THE FREQUENCY OF REMISSION AND LOW DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS, AND THEIR ABILITY TO IDENTIFY PEOPLE WITH LOW DISABILITY AND NORMAL QUALITY OF LIFE

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ABSTRACT

Objective

Treat-to-target in rheumatoid arthritis (RA) recommends targeting remission, with low disease activity (LDA) being an alternative goal. When deciding to target remission or LDA, important considerations are the likelihood of attaining them, and their impacts on function and health-related quality of life (HRQoL). We have addressed this by studying: (a) the frequency of remission and LDA/remission; (b) DAS28-ESR trends after remission; (c) ability of remission vs. LDA to identify patients with normal function (HAQ $\leq$0.5) and HRQoL (EQ-5D $\geq$ the normal population).

Methods

We studied 571 patients in two clinical trials, and 1,693 patients in a 10-year routine care cohort. We assessed the frequency and sustainability of remission and LDA/remission, variability in DAS28-ESR after remission, and sensitivity/specificity of remission and LDA/remission at identifying patients with low disability levels and normal HRQoL using Receiver Operator Characteristic (ROC) curves.

Results

Point remission and remission/LDA were common (achieved by 35-58% and 49-74% of patients, respectively), but were rarely sustained (sustained remission and remission/LDA achieved by 5-9% and 9-16% of patients, respectively). Following attaining remission, DAS28-ESR levels varied substantially. Despite this, of those patients attaining point remission, the majority (53-61%) were in remission at study end-points. Whilst remission was highly specific at identifying patients with low disability (85-91%) it lacked sensitivity (51-57%); similar findings were seen for normal HRQoL (specificity 78-86%; sensitivity 52-59%). The optimal

DAS28-cut-off to identify individuals with low disability and normal HRQoL was around the LDA threshold.

Conclusions

Our findings support both the treat-to-target goals. Attaining remission is highly specific for attaining low disability and normal HRQoL, although many patients with more active disease also have good function and HRQoL. Attaining a DAS28-ESR ≤3.2 has a better balance of specificity and sensitivity for attaining these outcomes, with the benefit of being more readily achievable. Although sustaining these targets over time is rare, even attaining them on a one-off basis leads to better function and HRQoL outcomes for patients.

Key Words

Rheumatoid arthritis, treatment targets, health-related quality of life, function.

1 LIST OF ABBREVIATIONS

CARDERA = Combination Anti-Rheumatic Drugs in Early RA; DAS28 = disease activity score for 28 joints; DMARD = disease-modifying anti-rheumatic drug; HAQ = health assessment questionnaire; HRQoL = health-related quality of life; LDA = low disease activity; RA = rheumatoid arthritis; ROC = receiver operating characteristic; T2T = treat-to-target; TACIT = tumour necrosis factor inhibitor versus combination intensive therapy with conventional disease modifying drugs in established RA.

2 INTRODUCTION

Treat-to-target (T2T) is the dominant treatment strategy for patients with rheumatoid arthritis (RA) (1,2). It involves escalating the intensity of treatment with disease-modifying anti-rheumatic drugs (DMARDs) until the desired disease activity target is attained. Key goals of T2T are to optimise health-related quality of life (HRQoL) and function, and minimise joint damage, by reducing disease activity (1,2).

T2T has two different treatment targets. The primary target is remission, often defined in clinical practice as a disease activity score for 28 joints (DAS28-ESR) of <2.6. This target is based on the extensive evidence that remission optimises HRQoL and function, and minimises radiological damage (3–7). Sustained remission over time is the preferred goal, as it associates with better outcomes than remission at a single time-point (8,9). The secondary target is low disease activity (LDA), defined as a DAS28-ESR ≤3.2, in recognition that patients with longstanding disease or multi-morbidity may be unable to achieve remission (1,2). Again, sustained LDA is preferable to LDA at a single time-point. T2T is recommended by both European and North American guidelines (1,10,11), with evidence from clinical trials and observational studies showing its benefits (12,13) and cost-effectiveness (14,15).

The issue of whether to target LDA or remission is a matter of ongoing debate (16). There are two important considerations in deciding which of these "targets" to aim for. The first is their achievability in routine practice. Observational studies show that DAS or DAS28-defined point-remissions are frequently achieved, with reported frequencies of 33-49% (8,17,18). In contrast, sustained remissions (lasting at least 6-months) appear less common. In one Swedish registry, of 2,416 established RA patients starting biologics, 49% reached DAS28 remission at any time-point, but only 16% had sustained DAS28 remission lasting 6-months (8). In another

Swedish registry, in 29,084 RA patients managed in routine care, 42% had sustained DAS28-remission at some stage, with sustained remission being significantly less likely in established disease (18). Similarly, a North American observational study found that whilst 45% of RA patients achieved point DAS28 remission, only 10% achieved sustained remission (17). There is little information about the frequency of point and sustained LDA in routine practice, although the goal of attaining a DAS28-ESR ≤3.2 must occur more often than attaining a DAS28-ESR <2.6.

The second consideration is which target (remission or LDA) best identifies patients with good function and normal HRQoL, which are outcomes of crucial importance to patients. At an individual-patient level it is clearly preferable to achieve sustained remission, with patients in remission having the best disease outcomes. However, at a group-level, LDA may be a preferable target, as it is likely that many patients in LDA will also have good function and HRQoL, and this target may be more readily achievable. To the best of our knowledge, this issue has not previously been evaluated.

Against this background, we have undertaken a detailed secondary analysis of two clinical trials (in early and established RA), alongside an observational study of RA patients managed according to T2T in routine care. We had three objectives: (a) to evaluate the frequency of attaining a point and sustained DAS28-ESR <2.6 (remission) and ≤3.2 (incorporating LDA and remission); (b) to evaluate the trends in DAS28-ESR once a patient has attained a DAS28-ESR <2.6; (c) to compare the discriminatory abilities of a DAS28-ESR cut-off of remission vs. LDA at identifying RA patients with normal function and HRQoL, and evaluate the optimal DAS28 cut-off to identify these individuals.

3 MATERIALS AND METHODS

3.1 Subjects

3.1.1 Clinical Trials

We used data from two trials: (1) the Combination Anti-Rheumatic Drugs in Early RA (CARDERA) trial, which randomised 467 patients with early, active RA to receive two years of intensive combination treatment with methotrexate, ciclosporin and/or corticosteroids vs. methotrexate monotherapy (19); and (2) the tumour necrosis factor inhibitor (TNFi) versus combination intensive therapy with conventional disease modifying drugs in established RA (TACIT) trial, which randomised 205 established, active RA patients to receive one year of intensive DMARD therapy or tumour necrosis factor inhibitors (20). Patients who did not complete the trials were omitted; there were 379 completers in CARDERA, and 192 in TACIT.

3.1.2 Observational Data

We evaluated patients from the Guy's Hospital RA Centre, which represents an electronic healthcare record cohort of patients attending routine rheumatology appointments at Guy's Hospital (South London); patients have their main clinical outcomes recorded at each clinic visit, and are managed in line with T2T (21). We used two different datasets derived from the Guy's RA centre in our analysis. Firstly, to identify the optimal DAS28 cut-off to identify patients with normal function and HRQoL we used the baseline visit data for each patient (representing their first clinic visit captured electronically); this was used as it was the time-point with the least missing outcome data. Secondly, for the longitudinal analyses (evaluating remission and LDA/remission rates and DAS28-ESR trends over time) we included patients in whom follow-up data were available for at least 3 years.

3.2 Assessments

We assessed patients using the DAS28-ESR. We assessed disability using the Health Assessment Questionnaire (HAQ) and HRQoL using the EQ-5D. In CARDERA these were captured every 6-months for 2-years. In TACIT the DAS28-ESR was captured monthly, and HAQ/EQ-5D captured 6-monthly for 1-year. In the RA centre, these were captured at every outpatient appointment.

3.3 Definitions

3.3.1 Remission and LDA/Remission

Remission and LDA/remission were defined using the recognised DAS28-ESR cut-offs of <2.6 and ≤3.2, respectively. There is no standardised definition of what represents sustained remission (9). In this study, we defined sustained remission in the trials as a DAS28-ESR <2.6 occurring from 6-months onwards, and being present at all subsequent assessments. In the RA centre, sustained remission was defined as a DAS28-ESR <2.6 at all assessments. Point remission in all cohorts was defined as achieving a DAS28-ESR <2.6 at any assessment. For sustained and point LDA/remission the same approach was taken, using a DAS28-ESR cut-off of ≤3.2.

3.3.2 Low Disability and Normal Health-Related Quality of Life

Low disability scores were defined as HAQ scores ≤0.5. As HRQoL falls with increasing age, normal HRQoL was defined as an EQ-5D score observed in the age-matched general UK population. We had access to EQ-5D summary statistics from the normal UK population stratified by certain age categories (from the 2008 Health Survey for England (22)) but not individual-level data. We therefore calculated the mean age in each of our RA datasets, and used the mean EQ-5D scores in the equivalent normal UK age category for comparison. These

comprised mean normative EQ-5D scores of 0.86 for CARDERA (which had a mean age of 54 years, with the corresponding normal UK age category being 45-54 years) and 0.82 for TACIT and the RA centre (which had mean ages of 57 and 55 years, respectively, with the corresponding normal UK age category being 55-64 years).

3.4 Remission vs. Optimal DAS28 Cut-Off at Identifying Low Disability and Normal HRQoL

The ability of the DAS28-ESR to distinguish between patients with and without low HAQ scores and normal EQ-5D scores was determined by plotting receiver operating characteristic (ROC) curves (plotting sensitivity against 1-specificity) and measuring the area under the curve (AUC), calculated using DeLong's method (23). The sensitivity and specificity of remission, LDA, and the DAS28-ESR cut-off that optimised sensitivity and specificity were calculated. ROC analyses were undertaken at patients' baseline visits in the RA centre, as this contained the most complete data and largest number of observations compared to later time points. In the clinical trials, ROC analyses were undertaken at end-points when the greatest proportion of patients had attained LDA and remission. We also evaluated the sensitivity and specificity of a point and sustained DAS28-ESR of <2.6 and ≤ 3.2 at identifying patients with and without low HAQ scores and normal EQ-5D scores at the cohort end-points.

3.5 Programs Used

Analyses were undertaken in R (version 3.5.0) and SPSS (version 23). ROC analyses were performed using the package "pROC" (24).

3.6 Ethical Approvals

Analysis of Guy's RA centre data was approved by the Health Research Authority (HRA; IRAS project ID 209418). CARDERA (ISRCTN32484878 and Research Ethics Committee (REC) reference: MREC (1) 99/04) and TACIT (ISRCTN 37438295 and REC reference: MREC Ref 07/Q0505/57) were approved by Research Ethics Committees. All patients recruited to the trials provided informed written consent (according to the Declaration of Helsinki). As the Guy's RA centre comprises routinely collected anonymised healthcare data, written consent was not required. No further ethical approvals for the analysis described in this manuscript were required.

3.7 Data Statement

These data have not been made publically available as informed consent was not taken from patients for this purpose.

4 RESULTS

4.1 Patients

The three cohorts had similar age and sex distributions (Table 1). CARDERA patients had early RA (mean duration 0.3 years) and TACIT patients established RA (mean duration 8 years). Most RA centre patients had established disease (mean 10 years). At the ROC analysis time-points, mean HAQ scores ranged from 1.17-1.47, mean EQ-5D scores from 0.52-0.60 and mean DAS28 scores from 3.83-4.14. The proportion of patients in remission ranged from 21%-25% and in low disease activity/remission from 30%-38%.

4.2 Remission and LDA/Remission Rates

In all three cohorts the proportion of patients in remission and LDA/remission increased over time (Supplementary Figure 1). In the trials, patients receiving more intensive treatment (triple therapy with methotrexate, ciclosporin, and corticosteroids in CARDERA; anti-TNF in TACIT) had higher rates of remission and LDA/remission, compared with patients receiving less intensive treatment (methotrexate monotherapy in CARDERA; combination synthetic DMARDs in TACIT). In the RA Centre, remission rates could not be evaluated by treatment intensities, as these varied over time. However, the proportion of patients in remission and LDA/remission increased over the decade of follow-up.

In all three cohorts, sustained remission was rare, occurring in only 5-9% of patients (Table 2). Sustained LDA/remission was commoner, occurring in 9-16% of patients. In keeping with previous research, point remission was readily achievable, occurring in 35-58% of patients. Point LDA/remission was even commoner, occurring in many patients in CARDERA (49%), and the majority of patients in TACIT (62%) and the RA centre (74%).

4.3 Within-Individual Disease Activity Variability Following Remission

Individual patients showed marked levels of variation in their subsequent DAS28-ESR scores following attaining remission. The extent of this within-individual variability was similar across all three cohorts. Figure 1 shows DAS28-ESR scores for all patients following attaining remission in CARDERA and TACIT, and for patients with at least 5 subsequent DAS28-ESR measures in the RA Centre.

Despite these marked within-individual variations in post-remission DAS28-ESR scores, an analysis of the end-point DAS28-ESR scores in patients who achieved point remission showed

a common pattern (Figure 2). Approximately half (53%-61%) of all patients were in remission, with 9%-18% having LDA, 21%-22% having moderate disease activity (MDA) and 4%-8% having high disease activity (HDA). The patients achieving point LDA/remission showed a similar pattern with 57%-68% patients being in LDA/remission, 27%-34% having MDA and 5%-9% having HDA. The mean end-point DAS28-ESR scores of patients attaining point remission was within the LDA range (Table 2).

4.4 DAS28-ESR Cut-Offs at Identifying Patients with Low Disability and Normal HRQoL

4.4.1 Sustained and Point Remission vs. LDA/Remission

Sustained and point remission had varying impacts on end-point rates of low disability and normal EQ-5D (Table 2). In all 3 cohorts, comparable findings were observed. Sustained remission was highly specific for low disability (97-98%) and normal EQ-5D (93-97%) but lacked sensitivity (low disability 19-29%; normal EQ-5D 19-36%), with many patients not attaining sustained remission having good function and HRQoL. Attaining point remission at any time during follow-up provided a better balance between sensitivity and specificity for these outcomes (low disability specificity 50-78% and sensitivity 68-89% and normal EQ-5D specificity 42-72% and sensitivity 70-93%).

Attaining sustained LDA/remission also had high specificity for low disability (92-96%) and normal EQ-5D (86-94%) but lacked sensitivity (low disability 26-41%; normal EQ-5D 33-41%). Point LDA/remission was highly sensitive (low disability sensitivity 87-97%; normal EQ-5D sensitivity 87-100%), with moderate specificity (low disability specificity 31-63%; normal EQ-5D specificity 25-58%). This means that the majority of patients with a HAQ ≤ 0.5 had attained a DAS28-ESR of <3.2 at some point in their follow-up. We repeated these analyses

excluding patients with baseline HAQ scores <0.50, with broadly similar results obtained (Supplementary Table 1).

4.5 End-Point Remission vs. Optimal DAS28-ESR Cut-Off

The end-point DAS28-ESR score had a moderate ability to identify patients with a HAQ ≤0.5 (Figure 3). AUC values in the RA centre, CARDERA and TACIT comprised 0.80 (95% CI 0.77-0.84), 0.81 (95% CI 0.76-0.85), and 0.80 (95% CI 0.71-0.88), respectively. The optimal DAS28-ESR cut-off to identify patients with a HAQ ≤0.5 in all 3 cohorts was around the LDA threshold of 3.2. In the RA centre, CARDERA, and TACIT the optimal cut-offs that maximised sensitivity and specificity were 3.01 (78% specificity/68% sensitivity), 3.47 (78% specificity/70% sensitivity), and 3.18 (73% specificity/74% sensitivity), respectively. In contrast, a cut-off of <2.60 whilst substantial more specific (87% RA centre, 91% CARDERA, 85% TACIT), was much less sensitive (57% RA centre, 51% CARDERA, 55% TACIT).

Similar findings were seen with the end-point EQ-5D (Figure 3). The AUC values for the DAS28-ESR at identifying patients with normal EQ-5D scores in the RA centre, CARDERA and TACIT comprised 0.72 (95% CI 0.65-0.78), 0.85 (95% CI 0.80-0.90), and 0.82 (95% CI 0.73-0.90), respectively. The optimal DAS28-ESR threshold to identify patients with a normal EQ-5D in all 3 cohorts was also around the LDA threshold. In the RA centre, CARDERA, and TACIT the optimal cut-offs that maximised sensitivity and specificity were 3.36 (61.1% specificity/74.6% sensitivity), 3.37 (75.9% specificity/83.3% sensitivity), and 3.75 (55.0% specificity/100.0% sensitivity), respectively. In contrast, a cut-off of <2.60 whilst substantial more specific (77.5% RA centre, 85.9% CARDERA, 81.9% TACIT), was much less sensitive (52.2% RA centre, 58.3% CARDERA, 58.8% TACIT).

5 DISCUSSION

Our analysis of three RA populations – spanning trials of early and established active RA, and a real-world routine care cohort – has three findings. Firstly, it demonstrates that whilst point remission and point LDA/remission are readily achievable, sustaining these targets over time is rare, with only 16% of patients in routine care having sustained LDA/remission. Secondly, it shows that once remission is attained, patients have marked variation in their subsequent disease activity. Thirdly, it shows that whilst targeting remission is highly specific for low disability levels and good HRQoL, many patients in higher disease activity states also have HAQ scores ≤0.5 and normal EQ-5D scores, with attaining LDA/remission offering the best balance of sensitivity and specificity for good function and normal HRQoL.

Our study replicates existing research that whilst point remission is common, sustained remission is rare, with the latter occurring in just 5-9% of our cohorts. It provides new perspectives on the likelihood of attaining a sustained DAS28-ESR below the LDA-threshold, which occurred more often in 9-16% of our patients. Although attaining the T2T "targets" at a sustained level over time was rare, attaining them at any point in a patient's journey associated with an increased likelihood of having good function and normal HRQoL at their final assessment. This highlights the importance of striving to attain these targets, even if they are only transient.

Our ROC curve analyses provide further support for both T2T "targets". At an individual patient level, attaining a DAS28-ESR <2.6 is the optimal goal, as it is highly specific for low levels of disability and normal HRQoL. At a group level, however, attaining a DAS28-ESR <3.2 is also a good target, providing a better balance of sensitivity and specificity at achieving low disability and normal HRQoL, with the added benefit of being more achievable.

To the best of our knowledge, the short-term variability in individual patient DAS28-ESR scores following remission we observed has not been reported before. Previous studies have, however, evaluated post-remission DAS28 scores at a group level. Mierau et al (25) reported that in patients attaining a DAS28 <2.6 at one of two visits 12-months apart, the non-remission visit mean DAS28 was 3.2, and Prince et al (17) reported that in 182 RA patients losing DAS28-CRP remission after 12-months, the subsequent median DAS28-CRP was 3.8. The marked within-individual variability we observed is well recognised in other diseases like hypertension (26,27), reflecting National Institute of Health and Care Excellence (NICE) recommendations to use ambulatory blood pressure monitoring for diagnosis (28).

An important implication of our results concerns selecting patients suitable for tapering biologics, which is relevant in a minority of individuals (29). Conventionally, tapering has been recommended in patients attaining LDA/remission lasting at least 3 months. However, our results suggest that many patients are unlikely to remain in LDA/remission, and extending it to a longer time-period, and considering other factors that predict flares on tapering (with low short-form 36 mental health scores associating with higher flare risks (30)) may be more appropriate.

Our study's strengths are that it evaluated a range of populations of RA patients across England (the trials were both multicentre) with its key findings replicated across all 3 cohorts. Its limitations were that it was a post-hoc analysis of existing data, we were unable to obtain age and sex-matched normative EQ-5D scores at an individual level, and the trials did not specifically pursue T2T strategies, with the impact of changing treatment in patients who did not achieve sustained remission not examined.

There are two outstanding issues with T2T strategies, which require resolution. Firstly, as many patients will not attain remission or LDA, and will continue to have disability and poor HRQoL, there is a strong case for developing alternative treatment strategies for these non-responders. Secondly, the frequency of follow-up in T2T strategies is uncertain. As changes in synthetic DMARD doses take months to be effective, and DAS28 scores over time can be highly variable, it may be that time intervals longer than monthly follow-up in those with active disease are appropriate, making it easier to implement T2T in routine care, which is an issue that remains challenging (31–33).

6 CONCLUSIONS

Our study provides further support for both of the "targets" described in the T2T strategy. The goal of a DAS28-ESR of <2.6 is highly specific for the attainment of low disability and normal HRQoL, although many patients with more active disease also have good function and HRQoL. The goal of a DAS28-ESR of ≤3.2 also has a good specificity for attaining these outcomes, and has the benefit of being more readily achievable. Although sustaining these targets over time is relatively rare, even attaining them on a one-off basis leads to better function and HRQoL outcomes for patients with RA.

7 STATEMENT OF CLINICAL SIGNIFICANCE

Whilst T2T has revolutionised the outcomes of patients with RA, there remains ongoing debate as to which of the treatment targets (remission or low disease activity) should be aimed for in routine care. Two issues of central importance to this debate are how often they are achieved, and their impacts on disability and HRQoL. Our study demonstrates that the

target of a DAS28-ESR ≤3.2 (indicating low disease activity and/or remission) is attained more often than a target of <2.6 (indicating remission) but is rarely sustained over time, with individual patients having marked variation in their DAS28-ESR scores following an episode of remission. It also shows that whilst targeting remission is highly specific for achieving low levels of disability and good HRQoL, a treatment target of a DAS28-ESR of approximately 3.2 offers the best balance of sensitivity and specificity for attaining the goals of good function and normal HRQoL. Our study provides further support for both of the T2T "targets"; although sustaining them over time is relatively rare, their achievement on even a one-off basis leads to better outcomes for patients with RA.

8 CONFLICTS OF INTEREST

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Table 1. Patient Characteristics

Characteristic	CARDERA	TACIT	RA Centre Cross-Sectional	RA Centre Longitudinal
Number of Patients	379	192	1,693	752
Females (%)	259 (68.3%)	144 (75.0%)	1,262 (75.4%)	579 (77%)
Mean Age (SD) In Years	54 (12)	57 (12)	55 (16)	55 (15)
Mean Disease Duration (SD) In Years	0.3 (0.4)	8 (9)	10 (10)	10 (10)
Mean HAQ (SD)	1.20 (0.80)	1.47 (0.81)	1.17 (0.83)	1.26 (0.88)
Mean EQ-5D (SD)	0.60 (0.26)	0.55 (0.30)	0.52 (0.34)	0.53 (0.33)
Mean DAS28-ESR (SD)	4.14 (1.65)	3.93 (1.61)	3.83 (1.63)	3.32 (1.26)
HAQ ≤0.5 (%)	91 (24%)	31 (16%)	272 (25%)	180 (24%)
Normal EQ-5D (%)	60 (16%)	17 (9%)	88 (10%)	59 (33%)
DAS28-ESR ≤3.2 (%)	114 (30%)	66 (36%)	439 (38%)	310 (41%)
DAS28-ESR <2.6 (%)	80 (21%)	41 (22%)	286 (25%)	167 (22%)

Age and disease duration are given at baseline in longitudinal datasets, and other outcomes are at study end-points. HAQ = Health Assessment Questionnaire. DAS28-ESR = Disease Activity Score for 28 joints using the ESR. Outcome data missing: RA Centre cross-sectional HAQ in 584 patients, EQ-5D in 784 patients; RA Centre longitudinal final HAQ in 29 patients and final EQ-5D in 66 patients; TACIT Final EQ-5D in 4 patients.

Table 2. Relationship Between Remission States, and End-Point Low HAQ Scores and Normal EQ5D Scores

Group	Remission/LDA Status	Patients	Mean End-Point DAS28 (95% CI)	End-Point HAQ			End-Point EQ-5D		
				HAQ ≤0.5	*Specificity*	*Sensitivity*	*Normal EQ-5D*	*Specificity*	*Sensitivity*
CARDERA (n=379)	*Sustained Remission*	26 (7%)	1.80 (1.61, 1.99)	19/91	98%	21%	16/60	97%	27%
	Point Remission	132 (35%)	2.81 (2.57, 3.04)	68/91	78%	75%	42/60	72%	70%
	End-Point Remission	80 (21%)	1.92 (1.80, 2.03)	48/91	91%	51%	35/60	86%	58%
	Sustained LDA/Remission	45 (12%)	2.02 (1.84, 2.19)	33/91	96%	36%	26/60	94%	33%
	Point LDA/Remission	187 (49%)	3.09 (2.89, 3.28)	79/91	63%	87%	52/60	58%	87%
	End-Point LDA/Remission	114 (30%)	2.20 (2.09, 2.32)	62/91	82%	68%	46/60	79%	77%
TACIT (n=192)	*Sustained Remission*	10 (5%)	1.66 (1.32, 2.00)	6/31	97%	19%	4/17	96%	19%
	Point Remission	80 (42%)	2.81 (2.53, 3.10)	19/31	63%	68%	13/17	62%	77%
	End-Point Remission	41 (22%)	1.92 (1.77, 2.08)	17/31	85%	55%	10/16	82%	59%
	Sustained LDA/Remission	17 (9%)	1.75 (1.50, 2.00)	8/31	94%	26%	6/17	94%	35%
	Point LDA/Remission	119 (62%)	3.18 (2.94, 3.43)	29/31	44%	94%	17/17	41%	100%
	End-Point LDA/Remission	66 (35%)	2.29 (2.14, 2.44)	23/31	72%	74%	13/17	69%	81%
RA Centre (n=752)	*Sustained Remission*	67 (9%)	1.56 (1.46, 1.67)	52/180	97%	29%	21/59	93%	36%
	Point Remission	437 (58%)	2.83 (2.75, 2.91)	160/180	50%	89%	55/59	42%	93%
	End-Point Remission	167 (22%)	1.98 (1.90, 2.05)	106/180	87%	57%	37/59	78%	52%
	Sustained LDA/Remission	120 (16%)	1.91 (1.81, 2.01)	73/180	92%	41%	24/59	86%	41%
	Point LDA/Remission	560 (74%)	3.07 (2.99, 3.14)	174/180	31%	97%	57/59	25%	97%
	End-Point LDA/Remission	310 (41%)	2.41 (2.34, 2.48)	142/180	70%	79%	50/59	62%	85%

Sustained remission: in TACIT and CARDERA this is a DAS28-ESR<2.6 from 6-months onwards and in the RA Centre at all time-points; point remission: a DAS28-ESR <2.6 at any time point; end-point remission: a DAS28-ESR <2.6 at the final time-point in each cohort. For LDA/remission a DAS28-ESR cut-off ≤3.2 is used. In TACIT and the RA centre normal EQ5D scores are ≥0.82; in CARDERA they are ≥0.86

Figure 1. Within-Individual Variability in DAS28-ESR Scores After an Episode of Remission

DAS28-ESR scores for each individual patient following an episode of remission are plotted.

In the RA Centre patients with at least 5 subsequent DAS28-ESR measures are plotted.

CARDERA and TACIT includes all patients.

Figure 2. End-Point DAS28 Category After Attaining Point Remission and Point Low Disease Activity/Remission

Figure 3. Ability of Remission vs. Optimal DAS28-ESR Cut-Off to Identify Patients with Low Disability and Normal HRQoL

The marks on each ROC curve are the specificity and sensitivity of the remission cut-off (DAS28-ESR of <2.60) and cut-off that optimises sensitivity and specificity (which is around the LDA cut-off of 3.20 in each dataset).