RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Flare during tapering of biological DMARDs in patients with rheumatoid arthritis in routine care: characteristics and predictors

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To cite: Terslev L, Ostergaard M, Georgiadis S, *et al*. Flare during tapering of biological DMARDs in patients with rheumatoid arthritis in routine care: characteristics and predictors. *RMD Open* 2022;**8**:e002796. doi:10.1136/rmdopen-2022-002796

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002796).

Received 13 October 2022
Accepted 1 December 2022

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ABSTRACT

Objective To identify predictors of flare in a 2-year follow-up study of patients with rheumatoid arthritis (RA) in sustained clinical remission tapering towards withdrawal of biological disease-modifying anti-rheumatic drugs (bDMARDs).

Methods Sustained clinical remission was defined as Disease Activity Score for 28 joints (DAS28)-C reactive protein (CRP) ≤2.6 without radiographic progression for >1 year. bDMARDs were tapered according to a mandatory clinical guideline to two-thirds of standard dose at baseline, half of dose at week 16 and discontinuation at week 32. Prospective assessments for 2 years included clinical evaluation, conventional radiography, ultrasound and MRI for signs of inflammation and bone changes. Flare was defined as DAS28-CRP ≥2.6 with ΔDAS28-CRP ≥1.2 from baseline. Baseline predictors of flare were assessed by logistic regression analyses.

Results Of 142 included patients, 121 (85%) flared during follow-up of which 86% regained remission within 24 weeks after flare. Patients that flared were more often rheumatoid factor positive, had tried more bDMARDs and had higher baseline ultrasound synovitis sum scores than those not flaring. For patients on standard dose, predictors of flare within 16 weeks after reduction to two-thirds of standard dose were baseline MRI-osteitis (OR 1.16; 95% CI 1.03 to 1.33; p=0.014), gender (female) (OR 6.71; 95% CI 1.68 to 46.12; p=0.005) and disease duration (OR 1.06; 95% CI 1.01 to 1.11; p=0.020). Baseline predictors for flare within 2 years were ultrasound grey scale synovitis sum score (OR 1.19; 95% CI 1.02 to 1.44; p=0.020) and number of previous bDMARDs (OR 4.07; 95% CI 1.35 to 24.72; p=0.007).

Conclusion The majority of real-world patients with RA tapering bDMARDs flared during tapering, with the majority regaining remission after stepwise dose increase. Demographic and imaging parameters (MRI-osteitis/ultrasound greyscale synovitis) were independent predictors of immediate flare and flare overall and may be of importance for clinical decision-making in patients eligible for tapering.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tapering or even discontinuing biological disease-modifying anti-rheumatic drugs (bDMARD) is possible in some patients with rheumatoid arthritis (RA). No consistent clinical predictors of flare during tapering bDMARDs in patients with RA in remission have been identified. Imaging modalities may be relevant for identifying patients who may flare prior to dose reduction, as both ultrasound and MRI have documented subclinical synovitis to be frequent in patients with RA in remission.

WHAT THIS STUDY ADDS

⇒ The study found that the presence of MRI-osteitis prior to initiating tapering indicates that tapering is likely to be unsuccessful and should be postponed—especially in female patients and patients with long disease duration. Furthermore, patients on their first bDMARD or with a low ultrasound (grey scale/Global OMERACT-European Alliance of Associations for Rheumatology Composite Score) sum score have a fair chance of not flaring during tapering.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study suggests that MRI of the hands prior to attempting tapering may help select patients in who tapering should be avoided.

INTRODUCTION

Clinical remission is an achievable goal in patients with rheumatoid arthritis (RA). For

patients in stable remission, the European Alliance of Associations for Rheumatology (EULAR) treatment recommendations advise tapering of especially biological(b) disease-modifying anti-rheumatic drugs (DMARD) therapy if possible[1] due to costs and potential safety issues for long-term use.[2 3] There is therefore an interest in tapering or even discontinuing bDMARD in patients with RA, though this is not applicable for all patients.[4–8] We have previously shown that approximately two out of three patients with RA in sustained clinical remission can be successfully tapered to a lower dose than standard dose, although flares occurred.[9 10] Ideally, tapering should be conducted avoiding flares as flare deteriorates functional status, general health, pain and morning stiffness and may worsen structural damage.[11–14] Few studies have aimed to identify risk factors for flare in patients with RA in remission attempting tapering of bDMARD. Anti-cyclic citrullinated protein (ACPA) positivity has been suggested to be associated with flare,[4] whereas being in persistent American College of Rheumatology (ACR)/EULAR Boolean remission may carry the lowest risk of flare.[15] With the lack of consistent clinical predictors of flare during tapering, imaging modalities may be relevant for identifying patients who may flare prior to dose reduction while tapering of bDMARDs. Subclinical synovitis detected by both ultrasound and MRI is frequent in patients with RA in stable remission during csDMARD or bDMARD therapy, independently of the composite remission criteria applied.[10 16–21] In patients with RA in stable remission and stable csDMARD treatment, the presence of Doppler positive synovitis is associated with an increased risk of flare[22–24] but no definite imaging predictors have been identified for bDMARD treated patients.[25 26] Further information on the potential value of imaging as well as clinical and demographic parameters for predicting flare in routine care while tapering bDMARDs is warranted to assess if and when further tapering should be avoided.

The aims of the current study were in the cohort of patients with RA in clinical remission tapering bDMARDS: (1) to assess baseline imaging, demographic and clinical predictors of flare during tapering towards withdrawal of bDMARDs within 16 weeks after dose reduction and within 2 years follow-up, (2) to assess differences in ultrasound and clinical parameters in patients regaining versus not regaining remission 24 weeks after flare, and finally, (3) to assess if ultrasound of hands-only is equally informative as a 24-joint assessment.

METHODS

All the patients included in this study were part of a clinical mandatory tapering guideline for bDMARDs (A Dose OPTimization of Biological Therapy) and fulfilled the ACR 1987 criteria and/or ACR/EULAR 2010 classification criteria for RA.[27 28] All had maintained clinical remission (Disease Activity Score for 28 joints (DAS28)-C reactive protein (CRP) ≤2.6) on stable bDMARD treatment (98% on TNF-inhibitors (adalimumab/etanercept/infliximab) and 2% on tocilizumab/abatacept)) for ≥1 year, documented by ≥3 consecutive clinical visits in the national DANBIO registry.[29] The bDMARDs were tapered at inclusion to two-thirds of standard dose; at week 16 to half of standard dose; and at week 32, bDMARD was discontinued.[9] Patients, who fulfilled the inclusion criteria but were at a lower baseline dose than standard, followed the same predefined step-down regimen. Dose reduction only occurred if the patient was still in clinical remission (see online supplemental appendix A, for details).

Clinical and laboratory assessments

All patients were scheduled for clinical and laboratory assessment at baseline, weeks 4, 8, 16, 24, 32, 40, 48 and 70. Patients who flared were scheduled for a flare-visit and follow-up was changed to 8, 16 and 24 weeks postflare. All patients had a final clinical visit at 2-year follow-up.

At each visit, routine clinical assessment, patient-reported outcomes (PROs) and CRP were assessed and DAS28 using CRP, Clinical Disease Activity Index (CDAI) and ACR/EULAR Boolean remission were calculated (table 1).

Flare

Clinical flare was defined as DAS28-CRP ≥2.6 with ΔDAS28-CRP ≥1.2 from baseline. A flare resulted in stepwise escalation of bDMARD-dose every 4 months until the patient achieved remission, and no further tapering was attempted. Similarly, if erosive progression on MRI or conventional radiography was reported by a radiologist during the tapering, bDMARD-dose was escalated, and further tapering stopped.

Imaging

MRI and radiography

As part of the mandatory tapering regimen radiography of hands, wrists and forefeet and MRI of dominant wrist and metacarpophalangeal joint (MCP) 2–5 were acquired at baseline, week 16 (only MRI), week 32 and year 2, and evaluated after each examination for absence/presence of erosive progression by a radiologist. MRI and radiography were also performed in case of flare.

After the 2-year follow-up, radiographs were scored for erosions and joint space narrowing (JSN) according to the Sharp-van der Heijde method[30] and MRIs according to the OMERACT RAMRIS method.[31–33]

MRIs were scored for single components (osteitis, synovitis, tenosynovitis, erosions and JSN) and combined inflammation and combined damage scores were calculated. Radiographs and MRIs were read by two different readers who were experienced and blinded to patient data and chronology of images.[9]

Ultrasound

Ultrasound was performed at the same time points as clinical examinations by experienced rheumatologists blinded to the clinical assessment (online supplemental appendix A for details on machine settings and training).

Table 1 Baseline demographics, clinical and imaging measures at baseline stratified by flare from baseline to 2 years for patients at standard dose (121 patients) and all patients (142 patients)

	Patients at standard dose				All patients			
	All (n=121)	No flare (n=16)	Flare (n=105)	P value	All (n=142)	No flare (n=20)	Flare (n=121)	P value
Demographics								
Female gender, n (%)	84 (69)	10 (62)	74 (70)	0.723	98 (69)	12 (60)	86 (71)	0.463
Age, years	59 (47–67)	54 (43–60)	59 (47–67)	0.248	58 (47–67)	55 (47–62)	59 (47–67)	0.539
Disease duration, years	11 (8–18)	8 (5–12)	11 (8–18)	0.112	11 (7–18)	9 (6–12)	11 (8–18)	0.137
Current smoker, n (%)	19 (17)	3 (21)	16 (17)	0.706	22 (17)	4 (22)	18 (16)	0.512
BMI, kg/m^2	25.0 (22.1–28.2)	25.2 (23.6–28.4)	24.9 (22.0–28.2)	0.431	24.9 (22.0–28.3)	27.1 (24.6–30.2)	24.5 (21.9–28.1)	0.068
Time in remission before tapering, years	2 (1–3)	2 (2–3)	2 (1–3)	0.647	2 (1–3)	2 (2–3)	2 (1–3)	0.851
Concomitant DMARD	108 (89)	15 (94)	93 (89)	1	125 (88)	19 (95)	105 (87)	0.467
No of previous bDMARDs	0 (0–1)	0 (0–0)	0 (0–1)	**0.017**	0 (0–1)	0 (0–0)	0 (0–1)	**0.016**
Previous bDMARDs, n (%)				0.179				0.169
0	74 (61)	14 (88)	60 (57)		88 (62)	17 (85)	70 (58)	
1	31 (26)	2 (12)	29 (28)		37 (26)	3 (15)	34 (28)	
2	10 (8)	0 (0)	10 (10)		11 (8)	0 (0)	11 (9)	
≥3	6 (5)	0 (0)	6 (6)		6 (4)	0 (0)	6 (5)	
RF positive	84 (69)	7 (44)	77 (73)	**0.036**	97 (68)	9 (45)	87 (72)	**0.033**
Anti-CCP positive	99 (82)	12 (75)	87 (83)	0.488	114 (80)	15 (75)	98 (81)	0.550
Clinical measures								
Tender joint count (0–28)	0 (0–0)	0 (0–0)	0 (0–0)	0.140	0 (0–0)	0 (0–0)	0 (0–0)	0.112
Swollen joint count (0–28)	0 (0–0)	0 (0–0)	0 (0–0)	0.381	0 (0–0)	0 (0–0)	0 (0–0)	0.361
Patient global (0–100)	12 (5–25)	14 (2–27)	11 (5–25)	0.988	12 (4–25)	14 (2–30)	11 (5–25)	0.899
Patient pain (0–100)	11 (4–20)	6 (2–24)	11 (4–19)	0.602	11 (4–20)	6 (2–24)	11 (4–19)	0.875
Physician global (0–100)	0 (0–4)	0 (0–4)	0 (0–4)	0.784	0 (0–4)	0 (0–4)	0 (0–4)	0.811
CRP, mg/L	5.0 (2.0–6.0)	5.0 (3.8–6.0)	5.0 (2.0–6.0)	0.886	5 (2–6)	5 (4–6)	5 (2–6)	0.841
CRP >5 mg/L*, n (%)	37 (31)	5 (31)	32 (30)	1	43 (30)	6 (30)	36 (30)	1
HAQ (0–3)	0.2 (0.0–0.8)	0.0 (0.0–0.4)	0.2 (0.0–0.8)	0.156	0.2 (0.0–0.8)	0.1 (0.0–0.4)	0.2 (0.0–0.8)	0.365
DAS28-CRP	1.8 (1.6–2.1)	1.8 (1.7–1.9)	1.8 (1.6–2.1)	0.579	1.8 (1.6–2.1)	1.8 (1.7–1.9)	1.8 (1.6–2.1)	0.884
CDAI	1.6 (0.7–3.0)	1.4 (0.6–2.8)	1.7 (0.8–3.0)	0.589	1.6 (0.6–3.0)	1.4 (0.4–3.5)	1.6 (0.7–2.8)	0.712
DAS28-CRP<2.6	116 (96)	16 (100)	100 (95)	1	137 (96)	20 (100)	116 (96)	1
CDAI<2.8	88 (73)	12 (75)	76 (72)	1	104 (73)	14 (70)	90 (74)	0.890
ACR/EULAR Boolean remission	48 (40)	7 (44)	41 (39)	0.933	56 (39)	9 (45)	47 (39)	0.784
Radiographic measures (hands and feet)								
TSS (0–448)	17 (5–50)	10 (4–32)	19 (6–50)	0.329	14 (4–45)	9 (2–23)	15 (4–45)	0.261

Continued

Table 1 Continued

	Patients at standard dose				All patients			
	All (n=121)	No flare (n=16)	Flare (n=105)	P value	All (n=142)	No flare (n=20)	Flare (n=121)	P value
JSN (0–84)	11 (3–34)	8 (2–28)	12 (4–34)	0.406	9 (2–31)	8 (0–18)	10 (2–32)	0.361
X-ray erosion	4 (1–15)	2 (1–6)	4 (1–15)	0.232	3 (0–12)	2 (0–5)	3 (0–15)	0.151
Presence of X-ray erosion, n (%)	88 (75)	12 (75)	76 (75)	1	100 (72)	14 (70)	86 (74)	0.957
MRI measures (dominant hand)								
Synovitis (0–21)	4 (2–7)	3 (1–4)	4 (3–7)	0.182	4 (2–7)	3 (2–4)	4 (3–7)	0.330
Tenosynovitis (0–39)	0 (0–2)	0 (0–0)	0 (0–2)	0.084	0 (0–2)	0 (0–0)	0 (0–2)	0.122
Osteitis (0–69)	1 (0–3)	0 (0–2)	1 (0–3)	0.251	1 (0–3)	0 (0–2)	1 (0–3)	0.393
Combined inflammation score (0–129)	7 (3–12)	4 (2–8)	8 (4–13)	**0.048**	6 (3–12)	5 (3–8)	8 (3–13)	0.107
Erosion (0–230)	4 (1–12)	2 (0–9)	4 (1–12)	0.373	4 (1–11)	2 (1–7)	4 (1–12)	0.339
JSN (0–84)	0 (0–6)	0 (0–3)	0 (0–6)	0.886	0 (0–5)	0 (0–1)	0 (0–5)	0.588
Combined damage score (0–314)	5 (1–18)	2 (0–13)	5 (1–20)	0.364	4 (1–17)	3 (1–10)	5 (1–17)	0.306
Ultrasound inflammatory measures								
24 joints								
Grey scale SH sum score (0–72)	5 (2–9)	2 (2–5)	5 (3–10)	**0.034**	5 (2–9)	2 (2–5)	5 (2–10)	**0.039**
Doppler sum score (0–72)	0 (0–2)	0 (0–0)	0 (0–2)	**0.021**	0 (0–1)	0 (0–0)	0 (0–2)	**0.011**
GLOESS (0–72)	5 (2–9)	2 (2–5)	5 (3–10)	**0.026**	5 (2–9)	2 (2–5)	5 (3–10)	**0.030**
Hands-only								
Grey scale SH sum score hands-only (0–30)	2 (0–5)	1 (0–2)	3 (1–5)	**0.013**	2 (0–5)	1 (0–2)	3 (0–6)	**0.013**
Doppler sum score hands-only (0–30)	0 (0–1)	0 (0–0)	0 (0–1)	0.088	0 (0–1)	0 (0–0)	0 (0–1)	**0.049**
GLOESS hands-only (0–30)	2 (1–5)	1 (0–2)	3 (1–5)	**0.009**	2 (0–5)	1 (0–2)	3 (1–6)	**0.009**

One patient was lost to follow-up and only 141 were included in the longitudinal analyses. Values are median (IQR) unless otherwise stated. Mann Whitney U test, χ^2 test or Fisher's exact test (as appropriate) was used for analysing between-group differences; bold indicates statistically significant p values; p<0.05 was considered statistically significant.
Flare: Clinical flare was defined as a DAS28-CRP ≥2.6 with ΔDAS28-CRP ≥1.2 from baseline to time of flare OR erosive progression on MRI or conventional radiography during the period of the tapering bDMARD.
*The departments of clinical biochemistry had different lower cut offs for CRP (varying from 1 to 5) and CRP outcome is therefore presented as ≤or>5.
ACR, American College of Rheumatology; Anti-CCP, anti-cyclic citrullinated protein antibodies; bDMARD, biological disease-modifying anti-rheumatic drug; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28-CRP, 28-joint Disease Activity Score with CRP; DMARD, Disease-Modifying Antirheumatic Drug; GLOESS, Global OMERACT/EULAR Ultrasound Synovitis Score; HAQ, Health Assessment Questionnaire; JSN, Joint Space Narrowing; RF, rheumatoid factor; SDAI, Simple Disease Activity Index; SH, synovial hypertrophy; TSS, Total Sharp van der Heijde score.

At each visit, synovitis was assessed in 24 joints (elbow, wrist, MCP 2–5, knee, ankle and MCP joint 2–5, bilaterally). Each joint was scored using the OMERACT-EULAR synovitis scoring system (0–3) for grey scale (GS) synovial hypertrophy (SH) and for Doppler activity: separately (single components) and in combination using the Global OMERACT-EULAR Composite Score (GLOESS).[34 35] Ultrasound sum scores for 24 joints (using the highest score of the radio-carpal and intercarpal joints for the wrist) were calculated for GS-SH, Doppler activity and GLOESS (range 0–72). To assess if ultrasound of the hands-only was sufficient, similar sum scores were subsequently calculated for the hands (range 0–30).[10]

Statistical analyses

Descriptive statistics were reported as frequency (percentage) for categorical variables and as mean and SD or median and IQR for continuous variables. Group differences were compared with χ^2 test, Fisher's exact test or Mann-Whitney U test, as appropriate. Changes in clinical and imaging parameters were tested by binomial sign test or Wilcoxon signed-rank test, as appropriate. A $p<0.05$ was considered statistically significant.

Potential predictors of flare from baseline to 2 years and within 16 weeks after dose reduction to a certain dose (ie, two-thirds and half of dose) were investigated by logistic regression models. Fourteen baseline demographical, clinical and radiographic variables were included in all models as independent variables: gender, current smoking status, IgM Rheumatoid Factor (RF) positivity, ACPA positivity, CDAI remission and ACR/EULAR remission as categorical variables, and age, disease duration, body mass index, time in remission before tapering, number of previous bDMARDs, HAQ score, DAS28-CRP and Total Sharp-van der Heijde score as numeric variables. Furthermore, baseline numeric imaging variables were tested in different models either as single components (synovitis, tenosynovitis, osteitis, erosion, JSN, GS-SH and Doppler activity) or as composite scores (combined inflammation score, combined damage score and GLOESS). The ultrasound inflammatory variable (GS-SH, Doppler activity and GLOESS were included either for all joints or for the hands only. Additional regression models included changes in clinical and ultrasound variables occurring during the previous tapering period as independent variables.

Missing values in independent variables were imputed by multiple imputation by chained equations (20 imputed datasets).[36] Univariable analyses were run for all independent variables and variables with a $p<0.10$ were included in the initial multivariable model. Backward selection was then performed in stacked imputed datasets with weighted regression using the likelihood ratio test.[37] Independent variables initially excluded in univariable analyses were reintroduced (one at a time) into the multivariable model to assess their potential significance. A significance level of 0.05 was applied in the variable selection procedure. The area under the receiver operating characteristic curve (AUC) was estimated by internal validation. The results of logistic analyses were presented by OR, 95% CI of the OR and p value of the likelihood ratio test.

Analyses were performed in R software V.4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In total, 142 patients followed the mandatory tapering guideline (one lost to follow-up) and 122 patients (86%) were also monitored by ultrasound. One-hundred and twenty-one patients (85%) tapered from standard dose while 13 patients (9%) tapered from two-thirds of standard dose and 8 (6%) from half of standard dose (figure 1).

Description of patients flaring

For the whole cohort, 121 of 142 patients experienced a flare (85%) at some stage during tapering; two of these only by imaging (erosive progression). Of the 121 patients tapering from standard dose, 105 patients (87%) flared (table 1). Baseline demographics, clinical and imaging parameters for patients receiving standard dose and for the whole cohort are shown in table 1. Data availability is given in online supplemental table S1.

Figure 1 displays time of flare by dose reduction step and baseline bDMARD-dose. Of the 121 patients flaring, 26 patients (22%) flared on two-thirds of standard dose, 25 (21%) on half of dose 68 (56%) after discontinuation.

In patients tapering from standard dose, there was a statistically significant difference between the flare group vs non-flare group for RF-positivity (p=0.036; 7 (44%) in the non-flare vs 77 (73%) in the flare-group), previous numbers of bDMARDs (p=0.017), baseline GS-SH, Doppler and GLOESS sum scores for 24 joints (p=0.034, 0.021 and 0.026, respectively, eg, median (IQR) GS-SH sum score 2 (2–5) in the non-flare vs 5 (3–10) in the flare group), and MRI combined inflammation score (p=0.048; 4 (2–8) in the non-flare vs 8 (4–13) in the flare group) (see table 1 for details). If assessing the hands-only by ultrasound the flare group had significantly higher baseline GS-SH and GLOESS sum scores (p=0.013 and 0.009, respectively). In the whole flare cohort, similar results were seen (see table 1 for details). No clinical parameters, composite scores, CRP or MRI parameters differed between the flare and non-flare group.

Changes from baseline to flare and from flare to 2-year follow-up

In table 2, both changes from baseline to flare and from flare to 2-year follow-up are shown for all flare patients (see online supplemental table S2 for data availability).

At time of flare, there was a significant increase in all clinical parameters, PROs, all composite scores and CRP ($p<0.001$ for all) with, for example, swollen joint count increasing from mean (SD)0.1 (0.4) at baseline to 2.3 (2.0) at time of flare, patient pain from 13.7 (14.1) to 40.4 (21.1) and CRP from 5.4 (4.9) mg/l to 9.9 (9.2) mg/L

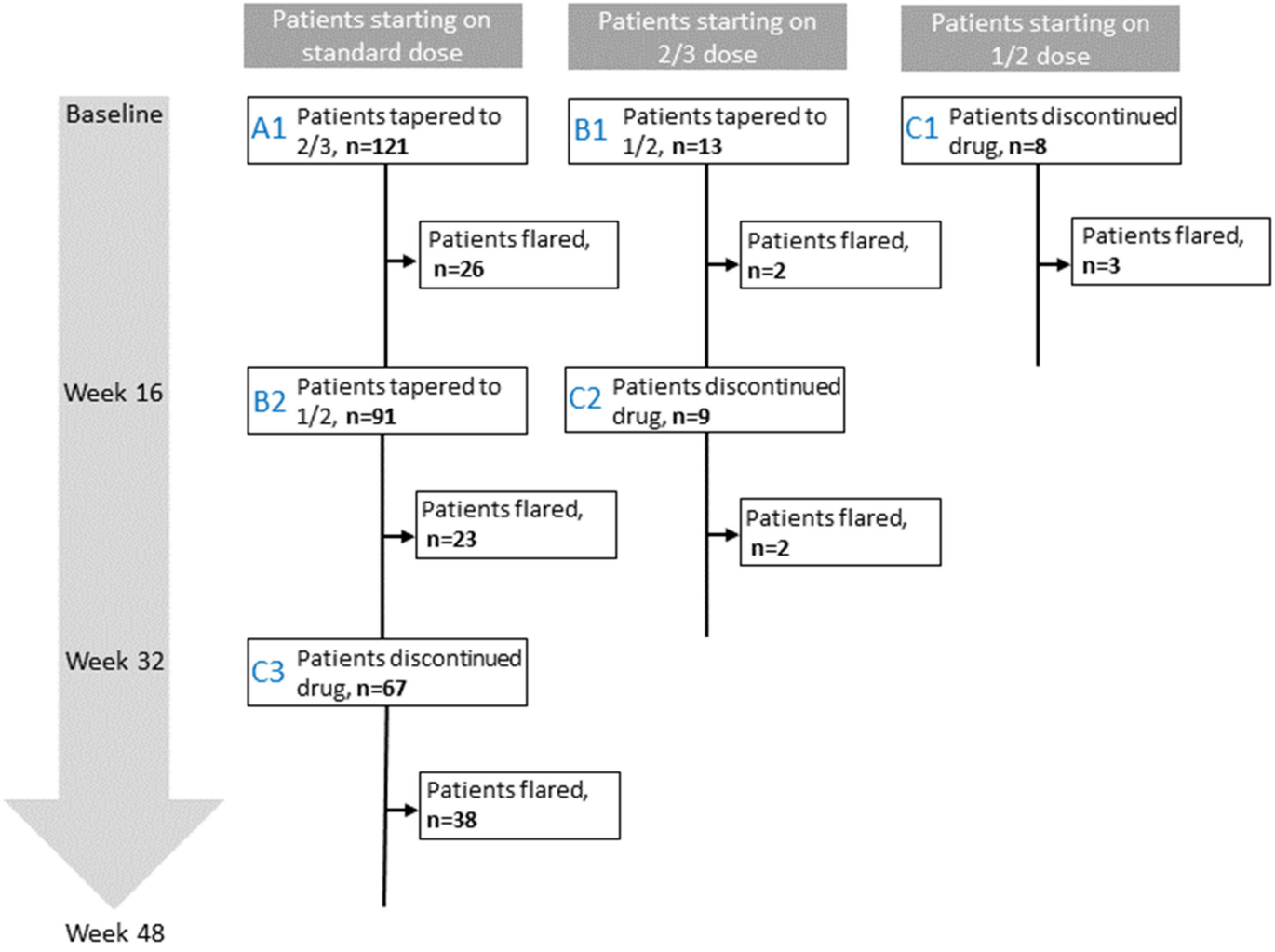

Figure 1 Number of patients flaring within 16 weeks after dose reduction of bDMARDS (n=142 patients with RA in sustained clinical remission). Group A (A1) including patients tapered from standard dose: 121 of which 95 had no flare and 26 had flare. Group B (B1+B2) including patients tapering from two-thirds of dose: 104 of which 79 had no flare and 25 had flare. Group C (C1+C2+C3) including patients tapered from half of dose: 84 of which 41 had no flare and 43 had flare. Seven patients did not follow the tapering Four patients did not flare in A1, but they were not included in B2. Similarly, two patients did not flare in B2, but they were not included in C3, while one patient did not flare in B1, but he/she was not included in C2. bDMARDS, biological disease-modifying antirheumatic drugs; RA, rheumatoid arthritis

(see table 2 for details). For imaging, GS-SH, Doppler and GLOESS sum scores for 24 joints (p<0.001 for each parameter) and for hands-only (p=0.004, 0.017 and 0.006, respectively) increased significantly. As example GS-SH sum score for 24 joints increased from 6.1 (4.7) at baseline to 8.2 (5.6) at time of flare as did MRI tenosynovitis score (p=0.004) (see table 2 for further details).

At 2-year follow-up, all clinical parameters, composite scores and CRP (p<0.001) had decreased significantly after flare (table 2). However, fewer fulfilled the remission criteria for remission at 2-year follow-up as compared with baseline (eg, 31% at 1 year fulfilling the Boolean remission criteria vs 39% at baseline). A significant decrease was seen in Doppler sum score for 24 joints (p=0.001, mean (SD) decrease from 2.2 (2.7) to 1.3 (2.6)) but not for GS-SH and GLOESS sum scores, with similar results for hands-only, while MRI parameters had not changed significantly at 2-year follow-up (table 2).

Predictors of flare

Independent predictors of flare within 16 weeks after dose reduction ('immediate flare') were investigated (table 3, top). For patients tapering from standard to two-thirds of dose, MRI-osteitis at baseline (OR 1.16; 95% CI 1.03 to 1.33; p=0.014,) gender (female) (OR 6.71; 95% CI 1.68 to 46.12; p=0.005) and disease duration (OR 1.06; 95% CI 1.01 to 1.11; p=0.020) were identified as independent predictors, when single ultrasound/MRI components were included in the models. When composite ultrasound/MRI scores were included in the models, independent predictors were gender (female) (OR 6.69; 95% CI 1.62 to 48.59; p=0.006), disease duration (OR 1.06; 95% CI 1.01 to 1.11; p=0.011) and number of previous bDMARDs (OR 1.69; 95% CI 1.03 to 2.83; p=0.037). No independent ultrasound predictors were found, neither for 24 joints nor for the hands-only, and no imaging composite scores were identified as

Table 2 Clinical and imaging measures at time of flare compared with baseline and 2 years' follow-up for all patients

	Baseline (n=121)	Flare (n=121)	Baseline vs flare	2 years (n=121)	Flare vs 2-year follow-up
Clinical measures					
Tender joint count (0–28)	0.2 (0.5)	4.0 (3.3)	**<0.001**	0.6 (1.6)	**<0.001**
Swollen joint count (0–28)	0.1 (0.4)	2.3 (2.0)	**<0.001**	0.3 (0.8)	**<0.001**
Patient global (0–100)	15.9 (14.8)	42.5 (22.8)	**<0.001**	21.1 (20.3)	**<0.001**
Patient pain (0–100)	13.7 (14.1)	40.4 (21.1)	**<0.001**	19.7 (18.8)	**<0.001**
Physician global (0–100)	2.0 (2.9)	23.3 (10.6)	**<0.001**	5.4 (8.9)	**<0.001**
CRP, mg/L	5.4 (4.9)	9.9 (9.2)	**<0.001**	5.2 (5.2)	**<0.001**
CRP >5 mg/L*, n (%)	36 (30%)	67 (56%)	**<0.001**	37 (32%)	**<0.001**
HAQ (0–3)	0.43 (0.51)	0.85 (0.64)	**<0.001**	0.53 (0.56)	**<0.001**
DAS28-CRP	1.85 (0.39)	3.69 (0.78)	**<0.001**	2.07 (0.74)	**<0.001**
CDAI	2.02 (1.72)	12.82 (6.46)	**<0.001**	3.54 (4.21)	**<0.001**
DAS28-CRP <2.6†	116 (96%)	4 (3%)	**<0.001**	97 (82%)	**<0.001**
CDAI <2.8†	90 (74%)	1 (1%)	**<0.001**	64 (55%)	**<0.001**
ACR/EULAR Boolean remission	47 (39%)	2 (2%)	**<0.001**	36 (31%)	**<0.001**
MRI measures					
Synovitis (0–21)	4.7 (3.3)	5.0 (3.6)	0.091	4.7 (3.1)	0.272
Tenosynovitis (0–39)	1.4 (2.0)	2.1 (2.6)	**0.004**	1.6 (2.3)	0.065
Osteitis (0–69)	2.6 (4.1)	2.7 (5.1)	0.616	3.0 (4.2)	0.905
Combined Inflammation score (0–129)	8.8 (6.8)	8.8 (6.5)	0.081	9.2 (7.5)	0.344
Erosion (0–230)	16.6 (32.1)	17.1 (33.4)	0.383	16.4 (29.4)	0.500
JSN (0–84)	7.0 (15.5)	7.2 (16.4)	–	7.5 (15.9)	–
Combined damage score (0–314)	23.1 (47.2)	23.6 (49.4)	0.578	21.8 (41.6)	0.064
Ultrasound inflammatory measures					
24 joints					
Grey scale SH sum score (0–72)	6.1 (4.7)	8.2 (5.6)	**<0.001**	7.7 (5.6)	0.094
Doppler sum score (0–72)	1.1 (1.5)	2.2 (2.7)	**<0.001**	1.3 (2.6)	**<0.001**
GLOESS (0–72)	0.8 (1.3)	1.4 (2.1)	**0.017**	0.8 (1.5)	**0.015**
Hands-only					
Grey scale SH sum score hands-only (0–30)	3.3 (3.1)	4.0 (4.1)	**0.004**	3.2 (3.0)	**0.034**
Doppler sum score hands-only (0–30)	3.4 (3.0)	4.0 (4.1)	**0.006**	3.3 (3.0)	**0.041**
GLOESS hands-only (0–30)	6.2 (4.6)	8.2 (5.6)	**<0.001**	7.7 (5.6)	0.085

Values are mean (SD) unless otherwise stated. '–' indicates that p value could not be calculated. Bold indicates statistically significant p values; p<0.05 was considered statistically significant. One-sided binomial sign test or Wilcoxon signed-rank test, as appropriate, were done to test if the value was significantly higher at flare than baseline and significantly lower at week 96 than flare.
*The departments of clinical biochemistry had different lower cut offs for CRP (varying from 1 to 5) and CRP outcome is therefore presented as ≤or >5.
†The opposite direction of the test was applied.
ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28-CRP, 28-joint Disease Activity Score with CRP; GLOESS, Global OMERACT/EULAR Ultrasound Synovitis Score; HAQ, Health Assessment Questionnaire; JSN, Joint Space Narrowing; SH, synovial hypertrophy.

predictors. Descriptive statistics for patients flaring/not flaring 16 weeks after tapering and all univariable and multivariable analyses are given in online supplemental tables S3–S5.

For patients on standard dose all models performed acceptably with AUC ranging from 0.75 to 0.80. For patients tapering from tw-thirds to half standard dose regression analyses identified only demographic variables as independent baseline predictors of flare within 16 weeks after dose reduction (online supplemental table S6) whereas for patients tapering from half of dose,

Table 3 Predictors of flare (in patients at standard dose) applying logistic regression analyses

Predictors for flare within 16 weeks after tapering from standard dose to two-thirds of dose				
	Model including MRI and ultrasound component scores as independent variables			
	All joints		**Hands only**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Female	6.71 (1.68 to 46.12)	0.005	6.71 (1.68 to 46.12)	0.005
Disease duration	1.06 (1.01 to 1.11)	0.020	1.06 (1.01 to 1.11)	0.020
Osteitis	1.16 (1.03 to 1.33)	0.014	1.16 (1.03 to 1.33)	0.014
AUC (95% CI)	0.80 (0.71 to 0.88)		0.80 (0.71 to 0.88)	
	Model including MRI and ultrasound composite scores as independent variables			
	All joints		**Hands only**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Female	6.69 (1.62 to 48.59)	0.006	6.69 (1.62 to 48.59)	0.006
Disease duration	1.06 (1.01 to 1.11)	0.011	1.06 (1.01 to 1.11)	0.011
No of previous bDMARDs	1.69 (1.03 to 2.83)	0.037	1.69 (1.03 to 2.83)	0.037
AUC (95% CI)	0.75 (0.66 to 0.83)		0.75 (0.66 to 0.83)	
Predictors for flare from baseline to 2 years				
	Model including MRI & ultrasound component scores as independent variables			
	All joints		**Hands only**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
No of previous bDMARDs	4.07 (1.35 to 24.72)	0.007	3.87 (1.26 to 23.88)	0.013
Grey scale SH sum score	1.19 (1.02 to 1.44)	0.020		
Grey scale SH sum score hands-only			1.37 (1.06 to 1.92)	0.011
AUC (95% CI)	0.76 (0.65 to 0.87)		0.75 (0.65 to 0.86)	
	Model including MRI and ultrasound composite scores as independent variables			
	All joints		**Hands only**	
	OR	**P value**	**OR**	**P value**
No of previous bDMARDs	4.02 (1.33 to 24.44)	0.008	3.86 (1.24 to 23.98)	0.014
GLOESS	1.18 (1.01 to 1.43)	0.030		
GLOESS hands-only			1.37 (1.06 to 1.92)	0.014
AUC (95% CI)	0.75 (0.65 to 0.87)		0.75 (0.64 to 0.85)	

Results derived in imputed datasets, where model estimates are pooled based on Rubin's rules. Predictors were selected by applying backward selection in stacked data after applying a fixed weight to all observations, accounting for the average fraction of missing data across all variables under consideration. Profile likelihood CIs calculated according to the Pseudo-Variance modification of Rubin's rule. P values calculated by likelihood ratio tests. AUC estimated based on internal validation by bootstrapping with 100 samples per imputed dataset. The bootstrap 0.632+ estimate was calculated to correct for optimism.
AUC, area under the curve; bDMARD, biological disease-modifying anti-rheumatic drug; GLOESS, Global OMERACT/EULAR Ultrasound Synovitis Score; SH, synovial hypertrophy.

sample size was not sufficient to assess predictors of flare 16 weeks after cessation.

Changes in clinical and ultrasound parameters within 16 weeks after the previous dose reduction were investigated as predictors of flare after the current dose reduction; however, none of the changes were predictors (data not shown).

For flare at any time within the 2 years follow-up, the selected independent baseline predictors in univariable and multivariable logistic regression analyses for patients on standard dose of bDMARD were as follows (table 3, bottom): When single ultrasound/MRI components were included in the model, statistically significant predictors were GS-SH sum score for 24 joints (OR 1.19; 95% CI 1.02 to 1.44; p=0.020) and number of previous bDMARDs (OR 4.07; 95% CI 1.35 to 24.72; p=0.007); When composite ultrasound/MRI scores were included, independent predictors were GLOESS for 24 joints (OR 1.18; 95% CI 1.01 to 1.43; p=0.030) and number of previous bDMARDs (OR 4.02; 95% CI 1.33 to 24.44; p=0.008). When assessing the hands-only the same predictors were selected. No clinical predictors of flare during tapering were identified. All univariable and multivariable analyses are shown in online supplemental tables S7 and S8.

To assess whether MRI parameters were independent predictors, when ultrasound parameters were not

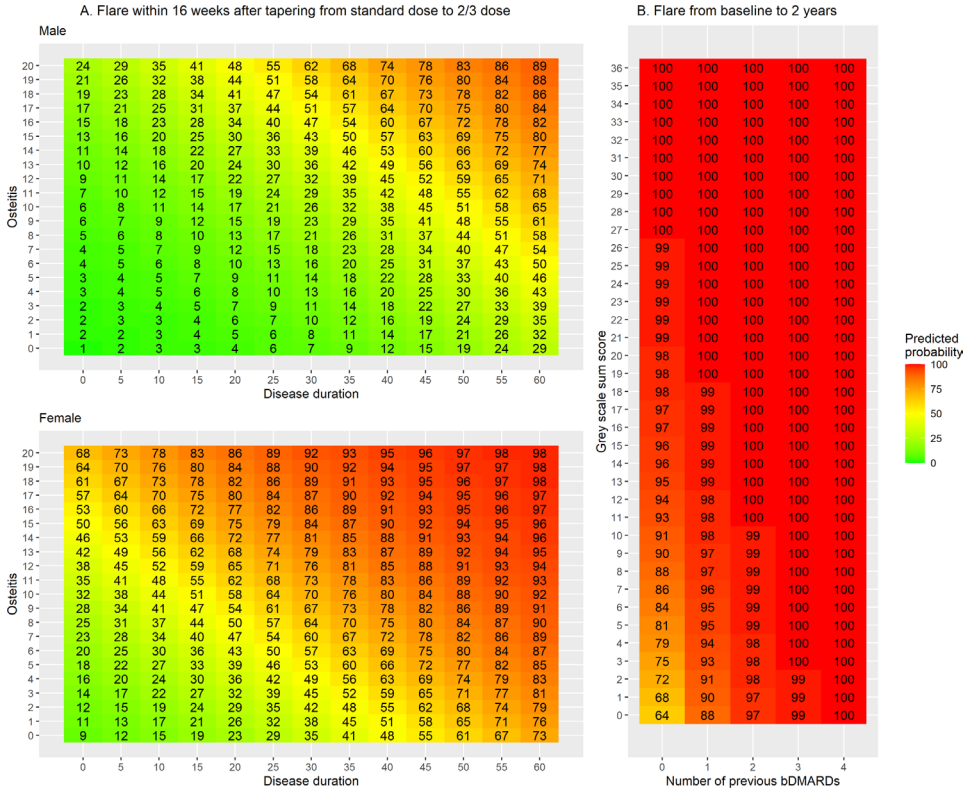

Figure 2 Heatmaps of predicted probabilities for (A): Flare from baseline to 2 years and (B): Flare within 16 weeks when tapering from standard dose to two-thirds of dose, stratified by gender. Predicted probabilities were derived based on logistic regression models including MRI and ultrasound component scores (table 3) with disease duration shown in years. bDMARD, biological disease-modifying antirheumatic drug.

available, additional analyses excluding the ultrasound parameters from independent variables were conducted. When ultrasound parameters were excluded, no MRI parameters were identified as statistically significant predictors (results not shown).

In figure 2, heatmaps of predicted probabilities are shown for flare within 16 weeks after dose tapering with osteitis scores vs disease duration, stratified by gender (A) and for flare from baseline to 2 years with GS-SH sum scores versus numbers of previous bDMARDs (B).

Differences in preflare and postflare assessment between patients regaining and not regaining remission-DAS28CRP 24 weeks after flare

Of the 121 patients who flared during tapering, 104 patients (86%) regained remission within 24 weeks after flare. In figure 3, the course of selected clinical, PRO and ultrasound parameters from 16 weeks before to 24 weeks after flare are shown stratified by regaining/not regain remission 24 weeks after flare (online supplemental table S9a-f for descriptive statistics).

For ultrasound parameters, a statistically significant difference was only seen 8 weeks prior to flare (GS-SH, Doppler and GLOESS 24-joint sum scores (p=0.028, p=0.046 and 0.023, respectively) in patients not regaining remission 24 weeks postflare. At time of flare and the subsequent 24 weeks, there were no differences in imaging parameters between the two groups.

In the 16 weeks prior to flare, there were no consistent difference in any clinical parameters between patients regaining/not regaining remission. At time of flare, there was a statistically significant difference in DAS28CRP between patients regaining/not regaining remission median (IQR) 3.5 (3.2–4.0) vs 3.9 (3.6–4.2); p=0.045), but no differences in CRP, clinical parameters or other composite scores. During the first 8 weeks postflare, all clinical parameters, composite scores and PROs were significantly different between the two groups (online supplemental table S9d). Similar differences were observed at 16 weeks postflare except for swollen joints, patient pain, patient global and physician global (online supplemental table S9e).

DISCUSSION

This study describes patients with RA in sustained clinical DAS28(CRP) remission for at least 1 year without erosive progression, who tapered bDMARDs according to a mandatory clinical guideline and were monitored clinically, with ultrasound and MRI. Most of the patients flared (85%), the majority after treatment discontinuation at week 32 (56%). We identified baseline MRI-osteitis, gender (female) and disease duration as independent predictors of immediate flare (ie, within 16 weeks after tapering to two-thirds of standard dose), whereas no predictors for flare were identified for the

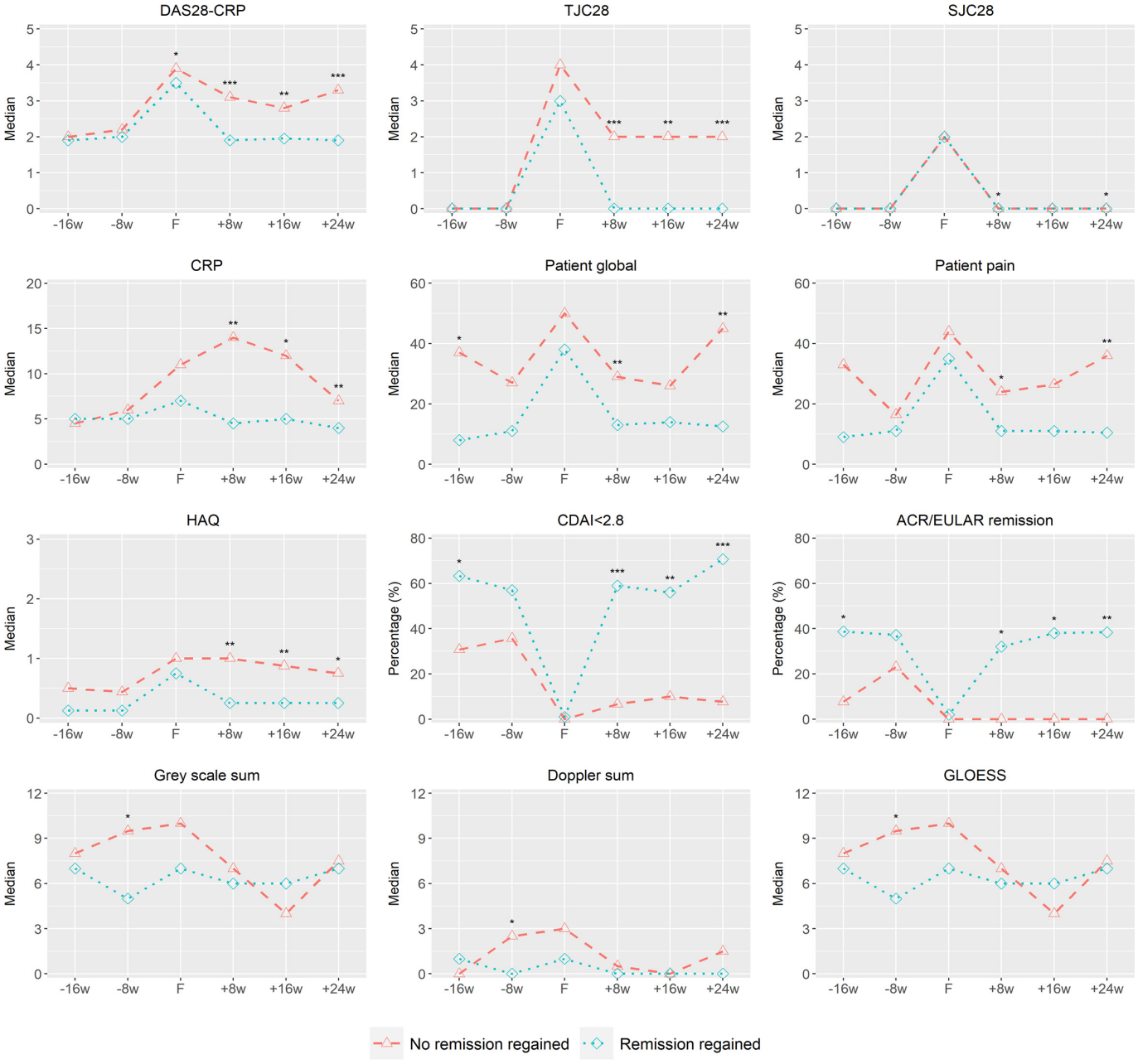

Figure 3 Clinical and imaging measures stratified by regaining remission at 16 and 8 weeks before flare, flare, and 8, 16 and 24 weeks after flare −16 w: 16 weeks before flare; −8 w: 8 weeks before flare; F: flare; +8 w: 8 weeks after flare; +16 w: 16 weeks after flare; +24 w: 24 weeks after flare. Mann-Whitney U test, χ^2 test or Fisher's exact test (as appropriate) was used for analysing between-group differences. *p<0.05, **p<0.01, ***p<0.001. ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, Disease Activity Score for 28 joints; EULAR, European Alliance of Associations for Rheumatology; GLOESS, Global OMERACT-EULAR Composite Score; HAQ, Health Assessment Questionnaire; SJC, swollen joint count; TJC, tender joint count.

subsequent dose reduction steps, probably due to low sample size. Independent predictors of flare at any time within the 2 years follow-up were identified as baseline ultrasound GS-SH and GLOESS sum scores and number of previous bDMARDs.

No consistent clinical predictors have been identified in previous studies[4 15] nor in the current study where gender, disease duration and previous number of bDMARDs were predictors of flare. These are all parameters that cannot be targeted in routine care and are not influenced by clinical monitoring strategies, and indicate a basic premise for the individual patient. Though other studies have suggested that DAS28 (Estimated Sedimentation Rate) and remission according to stringent remission criteria are related to not flaring after withdrawal of TNF-inhibitors,[38–40] this could not be confirmed in our study.

Longitudinal data of all independent variables (ie, at each dose reduction step) could have been used to build additional models. With the applied prediction models,

our study suggests a potential future role for imaging as predictors of flare during tapering of bDMARDS. We found that MRI-osteitis but not ultrasound to have predictive value for immediate flare after tapering from standard dose (within the following 16 weeks after first dose reduction) indicating that MRI-osteitis reflects subclinical insufficiently suppressed inflammation, which may quickly increase if the treatment dose is reduced. For flare at any time within the 2-year follow-up, ultrasound baseline GS-SH and GLOESS were identified as predictors of flare. The patients in our study had very low Doppler scores at baseline and we did not find Doppler activity alone to have predictive value for flare. In contrast, some previous studies have identified Doppler as a predictor of flare in stable csDMARD treated patients with RA in remission and in bDMARD treated patients attempting tapering.[22 24 26 41 42] An explanation could be that the patients in our study may have been in 'deeper' remission but also that other parameters than Doppler impacts the risk of flare in bDMARD treated patients. The fact that GS-SH had a predictive value emphasises that GS-SH without Doppler activity is not per se a sign of inactive disease.[43] It furthermore, makes our results applicable to rheumatology clinics with less advanced ultrasound equipment as the GS-SH component is independent of the Doppler sensitivity of the equipment. It has been shown that ultrasound of the hands-only capture ≥90% of patients with subclinical inflammation in RA bDMARD-treated patients in remission[44] and the patients flaring in our study had significantly higher baseline ultrasound GS-SH and GLOESS sum scores for the hands-only as well as for 24 joints assessment. However, the hands-only ultrasound results had no predictive value for flare.

The majority of the patients in our study flared during tapering, with more than half of these after bDMARD cessation (56%). Fortunately, 86% of the flare patients had regained remission within 24 weeks after escalation of bDMARD. This is in line with a recent systematic literature review of tapering and withdrawal of TNF-inhibitors.[45] Furthermore, we have previously demonstrated that after dose-increase 62% of the patients obtained remission on a lower dose than standard dose.[9]

As expected, we found flare to be related to a worsening of all clinical and ultrasound parameters, CRP, PROs and MRI tenosynovitis score as compared with baseline, as also reported in other studies.[46 47] The patients not regaining remission within 24 weeks (14%) had persistent and statistically significantly different values of clinical parameters 8 and 16 weeks postflare compared with those regaining remission. Before the flare, patients regaining and not-regaining remission only differed significantly in ultrasound sum scores. Whether ultrasound may serve as an indicator of patients having a more prolonged post-flare period needs to be established in future studies.

At 2-year follow-up, all parameters—except for GS-SH sum score and all MRI parameters—had improved compared with time of flare. MRI tenosynovitis has previously been reported to persist after flare whereas synovitis tends to resolve quicker both by MRI and ultrasound,[38] the latter also seen in our study. The fact that only MRI tenosynovitis increased at time of flare and that no significant improvement was seen in any MRI parameters at 2-year follow-up could partly be explained by the fact that only the dominant hand was investigated as compared with 24 joints by ultrasound and the dominant hand is not per se the most inflamed therefore not necessarily capturing all inflammatory activity.[39] As MRI only assess a limited number of joint as compared with ultrasound it may be less relevant as a flare instrument in routine care whereas ultrasound may be used to support the clinical assessment of flare. The lack of improvement of ultrasound GS-SH sum score at 2-year follow-up with higher scores than at baseline should be explored in future studies as a potential predictor of flare or persistent remission beyond the 2-year follow-up.

In our study, we found that the presence of MRI-osteitis prior to initiating tapering indicates that tapering is likely to be unsuccessful and should be postponed—especially in female patients and patients with long disease duration. Furthermore, patients on their first bDMARD or with a low GS/GLOESS sum score may have a fair chance of not flaring during tapering. Finally, our results suggest that caution is needed when tapering from half of dose to discontinuation of bDMARD as the majority of the patients flaring flared at that step. Figure 2 may guide the decision to taper by indicating the predicted probability of flare in relation to the patient's demographic parameters and imaging modalities. Tapering has been shown to be cost saving[48] but tapering should of course be based on shared decision making. Our data suggest in which situations a potential flare is most likely to occur when tapering is considered. However, cost-effectiveness analyses would be needed to study the added value of adding MRI and/or ultrasound to routine care of patients in whom tapering is considered. The strengths of the study are that patients originated from routine care and the findings are therefore expected to be more generalisable and hence more relevant to clinicians than data from clinical trials. Further, we have used standardised clinical assessment for disease activity, remission and flare and have applied validated ultrasound and MRI definitions for inflammation and validated scoring systems.

The limitations of the study are lack of a control group not tapering bDMARDs, that MRI was not conducted at all visits and that the ultrasound examinations were performed by several ultrasonographers (although all were skilled in musculoskeletal ultrasound and trained and calibrated in the applied scoring system), however, this reflects daily clinical practice. In addition, the majority of the patients were tapering TNFα blockers and hence our findings may not be representative for other bDMARD drugs. Finally, the small sample size and therefore the potential overfitting in the prediction models are also limitations despite the acceptable values of AUC, as estimated by internal validation. Hence, additional studies are needed to assess the generalisability of

our findings. Randomised controlled trial comparing tapering with and without the identified predictors would also be beneficial.

In conclusion, baseline MRI-osteitis, disease duration and gender were independent predictors for flare within 16 weeks after tapering from standard dose to two-thirds of dose whereas baseline sum scores for GS SH alone or as part of the combined score (GLOESS) and number of previous bDMARDs were independent predictors of flare at any time within 2-year follow-up. No clinical parameters had predictive value for flare. Imaging findings and demographic parameters may be important to review in patients considered for tapering. Further studies are needed to test the identified predictors.

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Acknowledgements We wish to thank Hanne Slott Jensen and Per Brown Frandsen for their participation in the project.

Contributors LT, CHB, MLH, MO, HR, AH, JN and SJ have made substantial contributions to study conception and design; LT, CHB, KE, LJ, KE, UMD, VF, TM, SK, DVJ, KA and NM have participated in acquisition of data; MB, ZR, LM-C, JMM and DG have read all X-ray and/or MRI SG has performed all statistical analyses; NSK has created all databases; LT, MO, SG and MLH have interpreted data and drafted the article. LT is guarantor for the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests LT: Speakers fee from Janssen, Roche, Novartis, Pfizer, UCB and Eli-Lilly, consultancy fee from Janssen. MO: research support, consultancy fees and/or speaker fees form Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Gilead, Hospira, Janssen, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB. LJ: Speakers fees and consultancy fees from AbbVie, Eli-Lilly, and Novartis. UMO: consultancy fees from Eli-Lilly, Roche, Novartis, speakers fee from Roche. SK: research support from AbbVie, MSD and Novartis. DG: Speakers fee from Eli-Lilly; AH: speakers fee from Eli-Lilly; KA: speakers fees and advisory board membership fees from AbbVie, Cellgene, Pfizer, Novartis, Roche, Berlin Chemie, Eli-Lilly and MSD; MB: research support, consultancy fees and/or speaker fees from Image Analysis Group, Esaote, Abbvie, Celgene, Eli-Lilly, Janssen, Novartis, Pfizer, UCB, Novo, GSK, Takeda, Geurbet, Biogen, Radiobotics, Chondrometrics. MLH: grants from Bristol-Myers Squibb, AbbVie, Roche and Novartis, grants and personal fees from MSD, Biogen, and Pfizer, and personal fees from Eli-Lilly, Orion Pharma, CellTrion, Samsung Bioepis, Janssen Biologics B.V.

Patient consent for publication Not applicable.

Ethics approval Ethical approval is not needed for clinical treatment guidelines according to Danish law. Only the ultrasound assessment was a research project approved by the research ethical committee of the Capital Region of Denmark (Protocol number: H-1-2012-127). All patients gave written informed consent and the study was carried out following the Declaration of Helsinki, Fortaleza, Brazil, October 2013.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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