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Predicting Flare in Patients With Rheumatoid Arthritis in Biologic Induced Remission, on Tapering, and on Stable Therapy

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Objective. The tapering of biologic disease-modifying antirheumatic drug (b-DMARD) therapy for patients with rheumatoid arthritis (RA) in stable remission is frequently undertaken, but specific guidance on how to successfully taper is lacking. The objective of this study is to identify predictors of flare in patients in stable b-DMARD–induced clinical remission, who did or did not follow structured b-DMARD tapering.

Methods. Patients with RA receiving b-DMARD treatment who had achieved sustained remission according to a Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) <2.6 for ≥6 months were offered tapering. Clinical, ultrasound (US) (total power Doppler [PD]/grayscale abnormalities), $CD4^+$ T cell subsets, and patient-reported outcomes (PROs) were collected at inclusion. The primary endpoint was the occurrence of flare (loss of DAS28-CRP remission) over 12 months. Logistic regression analyses identified predictors of flare. Dichotomization into high/low-risk groups was based on 80% specificity using the area under the receiving operator curve (AUROC).

Results. Of 63 patients choosing tapering, 23 (37%) flared compared with 12 of 60 (20%) on stable treatment ($P = 0.043$). All patients who flared regained remission upon reinstating treatment. In the tapering group, flare was associated with lower regulatory T cell (Treg) ($P < 0.0001$) and higher CRP levels ($P < 0.0001$), erythrocyte sedimentation rate ($P < 0.035$), and inflammation-related cells (IRCs) ($P = 0.054$); stepwise modeling selected Tregs (odds ratio [OR] = 0.350, $P = 0.004$), IRCs (OR = 1.871, $P = 0.007$), and CRP level (OR = 1.577, $P = 0.004$) with 81.7% accuracy and AUROC = 0.890. In the continued therapy group, modeling retained the tender joint count, total PD, and visual analog scale pain score, with 82.1% accuracy and AUROC = 0.899. Most patients in the study were considered low risk of flare (80 of 123 patients [65%]). Only 5 of 37 (13.5%) of the low-risk patients who tapered flared, which was notable compared with the continued therapy group (20% flare).

Conclusion. Flare on tapering b-DMARDs was predicted by lower Tregs and elevated inflammation biomarkers (IRCs/CRP level); flare on continued b-DMARDs was associated with raised pain parameters and US inflammation. Knowledge of these biomarkers should improve outcomes by targeted selection for tapering, and by increased monitoring of those on continued therapy predicted to flare.

INTRODUCTION

The achievement of clinical remission in rheumatoid arthritis (RA) is associated with the best patient outcomes. Increasing numbers of patients are achieving this treatment goal, aided by a treat-to-target approach.[1] Once a period of stable remission has been achieved, patients can be offered the choice to taper therapy with a view to discontinuation,[2,3] although without precise guidance.

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For patients receiving biologic disease-modifying antirheumatic drug (b-DMARD) therapy, tapering is of great interest, given the significant cost of b-DMARDs compared with conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs). Moreover, maintaining full doses of treatment in patients in remission could be viewed as overtreatment, potentially subjecting them to an unnecessary risk of toxicity.[4,5] Conversely, there is an increased risk of disease flare with tapering, with a potential detrimental impact on a patient's quality of life and function. Furthermore, there is concern that disease control may not be successfully recaptured when resuming therapy, possibly recapitulating disease progression.[6] Reassuringly, evidence suggests that control can be recaptured in 80% to 100% of patients within 3 to 6 months and is not associated with more adverse events or higher immunogenicity.[6,7]

The population considered for tapering are patients in a sustained stable state of remission.[1–3,8] Most studies of b-DMARD tapering were conducted using remission defined by the Disease Activity Score in 28 joints (DAS28), but this may not reflect absence of subclinical disease activity. Inflammation[9,10] and radiographic progression have been observed in a proportion of patients.[11] However, the use of stricter remission criteria (American College of Rheumatology [ACR]/Boolean) failed to demonstrate a significant advantage.[12]

Several potential biomarkers of successful b-DMARD tapering have been associated with successful tapering or discontinuation: disease duration,[13–16] absence of radiographic erosions[17,18] and low disease activity,[8,13,19–23] and markers of inflammation[24,25] and the presence of power Doppler (PD) on ultrasound (US) have shown utility in predicting flare.[26–29] In addition to clinical and imaging biomarkers, there is increasing interest in the role of T cell subsets in predicting RA outcomes across the disease continuum. T cell dysregulation is key to RA pathogenesis, and the value of T cell subsets across various outcomes in RA has been demonstrated.[30–32] In remission, it has been demonstrated that some T cell subsets return to normal (low percentage of inflammation-related cells [IRCs] suggesting absence of immunologic evidence of subclinical inflammation), whereas others remain disrupted, as observed in active RA (low percentage Tregs).[10] Reduced naive T cells have also been shown to predict flare in patients in remission on cs-DMARDs.[30,31,33]

Our previous cross-sectional study of remission characteristics demonstrated that multidimensional remission defined with clinical and imaging and naive T cell measures was associated with improved patient-reported outcomes (PROs).[10] The addition of PROs to clinical, imaging, and T cell measures demonstrated utility in predicting tapering of cs-DMARDs in patients who had achieved sustained remission.[33] To date, none of these potential biomarkers have been used in a multivariate model for the prediction of flare after tapering of b-DMARDs.

We hypothesized that multivariate models using clinical features (including PROs) and objective measures of inflammation, combined with T cell immunological markers, could predict successful tapering of b-DMARD therapy. Accordingly, the primary objective of this study was to identify predictors of flare in patients in stable b-DMARD–induced clinical remission, who followed structured b-DMARD tapering. Secondary objectives were to assess the rate of flare in both tapering and non-tapering groups, as well as identifying predictors of flare in the non-tapering cohort.

PATIENTS AND METHODS

Informed, written consent for participation was obtained from all patients upon inclusion. Regional ethical approval for the study was obtained on January 15th, 2020.

Patients with RA diagnosed according to the 2010 ACR/EULAR classification criteria who had achieved clinical remission while receiving b-DMARD therapy were recruited between 2014 and 2020 from the Leeds RA remission clinic. The details of this research clinic have been described in our previous publication.[33] Briefly, stable remission was based on achieving sustained DAS remission (ie, DAS28-CRP <2.6)[34] for at least 6 months while on stable therapy and without systemic corticosteroid therapy. All patients were reviewed every 3 months in the biologics clinic before being referred to the remission clinic and required evidence of serial DAS28 scores <2.6 for a minimum of 6 months to gain entry to the remission clinic. This was reviewed by the first author before enrollment.

Demographic, clinical, US, and T cell data were collected at inclusion/baseline (initiation of the tapering protocol), and participants completed standardized patient questionnaires for PROs. All clinical histories and joint examinations were performed by an experienced rheumatologist. Follow-up data included clinical parameters to allow for a DAS28-CRP calculation and documentation of corticosteroid use in the case of flare. Our local National Health Service (NHS) laboratory provides CRP measures from a <5 mg/L lower limit value. A zero value was used in the calculation of the DAS28 score, as is routinely done in clinical practice. US assessment was performed as an NHS service to the remission clinic by multiple sonographers. The US scans were performed and scored by the same operator, who was experienced in the use of musculoskeletal US, on the day of the examination. However, given the length of the study, multiple staff performed the US scans while they all participated in a training session and agreed on the scanning protocol.

A more detailed list of all parameters recorded is available in the Supplementary Material. All parameters included were chosen as validated tests or scores and routinely used in most rheumatology clinics (notably using standard musculoskeletal US imaging sequences and validated PROs), with the exception of T cell subsets, which remain a research biomarker, although they are provided by hospital services in Leeds, England.

In this study, most patients were receiving combination therapy with a cs-DMARD (45 of 63 patients, 71%) unless

contraindicated or not tolerated. Patients were given the option to either continue or taper their b-DMARD according to a predefined protocol (Supplementary Figure 1), aligned with the international recommendations for managing remission.

Patients were informed of the potential risk of disease flare on tapering (and the subsequent need for dose re-escalation ± corticosteroid treatment) and conversely the dose-dependent increased risk of infection and adverse events with continued therapy. They were observed prospectively for 12 months (reviewed every 3 months and as extra visits in case of disease flare, as per EULAR recommendations). Data capture occurred at these three-times-monthly visits or at flare visits. Flare was confirmed after clinical assessment (in-person or via telephone). Because of limited clinic capacity and patient availability (notably because of the COVID-19 pandemic), some patients did not have face-to-face follow-up visits at all study time points.

The primary end point was the proportion of patients who flared over 12 months. Flare was defined as loss of remission by DAS28-CRP ≥2.6 criteria and was treated with corticosteroids and/or increasing therapy to the previous effective dose (in the tapering group). No further attempt at tapering was made for patients who flared during the study.

Baseline data are described using median and interquartile range (IQR) or number and proportion (%). Continuous measures were explored comparing groups using the Mann–Whitney *U* test and nominal measures with chi-square tests. Corrections for multiple testing were not applied in the descriptive tables. Area under the receiving operating curve (AUROC) was used to assess predictive values. Every attempt was made to obtain complete data for clinical, imaging, immunologic, and PRO parameters. However, this was not always possible because of the availability of US and laboratory facilities during the pandemic.

Ninety-five patients had a complete data set for all variables tested, and the randomness of missing data was verified before modeling. Unadjusted odds ratios (ORs) (95% confidence intervals [95% CIs]) were calculated. Missing data were imputed (using five rounds of data imputation in SPSS [Statistical Package for the Social Sciences]). ORs were calculated again and compared to the original data set. Minimal differences were observed, allowing us to perform further analysis on n = 123.

Predicting sustained remission was performed using a forward logistic regression method, allowing the model to independently select the best predictors. This used a stepwise selection method with entry testing evaluating the significance of the model statistic, and removal of variables based on the probability of a likelihood-ratio statistic using the maximum partial likelihood estimates. A sensitivity analysis was performed for the prediction model with and without missing data and did not show any significant differences in the results.

Using the individual probability for flare calculated by the regression model, a cut-off set at 80% specificity was used to dichotomize patients for either a high or a low risk of flare. An 80% specificity cut-off was considered an acceptable risk in clinical practice as well as statistically.

Analyses were conducted using SPSS 27. All 95% CIs were automatically calculated within SPSS functionalities using an underlying bootstrapping method. *P* values <0.05 were considered significant. Analysis between drug categories could not be performed because of small numbers treated with non–tumor necrosis factor inhibitor (TNFi) therapy.

RESULTS

Cohort description. One hundred and twenty-three patients were recruited to the study. The clinical, imaging, and immunologic parameters are reported in Table 1. The cohort included patients receiving TNFi (107 of 123, 92%) (etanercept, adalimumab, infliximab, golimumab, and certolizumab-pegol), a selective T cell co-stimulation modulator (abatacept; n = 2 of 123, 1.6%), and an anti-interleukin-6 receptor [IL6R] (tocilizumab; n = 8 of 123, 6.5%).

Sixty-three patients chose to taper, and 60 chose to continue therapy (control group). The decision to taper was associated with better PROs (Table 1, also visually illustrated in Supplementary Figure 2, visual analog scale [VAS] pain and disease activity, both $P < 0.0001$ without correction for multiple testing) as well as a longer duration of remission ($P = 0.049$) and imaging measures (total PD $P = 0.021$ and grayscale scores $P = 0.019$, although with missing data in 23 of 123 patients, 19%), not significant after correction. Demographic, clinical measures, and T cell subsets did not differ between the two groups.

Twenty-three of 63 patients (37%) experienced a flare over 12 months in the tapering group (median time to flare was 196 days [IQR 147–287]) (Supplementary Figure 3) compared with 12 of 60 (20%) in the control group ($P = 0.042$), with a median time to flare of 266 days (IQR 187–369). Remission was objectively assessed at the next follow-up visit (ie, 3 months later) and was recaptured in all patients following treatment reinstatement after flare in the tapering group (and at the next visit for 19 of 23 [82%]). Three patients (4.8%) achieved drug-free remission by the last follow-up visit (ie, at 12 months). Nine patients (5.7%) chose to stop the tapering protocol despite being in remission at a follow-up visit. In the non-tapering group, 7 of 12 (58%) patients who flared recaptured remission upon treatment of flare with corticosteroids.

Predicting flare in the tapering group. There was no association among demographics, imaging, and PRO variables and flare (Table 2 and Supplementary Figure 4). The most significant association was with lower Tregs ($P < 0.0001$). Three more clinical parameters were retained, all suggesting less well-controlled inflammation: higher CRP level ($P = 0.001$) and

Table 1. Baseline characteristics of tapering vs nontapering cohort*

	Missing data, n	Tapering cohort (n = 63)	Nontapering cohort (n = 60)	*P* value
Demographic variables				
Female, n (%)	0	37 (59)	39 (65)	0.474
Age, median (IQR), y	0	56 (49 to 66)	59 (53 to 70.5)	0.631
Disease duration, median (IQR), mo	1	104.8 (61.5 to 163.5)	97 (54.8 to 157.2)	0.933
Remission duration, median (IQR), mo	0	21.5 (10.5 to 40.7)	17 (7.9 to 25.1)	0.049
RF^+, n (%)	0	39 (62)	29 (48)	0.130
$ACPA^+$, n (%)	0	53 (84)	46 (77)	0.297
Smoking (never), n (%)				
Never	7	29 (48)	22 (39)	
Ever		31 (52)	34 (61)	0.327
Missing		3	4	
Clinical variables, median (IQR)				
TJC28	0	0 (0)	0 (0 to 1)	0.148
SJC28	0	0 (0)	0 (0)	0.115
CRP level,[a] mg/L	0	<5 (<5)	<5 (<5)	0.382
ESR, mm/h	5	8 (4 to 16)	7 (3.5 to 15)	0.375
EMS, min	1	0 (0 to 5)	0 (0 to 5)	0.240
PRO variables, median (IQR)				
VAS PGA	0	10 (3 to 22)	19.5 (10 to 29)	0.068
VAS pain	2	4 (2 to 10)	8.5 (2.25 to 22.75)	<0.0001
VAS DA	3	4 (1 to 10)	5 (3 to 18)	<0.0001
VAS fatigue	3	11 (4 to 35)	12 (4 to 23)	0.204
HAQ-DI	1	0 (0 to 0.875)	0 (0 to 0.625)	0.322
RaQoL	1	1 (0 to 8)	1 (0 to 5)	0.420
Ultrasound variables, median (IQR)				
Total PD	23	0 (0 to 2)	0 (0 to 0)	0.021
Total GS	23	13 (11 to 26)	14 (5 to 19)	0.019
T cell variables, median (IQR)				
Normalized naive	28	9.4 (−5.7 to 21.7)	11.7 (1.3 to 21.7)	0.929
Normalized Tregs	27	−1.0 (−3.1 to −0.33)	−1.1 (−2.3 to −0.2)	0.151
IRCs	26	1.8 (0.8 to 2.8)	1.1 (0.4 to 3.3)	0.504
Flare data				
Loss of remission (3vDAS28 ≥2.6)		23 (35%)	12 (20%)	0.043

*Total n = 123. ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; DA, disease activity; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; GS, grayscale synovial hypertrophy score; HAQ-DI, health assessment questionnaire disability index; IQR, interquartile range; IRC, inflammation-related cell (percentage of total CD4+T cells); PD, power Doppler score; PGA, patient global assessment of disease; RAQoL, rheumatoid arthritis quality of life questionnaire; RF, rheumatoid factor; SJC28, swollen joint count out of 28 joints; T cell subsets, naive CD4+T cells (normalized percentage of total CD4+T cells); TJC28, tender joint count out of 28 joints; Treg, regulatory T cell (normalized percentage of total CD4+T cells); VAS, visual analog scale.
[a]CRP <5 mg/L = lowest detectable limit.

erythrocyte sedimentation rate (ESR) ($P = 0.035$), also reflected by higher percentage of IRCs ($P = 0.054$). ORs (95% CI) and AUROC were calculated for each parameter, showing predictive values for the same four variables (Table 2).

Logistic regression modeling (forward) was performed (Table 3), and the model selected variables with increasing performance. The first step provided 71.4% accuracy (AUROC = 0.764) and retained only Tregs (OR = 0.469, $P = 0.002$). The addition of CRP level (model 2) increased accuracy (76.2%, AUROC = 0.862), with both parameters being independently predictive. Lastly, adding IRCs (model 3, all independent predictors) did not change accuracy but improved the AUROC = 0.890 (Figure 1). IRC, despite being closely associated with inflammation, still added substantial improvement over model 2 (Tregs + CRP level). Adding ESR or any other parameters did not improve modeling. Model 3 showed 70% sensitivity, 89% specificity, 80% positive predictive value (PPV), and 82% negative predictive value (NPV). The data on PPV and NPV notably suggests an incremental value in the three variable models, whereas specificity was already quite high in models 1 and 2.

Using the individual probability for flare calculated by model 3 (at 80% specificity), patients were dichotomized for either a high or a low risk of flare. There were 26 and 37 patients categorized as high or low risk, respectively, in those tapering. Of the 23 patients who flared, 18 (78%) were high risk and 5 (22%) were low risk. Only 5 of 37 of the low-risk patients undergoing tapering (13.5%) flared, a lower rate than observed in patients in the continued therapy group (12 of 60, 21%), whereas all regained remission after treatment reinstallment. Conversely, 18 of 26 patients (69%) flared in the high-risk group.

Table 2. Univariate analysis of baseline characteristics associated with flare/loss of DAS28 remission*

	Flare (n = 23), 37%	Stable remission (n = 40), 63%	*P* value	OR (95% CI), *P* value	AUC (95% CI), *P* value
Demographic variables					
Female, n (%)	14 (61)	23 (58)	0.794	1.150 (0.404 to 3.273), 0.794	0.483 (0.334 to 0.632), 0.825
Age, median (IQR), y	63.0 (56.0 to 68.0)	58.5 (47.5 to 69.5)	0.307	1.028 (0.985 to 1.073), 0.204	0.578 (0.437 to 0.719), 0.307
Disease duration, median (IQR), months	97.9 (59.5 to 201.1)	104.8 (66.4 to 161)	0.732	1.000 (0.996 to 1.003), 0.764	0.526 (0.370 to 0.682), 0.732
Remission duration, median (IQR), months	19.6 (9.3 to 33.2)	22.6 (12.3 to 44)	0.141	1.000 (0.985 to 1.016), 0.970	0.437 (0.283 to 0.591), 0.414
RF^+, n (%)	16 (73)	23 (56)	0.342	0.592 (0.200 to 1.755), 0.344	0.560 (0.413 to 0.707), 0.428
$ACPA^+$, n (%)	19 (83)	34 (85)	0.803	1.193 (0.299 to 4.762), 0.803	0.488 (0.338 to 0.638), 0.875
Smoking, n (%)		n = 37	0.951	1.033 (0.365 to 2.929), 0.951	0.504 (0.353 to 0.656), 0.958
Never	11 (48)	18 (49)			
Ever	12 (52)	19 (51)			
Clinical variables, median (IQR)					
TJC28	0 (0)	0 (0 to 0.8)	0.150	0.625 (0.253–1.546), 0.309	0.425 (0.280–0.570), 0.325
SJC28	0 (0)	0 (0)	0.689	1.773 (0.106–29.760), 0.691	0.509 (0.359–0.659), 0.903
CRP level,[a] mg/L	<5 (<5 to 9.3)	<5 (<5)	<0.0001	1.312 (1.077 to 1.599), 0.007	0.701 (0.543 to 0.849), 0.009
ESR, mm/h	20.5 (76.5 to 35)	9 (5 to 15.5)	0.035	1.049 (0.996 to 1.999), 0.0.083	0.734 (0.555 to 0.849), 0.002
EMS, min	0 (0 to 1.3)	0 (0 to 1.5)	0.899	1.000 (0.970 to 1.030), 0.982	0.493 (0.341 to 0.644), 0.077
Patient-reported outcome variables, median (IQR)					
VAS PGA	10 (4.0 to 19.0)	13.5 (3.3 to 24.3)	0.577	0.987 (0.957 to 1.018), 0.412	0.458 (0.313 to 0.602), 0.578
VAS pain	5 (2.0 to 8)	3 (1 to 7.8)	0.409	0.998 (0.973 to 1.022), 0.844	0.563 (0.417 to 0.708), 0.412
VAS DA	3 (1.0 to 12)	3 (1.0 to 10)	0.880	0.992 (0.970 to 1.015), 0.511	0.511 (0.363 to 0.660), 0.881
VAS fatigue	11 (3.0 to 32.0)	11 (3.3 to 35.0)	0.983	0.993 (0.976 to 1.010), 0.421	0.498 (0.353 to 0.644), 0.983
HAQ-DI	0.1(0 to 0.9)	0 (0 to 0.1)	0.103	0.963 (0.875 to 1.061), 0.451	0.610 (0.457 to 0.762), 0.149
RaQoL	2 (1 to 4.0)	1 (0 to 2)	0.091	0.983 (0.943 to 1.026), 0.434	0.626 (0.482 to 0.770), 0.098
US variables, median (IQR)					
Total PD	0 (0 to 2)	0 (0 to 1.8)	0.739	0.991 (0.973 to 1.009), 0.322	0.523 (0.365 to 0.680), 0.764
Total GS	14 (12 to 21)	13 (9 to 21.8)	0.847	1.004 (0.957 to 1.054), 0.863	0.515 (0.364 to 0.665), 0.847
Immunologic (T cell variables), median (IQR)					
Normalized naive	8.9 (−7.7 to 20.8)	9.4 (−5.7 to 23.1)	0.191	0.972 (0.932 to 1.013), 0.177	0.380 (0.203 to 0.557), 0.191
Normalized Tregs	−2.4 (−3.9 to −1.5)	−0.80 (−2.3 to 0.2)	<0.0001	0.319 (0.160 to 0.633), 0.001	0.206 (0.095 to 0.318), <0.0001
IRCs	3.1 (1.1 to 4.6)	1.3 (0.8 to 2.0)	0.054	1.782 (1.113 to 2.856), 0.016	0.688 (0.531 to 0.811), 0.027

*ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; DA, disease activity; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; GS, grayscale synovial hypertrophy score; HAQ-DI, health assessment questionnaire disability index; IRC, inflammation-related cell (percentage of total CD4+T cells); IQR, interquartile range; PD, power Doppler score; PGA, patient global assessment of disease; RAQoL, rheumatoid arthritis quality of life questionnaire; RF, rheumatoid factor; SJC28, swollen joint count out of 28 joints; T cell subsets, naive CD4+T cells (normalized percentage of total CD4+T cells); Treg, regulatory T cells (normalized percentage of total CD4+T cells); TJC28, tender joint count out of 28 joints; US, ultrasound; VAS, visual analog score; 95% CI, 95% confidence interval.
[a]CRP <5 mg/L = lowest detectable limit.

Table 3. Modeling the prediction of flare in the tapering cohort*

Variables	Step 1	Step 2	Step 3
Tregs, OR (95% CI), *P* value	0.469 (0.293–0.751), 0.002	0.371 (0.198–0.694), 0.002	0.350 (0.172–0.709), 0.004
CRP level, OR (95% CI)		1.714 (1.161–2.529), *P* = 0.007	1.871 (1.191–2.940), *P* = 0.007
IRCs, OR (95% CI)			1.577 (1.020–2.458), *P* = 0.044
Accuracy	71.4%	76.2%	81.7%
SEN	47.71%	65.2%	69.5%
SPE	85%	86.5%	89.2%
PPV	64.7%	75%	80%
NPV	74%	80%	82.5%
AUROC	0.764	0.862	0.890
95% CI	0.634–0.894	0.774–0.950	0.813–0.967
P value	<0.0001	<0.0001	<0.0001

*AUROC, area under the receiving operator curve; CRP, C-reactive protein; IRC, inflammation-related cell; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SEN, specificity; SPE, sensitivity; Treg, regulatory T cell; 95% CI, 95% confidence interval.

Predicting flare in the non-tapering group. In the non-tapering group, no associations were observed between demographic variables and flare (Table 4). Parameters related to pain (tender joint count [TJC], $P = 0.004$ and VAS pain, $P = 0.038$) and inflammation (total PD score, $P = 0.001$) were higher in patients who flared, whereas naive T cells were lower ($P = 0.022$). Further variables with low level association (ie, $P < 0.200$) such as age, smoking, ESR, VAS-disease activity, and Tregs may have potential contribution in multiple variables models.

ORs for flare remained individually significant for TJC, ESR, VAS pain, VAS-disease activity, total PD scores, and naive T cells; the highest individual OR was 2.1 for TJC, while the best AUROC (AUROC = 0.734) was for total PD. Again, multiple other parameters demonstrated trends for prediction (OR >1, but nonsignificant), notably adding grayscale changes to the previous list.

Regression modeling suggested three steps: the first using TJC only and then sequentially adding, total PD (second step), and VAS pain score (third step) (Table 5 and Supplementary Figure 5). The three steps retained resulted in models with the same accuracy (82.1%), while increasing sensitivity, NPV, and the AUROC but reducing specificity and PPV. The final model had an AUROC of 0.899 (Figure 1), with all three variables contributing independently to the prediction.

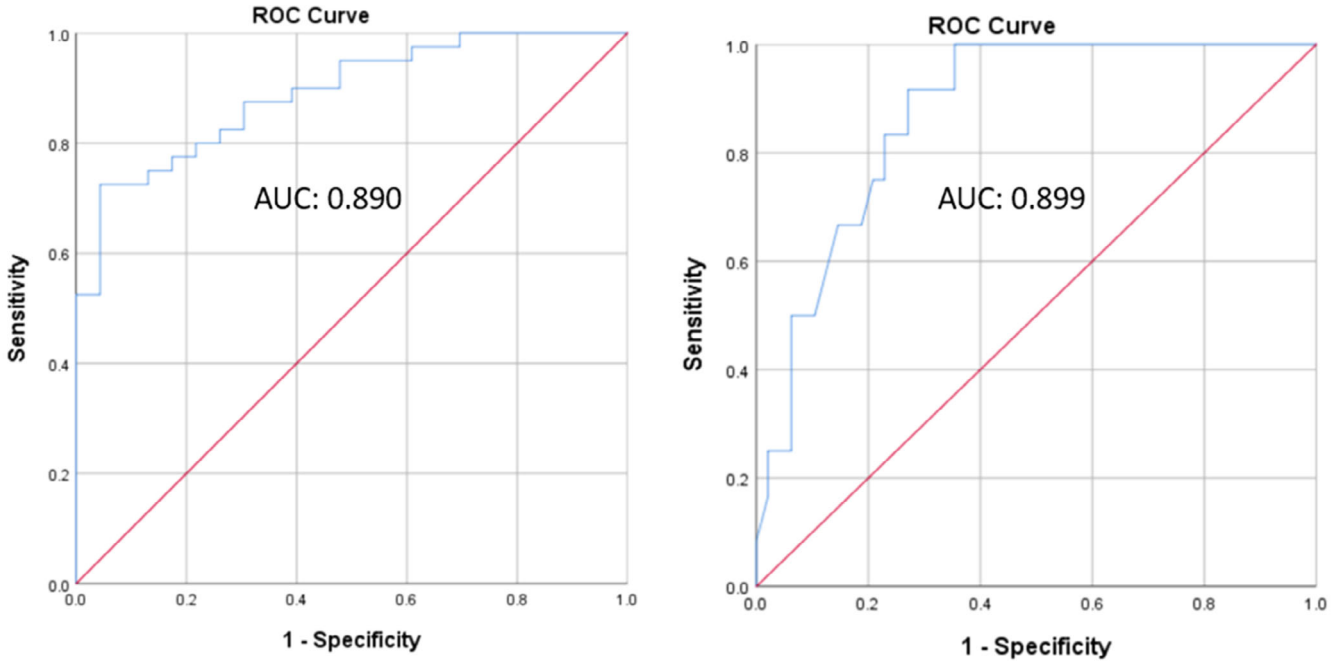

Figure 1. Final model AUROC for both groups: (A) taper group and (B) control group. AUROC, area under the receiving operator curve.

Table 4. Univariate analysis of baseline characteristics of flare vs sustained remission in the nontaper cohort*

	Flare (*n* = 12) 20%	Stable Remission (n = 48) 60%	*P* value	OR (95% CI), *P* value	AUROC (95% CI), *P* value
Demographic variables					
Female, n (%)	9 (75)	30 (63)	0.417	1.800 (0.430 to 7.532), 0.421	0.438 (0.260 to 0.615), 0.438
Age, median (IQR), y	65 (59 to 71)	59 (53 to 69)	0.136	1.049 (0.984 to 1.119), 0.140	0.640 (0.496 to 0.783), 0.073
Disease duration, median (IQR), months	124.1 (43.9 to 260)	107.3 (58.6 to 160.2)	0.706	1.003 (0.997 to 1.009), 0.313	0.535 (0.317 to 0.754), 0.706
Remission duration, median (IQR), months	11.8 (6.5 to 25)	16.9 (9.0 to 26.5)	0.401	1.007 (0.975 to 1.040), 0.671	0.418 (0.207 to 0.629), 0.401
RF^+, n (%)	5 (42)	24 (50)	0.605	1.400 0.389 to 5.033), 0.606	0.458 (0.276 to 0.641), 0.657
$ACPA^+$, n (%)	10 (83)	36 (75)	0.542	0.600 (0.115 to to 3.133), 0.545	0.543 (0.364 to 0.720), 0.657
Smoking, n (%)			0.184	0.360 (0.100 to 1.364), 0.135	0.379 (0.196 to 0.561), 0.201
Never	7 (58)	15 (31)			
Ever	5 (42)	29 (60)			
Clinical variables, median (IQR)					
TJC28	1.5 (0 to 3)	0 (0)	0.004	2.081 (1.228 to 3.536), 0.006	0.713 (0.528 to 0.897), 0.024
SJC28	0 (0)	0 (0)	0.859	1.000 (0.297 to 3.362), 1.000	0.491 (0.308 to 0.675), 0.926
CRP level,[a] mg/L	<5 (<5 to 22)	<5 (<5)	0.552	1.035 (0.931 to 1.152), 0.520	0.465 (0.284 to 0.647), 0.712
ESR	10.5 (7 to 30)	7 (3.3 to 25)	0.057	1.043 (1.005 to 1.083), 0.028	0.701 (0.528 to 0.826), 0.033
EMS	0 (0 to 8.8)	0 (0 to 5)	0.501	0.996 (0.956 to 1.038), 0.851	0.553 (0.367 to 0.739), 0.573
Patient-reported outcome variables, median (IQR)					
VAS PGA	22 (14.3 to 38)	15.2 (8.5 to 28)	0.165	1.024 (0.988 to 1.061), 0.194	0.630 (0.455 to 0.805), 0.166
VAS pain	19 (8.1 to 28.5)	8.5 (3 to 20.8)	0.038	1.042 (0.998 to 1.087), 0.060	0.719 (0.579 to 0.856), 0.020
VAS DA	16 (10.3 to 35.8)	8.5 (3.3 to 18)	0.057	1.021 (0.995 to 1.050), 0.096	0.717 (0.576 to 0.857), 0.021
VAS fatigue	10 (4.3 to 58)	14 (7 to 40)	0.643	0.992 (0.971 to 1.013), 0.432	0.457 (0.249 to 0.664), 0.644
HAQ-DI	0.25 (0 to 0.8)	0 (0 to 0.8)	0.740	1.105 (0.343 to 3.566), 0.867	0.529 (0.345 to 0.712), 0.760
RaQoL	2 (0.3 to 7.7)	1 (1 to 5)	0.826	1.018 (0.890 to 1.163), 0.800	0.520 (0.331 to 0.709), 0.832
Ultrasound variables, median (IQR)					
Total PD	1 (0 to 3)	0 (0)	0.001	1.749 (1.045 to 2.927), 0.033	0.734 (0.559 to 0.908), 0.013
Total GS	17 (10 to 24)	14 (6 to 20)	0.237	1.052 (0.971 to 1.136), 0.197	0.622 (0.440 to 0.796), 0.196
Immunologic (T cell variables), median (IQR)					
Normalized naive	0.7 (−9.3 to 7.4)	12.5 (2.4 to 25.7)	0.022	0.923 (0.910 to 0.997), 0.032	0.295 (0.136 to 0.455), 0.029
Normalized Tregs	−2.8 (−4 to 0.1)	−0.9 (−2.0 to −1.2)	0.133	0.628 (0.379 to 1.040), 0.070	0.349 (0.152 to 0.544), 0.108
IRCs	2.9 (2.2 to 9.2)	1.0 (0.4 to 3)	0.382	1.1014 (0.851 to 1.187), 0.866	0.604 (0.408 to 0.801), 0.383

*Baseline flare characteristic is loss of DAS28 remission; n = 60. ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; DA, disease activity; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate, mm/h; GS, grayscale; HAQ-DI, health assessment questionnaire disability index; IQR, interquartile range; IRC, inflammation-related cell (percentage of total CD4+T cells); PD, power Doppler; PGA, patient global assessment of disease; RAQoL, rheumatoid arthritis quality of life questionnaire; RF, rheumatoid factor; SJC28, swollen joint count out of 28 joints; TJC28, tender joint count out of 28 joints; T cell subsets, naive CD4+T cells (normalized percentage of total CD4+T cells); Treg, regulatory T cell (normalized percentage of total CD4+T cells); VAS, visual analog score; 95% CI, 95% confidence interval.
[a]CRP <5 mg/L = lowest detectable limit.

Table 5. Modeling the prediction of flare in the nontapering cohort*

Variables	Step 1	Step 2	Step 3
TJC, OR (95% CI), *P* value	2.007 (1.186–3.398), 0.009	2.304 (1.159–3.367), 0.006	2.124 (1.192–3.785), 0.011
Total PD, OR (95% CI), *P* value		1.975 (1.159–3.367), 0.012	2.394 (1.321–4.337), 0.004
Pain, OR (95% CI), *P* value			1.067 (1.007–1.132), 0.029
Accuracy	82.1%	82.1%	82.1%
SEN (%)	84.4%	85.4%	87%
SPE (%)	66.7%	62.5%	55.5%
PPV (%)	95.5%	93%	91%
NPV (%)	33.3%	41.7%	45.5%
AUROC	0.713	0.876	0.899
95% CI	0.528–0.897	0.788–0.964	0.803–0.997
P value	0.002	<0.0001	<0.0001

*AUROC, area under the receiving operator curve; NPV, negative predicted value; OR, odds ratio; PD, power Doppler; PPV, positive predicted value; SEN, sensitivity; SPE, specificity; TJC, tender joint count; 95% CI, 95% confidence interval.

DISCUSSION

This study confirmed that, in a population of patients with RA who were experiencing sustained DAS28 remission and receiving b-DMARD therapy, the rate of flare was higher in the group that tapered b-DMARDs than in those who remained on stable therapy. Three objective biomarkers (low Tregs, higher IRCs, and higher CRP level) predicted high/low risk of flare on tapering with high accuracy, with the few flares in low risk successfully regaining remission. This suggests that safe and successful tapering may be performed in a selected group of patients with the use of these biomarkers. In the stable therapy group, two pain-related markers were retained in the model for flare (ie, TJC and VAS pain), in addition to the presence of PD on US.

Heterogeneity in clinical, imaging, and immunologic parameters was seen among patients despite being in DAS28 remission, confirming previous remission work.[10] Overall, participants in this b-DMARD cohort demonstrated very low levels or were absent of clinically apparent inflammation (ie, TJC/swollen joint count), and this was as expected given the fact that the criteria for inclusion in the current study (ie, DAS28 <2.6) is heavily weighted on the assessment of these two parameters. However, subclinical inflammation on US and particularly PD scores were also low, especially in the non-tapering cohort.

From a patient perspective, the burden of injections/infusions plus concerns regarding the potential long-term side-effects of biologic therapy are major incentives for tapering, and poor adherence is also an issue.[35,36] Patients were given the choice of whether to taper or not. This approach was decided upon as replicating clinical practice and in line with recommendations for full patient involvement in management decisions (EULAR recommendations[2]). It also showed interesting differences between the two groups, in which those who chose tapering experienced a longer duration of remission as well as lower perceived disease activity and pain scores.

Our prediction model in the tapering group identified three objective measures (Tregs, CRP levels, and IRCs) and demonstrated high accuracy and a good AUROC for predicting flare. The high specificity and PPV/NPV (all over 80%) suggest that the model is reasonably robust, and with the sensitivity at 70%, it can be applied to many patients achieving remission on biologics with a potentially large economic benefit. Accordingly, our findings provide a basis for informed tapering decisions in the outpatient clinic for patients in b-DMARD–induced sustained remission. An initial approach for considering/offering tapering could be to include patients in stable remission with a normal CRP level (in this study, 101 of 123 patients). Patients in remission who still have tender joints may then benefit from T cell subset evaluation to help differentiate those with active inflammation versus pain due to another pathology (eg, osteoarthritis or fibromyalgia/chronic pain state).

In the stable treatment group, the prediction model was also reasonably accurate (82.1%) and included only three parameters (TJC, total PD, and pain-VAS). Each variable contributed significantly and increased the model AUROC, but not its accuracy. The TJC and pain score suggest that the patients still experience pain in this group, which is also reflected in the fact that they decided not to taper. This supports the need to include a patient's perception of pain in the management of b-DMARD tapering.

The multidimension prediction model offers a major improvement compared to previous studies reporting individual associations of various parameters with successful TNFi discontinuation.[10,18,23,37–42] Furthermore, the retention of Tregs in the model suggests that there is an immunologic state contributing to successful biologics tapering, which aligns with previous observations that a good response to TNFi is associated with an increase in Treg cell frequencies over time.[43] This is in contrast to data observed for patients tapering csDMARDs, for whom higher naive T cell levels were associated with the ability to sustain remission upon tapering.[33]

If the final tapering model was applied to the total cohort, 80 patients would have been eligible for tapering based on a low risk for flaring. This could then be associated with a lower flare rate of 13.5% compared with the 20% rate observed in the control group and with a very high likelihood of regaining remission with treatment reinstallment (100% overall and 82% by the next visit, independent of being in the low or high-risk group). This information will be invaluable for guiding future tapering decisions. High-risk patients would be advised against tapering, whereas low-risk patients would be encouraged to do so, although ultimately patient choice must be respected. With respect to the continued therapy group, those with high risk of flare may benefit from more frequent clinical monitoring, even increasing therapy, considering the lower recapture of remission rates (58%).

This study has several limitations, notably the small size of the cohort (specifically the taper group), missing data (due to using NHS services for US/flow cytometry), and the fact that the COVID-19 pandemic limited face-to-face interactions, although only at follow-up visits.[44] To enable statistical modeling, data imputations were used, but a sensitivity analysis performed for the prediction model showed no significant differences in the results with or without missing data, suggesting that the model is robust to missing data. Additionally, we recognized that having multiple US operators could give rise to interoperator variability of the results, although using the NHS US services guaranteed that experienced staff would be involved. Furthermore, comparisons between different biologic therapies and patients receiving cs-DMARD and b-DMARD therapy, whether combined or not, could not be performed because of the small number of patients in this study. Finally, we employed internal validation techniques, including bootstrapping to assess our model's performance within the existing data set. These are valid procedures[45] that do not replace the need for external validation, which remain crucial to evaluate the generalizability of our model in an independent patient population.

A notable strength of the study is that the inclusion criteria required the absence of systemic corticosteroid therapy for at least 6 months. The general consensus among the international guidance is that these should be tapered and discontinued before considering DMARD tapering.

The intention of the study was to follow standard practice and remain consistent with EULAR guidance in our approach to tapering, although a fully anonymized study could be argued as more suitable. However, ensuring that patients are involved in the decision to taper is essential and in line with EULAR recommendations. Our model could be used to inform patients' decision to taper and indeed identify those that have a high risk of flare, enabling a physician to advise against tapering if deemed high risk.

It remains important to further validate/replicate our proposed biomarker model as a necessary step before considering its use in routine clinical practice. This study identified objective biomarkers Tregs, IRCs, and CRP levels, which predicted the outcome of b-DMARD tapering in real-life outpatient settings. This could help inform future tapering decisions, in which high-risk individuals would be advised not to taper and low-risk individuals would be permitted to taper with the reassurance of high remission recapture rates for those who flare. The identification of separate factors predicting flare while continuing b-DMARDs also has practical implications if validated.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Emery had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gul, Emery.
Acquisition of data. Gul, Di Matteo, Anioke, Mankia, Ponchel.
Analysis and interpretation of data. Gul, Shuweidhi, Ponchel.

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