TJC28, SJC28, CRP mg/dl, and PGA all ≤1

Near-remission = TJC28, SJC28, and CRP mg/dl all ≤1; PGA>1

Non-remission (TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value)

* p<.05

**p<.001

Table 4 – Multivariable linear regression models to explain PGA according to remission state categories in RA patients (n=292)

	All Patients (n=292)		**Remission# (n=28)**		**Near-remission## (n=106)**		**Non-Remission### (n=158)**	
	β stand.	p-value	β stand.	p-value	β stand.	p-value	β stand.	p-value
Pain	.28	**<.001**	--	--	.25	**.012**	.32	**<.001**
Fatigue	.22	**<.001**	.62	**<.001**	.36	**<.001**	--	--
Function	.26	**<.001**	--	--	.14	.078	.35	**<.001**
HADS-Anxiety	.16	**.001**	--	--	.16	**.041**	.25	**<.001**
TJC28	--	--	.33	**.024**	--	--	--	--
SJC28	.11	**.003**	--	--	--	--	.18	**<.001**
Formal education	-.08	**.039**	--	--	--	--	-.12	**.030**
R^2 adj.	.62		.49		.50		.62	

CRP = C-reactive protein; HADS = Hospital Anxiety and Depression Scale; PGA = patient global assessment; SJC28 = swollen joint counts using 28 joints; TIPI = Ten Item Personality Inventory; TJC28 = tender joint counts using 28 joints.

Remission = TJC28, SJC28, CRP mg/dl, and PGA all ≤1

Near-remission = TJC28, SJC28, and CRP mg/dl all ≤1; PGA>1

Non-remission (TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value)

Variables included in all models: age, disease duration, formal education, Nr of comorbidities, TJC28, SJC28, CRP, pain, fatigue, function, HADS anxiety, HADS depression, happiness, TIPI extraversion, TIPI conscientiousness, TIPI emotional stability, TIPI openness to experience

Table 5 – Multivariable linear regression models to explain pain and fatigue in near-remission and non-remission state categories in RA patients

		Near-remission# (n=106)		Non-Remission## (n=158)	
		β stand.	p-value	β stand.	p-value
PAIN	Fatigue	.64	**<.001**	.52	**<.001**
	Formal education	-.16	**<.026**		
	HADS-Anxiety	.14	.065	.13	.061
	TIPI Extraversion	.14	.058		
	Function			.25	**<.001**
	Happiness			.14	**.029**
	R^2 adj.	.51		.54	
FATIGUE	Pain	.58	**<.001**	.50	**<.001**
	Function	.21	**.006**	.19	**.006**
	TIPI Open. Exp.	-.16	.091		
	TIPI Emot. Stab.	-.13	.050		
	HADS-Anxiety			.20	**.001**
	R^2 adj.	.53		.55	

HADS = Hospital Anxiety and Depression Scale; TIPI = Ten Item Personality Inventory;

Near-remission = TJC28, SJC28, and CRP mg/dl all ≤1; PGA>1

Non-remission (TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value)

Variables included in all models: age, disease duration, formal education, Nr of comorbidities, TJC28, SJC28, CRP, pain OR fatigue, function, HADS anxiety, HADS depression, happiness, TIPI extraversion, TIPI emotional stability, TIPI openness to experience

Figure 1 - Proposed concept of remission based on 3v versus 4v Boolean definition in rheumatoid arthritis patients, and their therapeutic implications