Selection of treatment regimens based on shared decision-making in patients with rheumatoid arthritis on remission in the FREE-J study

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Abstract

Objective. To compare the outcome of various treatment de-escalation regimens in patients with RA who achieved sustained remission.

Methods. At period 1, 436 RA patients who were treated with MTX and bDMARDs and had maintained DAS28(ESR) at <2.6 were divided into five groups based on shared patient/physician decision-making; continuation, dose reduction and discontinuation of MTX or bDMARDs. At end of year 1, patients who achieved DAS28(ESR) <3.2 were allowed to enrol in period 2 for treatment using the de-escalation regimens for another year. The primary and secondary endpoints were the proportion of patients with DAS28(ESR) <2.6 at year 1 and 2, respectively.

Results. Based on shared decision-making, 81.4% elected de-escalation of treatment and 48.4% selected de-escalation of MTX. At end of period 1, similar proportions of patients maintained DAS28(ESR) <2.6 (continuation, 85.2%; MTX dose reduction, 79.0%; MTX-discontinuation, 80.0%; bDMARD dose reduction, 73.9%), although the rate was significantly different between the continuation and bDMARD-discontinuation. At end of period 2, similar proportions of patients of the MTX groups maintained DAS28(ESR) <2.6 (continuation or de-escalation), but the rates were significantly lower in the bDMARD-discontinuation group. However, half of the latter group satisfactorily...
discontinued bDMARDs. Adverse events were numerically lower in MTX and bDMARD-de-escalation groups during period 1 and 2, compared with the continuation group.

Conclusions. After achieving sustained remission by combination treatment of MTX/bDMARDs, disease control was achieved comparably by continuation, dose reduction or discontinuation of MTX and dose reduction of bDMARDs at end of year 1. Subsequent de-escalation of MTX had no impacts on disease control but decreased adverse events in year 2.

Key words: rheumatoid arthritis, treatment, DMARD, biologics, remission

Rheumatology key messages

- By shared decision-making, >80% of RA patients with remission selected de-escalation of treatments, especially MTX.
- 80% of RA patients with MTX de-escalation maintained DAS28(ESR)<2.6 for 2 years with lower AEs.
- Half of patients satisfactorily discontinued bDMARDs for 2 years, but dose reduction at year 1 decreased chance.

Introduction

The combined use of conventional synthetic DMARDs (csDMARD), such as MTX, and biological DMARDs (bDMARD) has revolutionized the treatment of RA [1–3]. Induction of remission is now a realistic goal of treatment, achieved in the majority of patients, though maintenance of remission through high adherence and safety is necessary for successful long-term outcome [4, 5]. Meanwhile, de-escalation of treatment, including dose reduction or discontinuation, after achieving the treatment target could bring its own benefits and risks and such approaches should have the potential impact on both the patients and healthcare system in terms of efficacy, safety and economy [6–9].

We first reported the results of the remission induction by remicade in RA (RRR) study in which TNF-targeting infliximab was discontinued successfully after sustained remission, without radiologic progression in patients with established RA who showed inadequate response to MTX (MTX-IR) [10]. The study has been followed by multiple reports: bDMARDs could be tapered in more than half of the patients with early RA, re-treatment with TNF inhibitors could be effective and safe in the vast majority of patients at a flare following bDMARDs discontinuation, established RA patients who sustained deep remission showed relatively high probability of remaining in remission following discontinuation of bDMARDs, and the incidence of adverse events (AEs) was lower in the bDMARD discontinuation group than in the continuation group, implying that withdrawal of bDMARDs is beneficial in terms of safety concerns [11–17].

However, there is no defined treatment protocol on how and when to stop treatment. Schett et al. proposed that DMARD tapering should be considered when the patients fulfill standardized clinical criteria for remission state, show sustained remission for at least 6 months, had used DMARDs continuously over the last 6 months, and had not used glucocorticoids to maintain the remission state [18]. The discontinuation of csDMARDs such as MTX has not been recommended because it results in an increase in the flare rate and because the retreatment with MTX often fails to recover to the situation before the discontinuation. In the recent TApering strategies in Rheumatoid Arthritis (TARA) study, tapering TNF inhibitors was not superior to tapering csDMARDs, which indicates tapering the TNF inhibitor first [19]. Thus, de-escalation of bDMARDs is prioritized over that of csDMARDs based on clinical and economic perspectives. However, there are many concerns about compliance and adherence to MTX therapy in both short-term and long-term users. In this regard, many patients treated with MTX develop upper gastrointestinal symptoms, fatigue, headache and other symptoms [20, 21]. Common side effects associated with long-term use of MTX include liver injury, renal injury, lymph-proliferative disease, interstitial lung disease, serious infection and opportunistic infection, and most of them remain unsolved. Thus, long-term use of MTX is not often welcomed by many patients.

Based on the above background, it is important to answer the following clinical questions: (i) after achieving sustained remission by the combination of MTX and a bDMARD, can remission be maintained for 1 year by dose reduction or discontinuation of MTX or bDMARDs, as with continuous use of MTX and bDMARDs?; (ii) which treatment is more efficacious in maintaining remission for another one year following discontinuation of MTX or bDMARDs?; and (iii) is drug-free remission feasible at year 1 of the protocol?

In order to assess de-escalation of MTX and/or bDMARDs at 1 or 2 years after sustained remission in patients with established RA, a nationwide multicentre prospective and real-world study, the FREE-J study, was conducted in Japan. Patients who showed sustained remission for 1 year following the combination treatment of MTX and bDMARDs were divided into five groups: (i) patients who continued all DMARDs; (ii) reduced the dose of MTX; (iii) discontinued MTX; (iv) reduced dose of bDMARDs; and (v) discontinued bDMARDs.
Patients and methods

Study design and patients

The FREE-J study was conducted as an open-label, real-world, five-parallel groups based on shared decision-making between patients and rheumatologists, nationwide multicentre trial for patients with RA. A total of 436 patients from 18 locations were enrolled in this study between August 2014 and March 2020. This trial was registered with University Hospital Medical Information Network (UMIN; UMIN000014856). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice. The protocol and the informed consent form received institutional review board/independent ethics committee approval before the conduct of the study and all patients provided written informed consent before participation.

Patients aged ≥18 years with RA defined by ACR/EULAR 2010 criteria were included if they maintained stable DAS28(ESR) at <2.6 for at least two consecutive visits to the outpatient department while under the combination treatment of a bDMARD and MTX (dose: ≥8 mg/week). The exclusion criteria were contraindication to MTX and bDMARDs or any other reasons for unsuitability to participate in this study, as judged by the attending rheumatologist.

Patients with RA who showed MTX-IR but were treated with a bDMARD in addition to MTX were enrolled in the study if they had achieved DAS28(ESR) <2.6 on at least two continuous visits. The enrolled patients were divided into five groups: (i) continuation of MTX + a bDMARD; (ii) 50% reduction in MTX dose; (iii) discontinuation of MTX; (iv) dose reduction or spacing of the bDMARD; and (v) discontinuation of the bDMARD (Fig. 1) according to the shared decision-making between patients and rheumatologists. The dose reduction or spacing of the bDMARD was done according to the discretion of the site investigators. Blinded randomization including the discontinuation arms was not permitted by inspection in the Japan Agency for Medical Research and Development (AMED) mainly due to ethical reasons. Accordingly, patients of each group were treated with the designated regimen for up to year 1 during the first period.

Patients of each group who completed period 1 and achieved DAS28(ESR) <3.2 at year 1 were allowed to proceed to the next subgrouping for the second period. In this period, the patients were subdivided into continuation of treatment regimen at period 1, discontinuation

![Fig. 1 Study design](https://academic.oup.com/rheumatology/article-lookup/10.1093/annrheumdis/raab115)

Patients with RA and with MTX-IR who were being treated with bDMARD in addition to MTX were enrolled in the study if they had achieved DAS28(ESR) <2.6 at least on two successive visits to the outpatient departments. The enrolled patients were divided into five treatment groups according to shared decision-making between patients and rheumatologists. Patients of each group were treated with the selected regimen for year 1 (period 1), then allowed to proceed to the next period (period 2) for another one year if they achieved DAS28(ESR) <3.2 at the end of year 1.
of MTX from period 1, discontinuation of the bDMARD from period 1 and discontinuation of both MTX and the bDMARD (Fig. 1) according to shared decision-making. During the second period, patients of each group were treated with the designated regimen up to the end of year 2. Discontinuation of corticosteroids and NSAIDs was recommended before study entry, though their temporary use was allowed during the 2-year period.

The shared decision-making was undertaken among patients, physicians and medical staff according to a three-step model reported by Elwyn et al., namely: (i) introducing choice; (ii) describing options, often by integrating the use of patient decision support; and (iii) helping patients explore preferences and make decisions [22]. As basic information for patients, #12 and #13 in the 2013 Update of the EULAR recommendations were shared with patients: #12 – if a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs and #13 – in cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician [23].

Study endpoints
The primary end point of the FREE-J study was the proportion of patients with DAS28(ESR) <2.6 at the end of year 1. The secondary endpoints were the proportion of patients with DAS28(ESR) <2.6 at the end of year 2 and the proportion of patients achieving simplified disease activity index (SDAI) remission (≤3.3) and clinical disease activity index (CDAI) remission (≤2.8) at years 1 and 2.

The flares during the periods 1 and 2 were defined as DAS28(ESR)≥3.2 at two continuous visits and the treatment regimens at year 0 and year 1, respectively, were restored. All AEs, including serious AEs (SAEs), discontinuation due to AEs and AEs of special interest (including those associated with immunomodulatory drugs, such as infections, prespecified autoimmune disorders and malignancies) were recorded throughout the study.

Statistical analysis
The period 1 analysis population (intention-to-treat population) included 436 patients who were divided into the five groups of the first 1 year and their data was analysed for the primary and some secondary endpoints at year 1 (i.e. period 1). Among the 381 patients who completed period 1 and achieved DAS28 (ESR) <3.2 at year 1, informed consents to continue into period 2 were obtained from 348 patients, whose data was analysed for some secondary endpoints at year 2.

Baseline demographics and disease characteristics were analysed descriptively. The primary end point was assessed using a logistic regression model. The odds ratios (ORs) and 95% CIs were calculated for the four treatment arms, compared with those of the continuation arm as the reference during period 1. Other binary variables during period 1 were also analysed in the same fashion. Continuous variables during period 1 and 2 were analysed using a longitudinal repeated measures model. For period 2 analysis, all efficacy summaries were presented over time (from year 1 to year 2) and by treatment groups. The ORs and 95% CIs were provided for the three treatment arms, continuation, dose reduction or discontinuation of MTX or bDMARD during period 2. When treatments were restarted, the value of disease activity at the time was used. During period 1 and period 2 for categorical response parameters, groups were compared by χ² test and continuous variables were analysed using the Kruskal–Wallis’ multiple comparison test among three or five groups. The data on DAS28(ESR) <2.6 achievement at year 2 were calculated by pairwise comparison adjusted Bonferroni’s multiple comparison test. P-values <0.05 were considered to denote statistical significance. As an exploratory analysis, logistic regression analysis was performed to identify the baseline predictors of achieving DAS28(ESR) <2.6 at year 1 and year 2 after enrolment.

Safety analysis was conducted based on the safety population, which included all patients who enrolled in the study and received MTX or bDMARDs at least once. The combined results of all the five arms are shown before subgrouping, and the results for each treatment arm are shown separately for each subgrouping. The numbers and proportions of AEs were calculated. All P-values calculated in the analysis were two-sided and not adjusted for multiple testing because no interim analysis was planned. P-values <0.05 denoted the presence of statistical significance. All statistical analyses were conducted using STATA ver 15.0 (Stata, College Station, TX, USA).

Ethics approval
The FREE-J study was conducted as an open-label, five-parallel groups based on shared decision-making between patients and rheumatologists, nationwide multicentre trial for patients with RA. This trial was registered with University Hospital Medical Information Network (UMIN; UMIN000014856). The protocol and the informed consent form received approval from The Ethics Committee of University of Occupational and Environmental Health, Japan (#H26-07), before the conduct of the study and all patients provided written informed consent before participation.

Results
Study populations
Fig. 1 summarizes the study protocol and number of RA patients at each period. Patients with MTX-IR who were treated with bDMARDs and MTX were enrolled in the study if they achieved DAS28(ESR) <2.6 on at least two continuous visits. A total of 436 patients were enrolled in the study and assigned to five different treatment
Selection of treatment regimens based on shared decision-making in patients with RA

Achievement of DAS28(ESR) <2.6 at 1 year following dose and treatment manipulation

During the first year of treatment with both MTX and bDMARDs, 69 of the 81 patients (85.2%) maintained DAS28(ESR) < 2.6 and the latter increased to ≥2.6 in only two (2.5%) patients. There were no significant differences in the prevalence of maintenance of DAS28(ESR) < 2.6 among the MTX continuation, MTX dose reduction (79.0%), MTX discontinuation (80.0%) and bDMARDs dose reduction (73.9%) groups at end of year 1 and met the primary end point at period 1, whereas such prevalence was significantly lower in the bDMARD discontinuation group [52.0%, OR=0.21 (0.10–0.46), P < 0.001] than the continuation group (Fig. 2A and B).

At year 1, CDAI was ≤2.8 and SDAI was ≤3.3 in 82.7% and 86.4% of the continuation group, and 72.0% and 75.3% of the MTX dose-reduction group, 60.0% and 72.0% of the MTX discontinuation group, 72.5% and 73.9% of the bDMARD dose-reduction group, and 53.3% and 54.7% of the bDMARD discontinuation group, respectively (Supplementary Table S1, available at Rheumatology online). Furthermore, HAQ-DI ≤0.5 was comparably achieved by 84.0%, 81.7%, 80.0%, 76.8%, 73.3% of the continuation, MTX dose reduction, MTX discontinuation, bDMARD dose reduction and bDMARD discontinuation group, respectively.

The percentages of patients who maintained DAS28(ESR) at ≥2.6 and DAS28(ESR) at ≥3.2 for 1 year were similar among the five groups (Fig. 2B). However, a higher percentage of patients with DAS28(ESR) of ≥3.2 was noted in the bDMARD discontinuation group, compared with the other four groups.

Univariable followed by multivariable analysis of the factors that could predict the maintenance of DAS28(ESR) at <2.6 for 1 year identified the use of bDMARDs, lower scores of DAS28(ESR), lower serum levels of RF and less use of glucocorticoid and NSAIDs at baseline to correlate with higher prevalence of sustained DAS28(ESR) <2.6 (Supplementary Table S2, available at Rheumatology online).

After the completion of period 1, achieving DAS28(ESR) of <3.2 at year 1 and obtaining informed consent, 348 patients were treated with continuation, dose reduction or discontinuation of MTX and/or bDMARD for another 1 year (period 2, MTX: n = 133 for continuation, n = 113 for dose reduction, n = 102 for discontinuation, bDMARD: n = 206, 49, and 93, respectively, Figs 1, 3A, 3B and 4A). Among them, 88, 79 and 14 patients discontinued MTX, bDMARD and both, respectively.

Analysis of the period 2 arm of the study confirmed that 68.4%, 67.3% and 66.7% of the patients maintained DAS28(ESR) <2.6 at the end of year 2 by the MTX continuation, MTX dose reduction and MTX discontinuation groups, respectively (Fig. 3A). The pattern of achievement of DAS28(ESR) <2.6 and DAS28(ESR) <3.2 at year 2 was similar to that at 1 year among the above three MTX groups (Fig. 3C). In contrast, 74.3%, 61.2% and 55.9% patients of the bDMARD continuation, bDMARD dose reduction and bDMARD discontinuation groups maintained DAS28(ESR) <2.6 at year 2, respectively (Fig. 3B). Interestingly, the percentage of patients of the bDMARD discontinuation group who revealed DAS28(ESR) ≥3.2 was the highest among the three groups, followed by the bDMARD dose-reduction group and the bDMARD continuation group (Fig. 3C), indicating differences to MTX, and suggesting that bDMARD discontinuation might worsen disease control.

Multivariable analysis identified lower DAS28(ESR) at 1 year as a significant predictor of achieving DAS28(ESR) <2.6 at year 2 (Supplementary Table S2, available at Rheumatology online). Therefore, we assessed the impacts of bDMARD during period 1 on the discontinuation of bDMARDs during period 2. After discontinuing bDMARD at end of period 1, 58.6%, 21.1% and 68.9% of patients who continued, dose-reduced and discontinued the bDMARD during period 1, respectively, achieved DAS28(ESR) <2.6 at year 2.

There were significant differences in the percentages of patients who could achieve DAS28(ESR) <2.6 at year 2 between the dose reduction of bDMARD and continuation or discontinuation at period 1. There were no differences in DAS28(ESR) <2.6 achievement at year 2 between patients treated with TNF inhibitors or non-TNF inhibitors (Fig. 4C). Finally, although the number of subjects was small, 42.9% of the 14 drug-free patients were able to maintain DAS28(ESR) <2.6 at year 2 (Fig. 4A and B).

Safety

During period 1 of the study, AEs were observed at the rate of 14.8%, 8.1%, 8.0%, 7.2% and 9.3% in the continuation arm, MTX dose-reduction arm, MTX discontinuation, bDMARD dose reduction and bDMARD discontinuation group, respectively (Table 2). Thus, AEs tended to highly occur in the continuation group, compared with the four de-escalation groups and AEs were
|                        | Continuation | MTX dose reduction | MTX discontinuation | bDMARDs dose reduction | bDMARDs discontinuation |
|------------------------|--------------|--------------------|---------------------|------------------------|-------------------------|
| **n**                  | 81           | 186                | 25                  | 69                     | 75                      |
| **Female, n (%)**      | 65 (80.2)    | 145 (78.0)         | 20 (80.0)           | 56 (81.2)              | 54 (72.0)               |
| **Age (years)**        | 56.7 (13.2)  | 57.4 (12.4)        | 58.6 (17.6)         | 55.6 (12.2)            | 59.9 (12.2)             |
| **Disease duration (mo)** | 107.1 (82.3) | 107.3 (91.8)     | 149.8 (117.3)       | 103.2 (95.5)           | 85.6 (80.7)             |
| **Comorbidities, n (%)** |              |                    |                     |                        |                         |
| Other IMDs             | 5 (6.2)      | 15 (8.1)           | 1 (4.0)             | 7 (10.1)               | 6 (8.0)                 |
| Pre-existing lung diseases | 2 (2.5)    | 11 (5.9)           | 1 (4.0)             | 8 (11.6)               | 6 (8.0)                 |
| Bone and mineral metabolism | 4 (4.9)    | 15 (8.1)           | 4 (16.0)            | 4 (5.8)                | 5 (6.7)                 |
| Cardiovascular diseases | 7 (8.6)      | 13 (7.0)           | 2 (8.0)             | 6 (8.7)                | 5 (6.7)                 |
| **MTX (mg)**           | 10.2 (2.3)   | 11.4 (2.7)         | 8.8 (4.0)           | 10.3 (3.3)             | 11.0 (3.6)              |
| **GCs, n (%)**         | 6 (7.4)      | 14 (7.5)           | 2 (8.0)             | 2 (2.9)                | 6 (8.0)                 |
| **Prior bDMARDs administration (mo)** | 43.9 (30.0) | 34.4 (23.2)       | 39.6 (23.0)         | 34.9 (27.9)            | 30.1 (25.3)             |
| **Prior bDMARDs used, n (%)** |            |                    |                     |                        |                         |
| One                    | 64 (79.0)    | 130 (69.9)         | 18 (72.0)           | 60 (87.0)              | 64 (85.3)               |
| Two                    | 15 (18.5)    | 35 (18.8)          | 3 (12.0)            | 8 (11.6)               | 9 (12.0)                |
| >Three                 | 2 (2.5)      | 21 (11.3)          | 4 (16.0)            | 1 (1.4)                | 2 (2.7)                 |
| **bDMARD, n (%)**      |              |                    |                     |                        |                         |
| TNF                    | 67 (82.7)    | 136 (73.1)         | 14 (56.0)           | 52 (75.4)              | 61 (81.3)               |
| TCZ                    | 10 (12.3)    | 35 (18.8)          | 8 (32.0)            | 10 (14.5)              | 10 (13.3)               |
| ABT                    | 4 (4.9)      | 15 (8.1)           | 3 (12.0)            | 7 (10.1)               | 4 (5.3)                 |
| **DAS28(ESR)**         | 1.7 (0.5)    | 1.7 (0.6)          | 1.8 (0.6)           | 1.7 (0.6)              | 1.8 (0.5)               |
| **DAS28(ESR) <2.6 period (mo)** | 24.8 (22.4) | 18.9 (14.2)       | 15.4 (14.4)         | 16.3 (12.7)            | 19.9 (21.9)             |
| **CDAI**               | 1.1 (1.3)    | 1.3 (1.8)          | 1.6 (2.6)           | 1.2 (1.4)              | 0.8 (1.2)               |
| **SDAI**               | 1.1 (1.3)    | 1.3 (1.8)          | 1.6 (2.6)           | 1.2 (1.5)              | 0.8 (1.2)               |
| **TJC**                | 0.1 (0.4)    | 0.1 (0.4)          | 0.0 (0.2)           | 0.1 (0.3)              | 0.0 (0.2)               |
| **SJC**                | 0.0 (0.2)    | 0.1 (0.4)          | 0.2 (0.7)           | 0.0 (0.2)              | 0.1 (0.4)               |
| **PiGA (mm)**          | 7.4 (10.8)   | 8.2 (11.4)         | 9.8 (18.9)          | 9.3 (13.1)             | 4.9 (9.0)               |
| **PnPain (mm)**        | 6.9 (10.4)   | 7.5 (12.5)         | 8.4 (16.5)          | 6.0 (8.5)              | 3.8 (10.9)              |
| **PhGA (mm)**          | 1.9 (3.3)    | 2.1 (4.0)          | 3.7 (8.9)           | 1.4 (2.7)              | 1.7 (3.2)               |
| **CRP (mg/dL)**        | 0.0 (0.1)    | 0.1 (0.1)          | 0.0 (0.0)           | 0.0 (0.0)              | 0.1 (0.2)               |
| **ESR (mm/h)**         | 12.0 (8.0)   | 12.2 (9.1)         | 12.7 (9.0)          | 12.3 (8.1)             | 13.2 (8.3)              |
| **HAQ-DI**             | 0.2 (0.5)    | 0.2 (0.4)          | 0.3 (0.6)           | 0.2 (0.4)              | 0.1 (0.3)               |
| **Steinbrocker’s classification stage, n (%)** |            |                    |                     |                        |                         |
| I                      | 21 (25.9)    | 37 (19.9)          | 5 (20.0)            | 17 (24.6)              | 21 (28.0)               |
| II                     | 35 (43.2)    | 98 (52.7)          | 8 (32.0)            | 32 (46.4)              | 39 (52.0)               |
| III                    | 12 (14.8)    | 24 (12.9)          | 5 (20.0)            | 7 (10.1)               | 8 (10.7)                |
| IV                     | 13 (16.0)    | 27 (14.5)          | 7 (28.0)            | 13 (18.8)              | 7 (9.3)                 |
| **RF, %positivity and means (U/mL)** | 55.1 (73.0) | 51.7 (47.2)       | 69.3 (70.5)         | 59.7 (49.6)            | 59.4 (53.1)             |
| **ACPA, %positivity and means (U/mL)** | 70.7 (199.8) | 72.7 (156.6) | 81.0 (220.9) | 78.8 (210.3) | 75.4 (180.6) |

Continuous data are expressed as means (s.d.) and categorical data are as number (%). ABT: abatacept; ACPA: anti-citrullinated peptide antibody; bDMARDs: biological disease-modifying antirheumatic drug; CDAI: clinical disease activity index; DAS28: disease activity score 28; GCs: glucocorticoids; HAQ-DI: HAQ-Disability Index; IMD: immune-mediated disease; PhGA: physician global assessment; PiGA: patient global assessment; PiPain: patient pain; SDAI: simplified disease activity index; SJC: swollen joint count; TCZ: tocilizumab; TJC: tender joint count.
comparably observed among the four de-escalation groups. Marked differences in SAEs, discontinuation by the patients, and deaths were not observed among the five groups.

During period 2, AEs occurred in 15.6%, 5.7% and 10.1% of the patients of the continuation group, including the dose reduction of MTX and/or bDMARD group, MTX discontinuation group and bDMARD discontinuation group, respectively (Table 2). The rate of AEs, most notably infections, was higher in the continuation/de-escalation group compared with the MTX- and/or bDMARD-discontinuation group.

### Discussion

The shared decision-making on the selection of treatment regimens can support conversations and discussions that lead to better informed decisions congruent with the needs of patients and physicians. Such decisions are more likely to be followed through, often leading to more favorable health outcomes, which has been also reported in patients with RA [24–28]. It is noteworthy that 81.4% of our patients who achieved sustained remission selected dose reduction or discontinuation of MTX or bDMARD. This tendency can be partly supported by a Canadian study on perspectives of patients and rheumatologists for tapering DMARDs in RA [29]. Furthermore, approximately half (48.4%) of the participants selected MTX dose reduction or discontinuation. Although our patients had to pay 30% of all their medical fees, including pharmaceutical purchases, according to the Japanese government-supported medicare system, about half of them elected to de-escalate MTX, which is in fact much cheaper than bDMARDs, suggesting that safety concerns related to MTX raised by the patients

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**Fig. 2** Disease activity and achievement of DAS28(ESR) < 2.6 at end of period 1

(A) Allocation to the different treatment groups at baseline and achievement of DAS28(ESR) < 2.6 (%) after treatment for 1 year. Odds ratio and significant differences were assessed using logistic regression analysis. \( P < 0.05 \). (B) Distribution of disease activity based on DAS28(ESR) for the different treatment groups at the end of year 1.
and physicians and adherence to MTX therapy, in addition to the preferable efficacy of bDMARD, might be beyond the economic burden of bDMARDs in our patients. Actually, it is surprising that retention rate of the treatments for 1 year during period 1 was 97.9% and that only 9 of 436 patients were withdrawn from the study.

After one year of treatment with different regimens (i.e. period 1 of the study), significant differences in maintaining DAS28(ESR) < 2.6 for 1 year were observed between patients in the continuation of MTX and bDMARD group (85.2%) and those in the bDMARD discontinuation group (52.0%). Thus, withdrawal of bDMARDs seems to weaken disease control within 1 year. Alternatively, the results could be interpreted to show that DAS28(ESR) < 2.6 was maintained in 52.0%, i.e. more than half of the patients, who discontinued bDMARD for 1 year. However, the percentage of patients who maintained DAS28(ESR) < 2.6 was comparable among the continuation, MTX dose-reduction, MTX discontinuation and bDMARD dose-reduction group.

The proportion of patients with HAQ-DI ≤ 0.5 at year 1 was also comparable among the groups. These results suggest that MTX can be satisfactorily withdrawn after achieving sustained remission, upon request by the patient. Our multivariable analysis indicated that patients with low disease activity and RF levels induced by bDMARD-based regimens have more chances to de-escalate MTX.

At enrolment into period 2, comparable percentages of patients elected to continue (38.2%), dose-reduce (32.5%) and discontinue (29.3%) MTX at the end of year 1, whereas the majority of patients preferred to continue the bDMARD (59.2%). It is interesting that the preferences through shared decision-making between patients and physicians were continuation of the bDMARD rather than MTX. This could reflect the desire to achieve a balance between safety and efficacy despite economic burden. At the end of period 2 (i.e., year 2), almost identical proportions of patients [MTX continuation (68.4%), MTX dose reduction (67.3%) and MTX discontinuation
were able to maintain DAS28(ESR) <2.6, indicating that MTX withdrawal did not affect disease activity when disease control was well achieved by MTX and bDMARDs.

In contrast, there were significant differences in the rates of patients who could achieve DAS28(ESR) <2.6 at year 2 among the bDMARD continuation (74.3%), dose reduction (61.2%) and discontinuation (55.9%) groups, suggesting that withdrawal of bDMARDs seems to jeopardize the process of disease control [15–18]. However, the results could be interpreted as more than half (55.9%) of the patients who discontinued bDMARDs continued to maintain DAS28(ESR) <2.6 for another 1 year. Interestingly, successful discontinuation of the bDMARD in period 2 did not depend on the bDMARD regimen in period 1 and there were no significant differences between those with and without TNF inhibitors. However, discontinuation of the bDMARD during period 2 depended significantly on the use of bDMARD during period 1; continuation (58.6%), dose reduction (21.1%) and discontinuation (68.9%), indicating that the dose reduction of the bDMARD did not add preferable impacts on its subsequent withdrawal and that the bDMARD could be stopped without dose reduction or extension of the bDMARD treatment interval. Although the bDMARD dose reduction may be an easier strategy than stopping it, one should pay particular attention to immunogenicity, as an increase in anti-drug antibodies is often observed in patients on lower doses of bDMARDs [30].

The concept that only treatment de-escalation followed by treatment holiday leads to real cure of the disease is important [31]. Our study included only 14 drug-free patients, including glucocorticoid, MTX, bDMARDs and other csDMARDs, and 42.9% of these patients had DAS28(ESR) <2.6 at year 2. Although the number of patients who discontinued bDMARDs was small, this finding suggests the importance of shared decision-making in patients with RA.
patients was somewhat small, the study has entered in the period 3 in order to assess more patients with drug-free remission as well as long-term safety of de-escalation of the treatment regimens. The cost-effectiveness in patients continuously treated with bDMARDs rather than MTX is another issue to be addressed and should be estimated in future. In terms of patients’ characteristics, comorbidities of liver and renal diseases and weight/BMI were not available, although these variables could have confounded the choice of the de-escalation strategy.

The main limitation of the study was the observational design and the five arms of treatment regimens were selected by shared decision-making between patients and physicians. Blinded randomization including the discontinuation arms was not permitted by inspection in the Japan AMED mainly due to ethical reasons; the discontinuation of MTX in RA patients results in an increase in the flare and the restitution of MTX to the situation before the discontinuation may not be satisfied. Because dose reduction and/or discontinuation of any drug is associated with risks as well as benefits, informed consent from each patient is required even in the case of de-escalation. Finally, there are several concerns about shared decision-making; for example, many patients do not want to participate in treatment decision-making due to uncertainties about clinical care, feasibility of providing detailed information about potential risks and treatment options [22, 25, 26].

Taken together, in the real-world FREE-J study, patients with RA who showed sustained remission in response to treatment with MTX and bDMARDs were divided into five treatment groups; continuation of the same treatment, MTX dose reduction, MTX discontinuation, bDMARD dose reduction and bDMARD discontinuation. Based on patient–physician shared decision-making, 81.4% of the patients elected de-escalation of the treatment while 48.4% selected de-escalation of MTX. During both period 1 and period 2, we found comparable disease control among continuation, dose reduction and discontinuation of MTX, suggesting that MTX can be satisfactorily withdrawn after securing disease control. In contrast, more patients who discontinued bDMARD showed failure of disease control compared with those who continued the same, although more than half of the patients satisfactorily discontinued bDMARD after period 1. Moreover, because withdrawal of MTX and/or bDMARD was associated with numerically lower incidence of AEs, particularly infections, we must weigh the risks and benefits when we decide to de-escalate medications after the achievement of sustained remission. The take-home message is

### Table 2: Adverse events during period 1 and period 2

|                      | 1st period | 2nd period | P-value |
|----------------------|------------|------------|---------|
| **Continuation**     | 81         | 186        |         |
| **MTX dose reduction** | 69         | 5          | 0.051   |
| **MTX withdrawal**   | 75         | 17         | 0.461   |
| **bDMARD dose reduction** | 167       | 26         | 0.014   |
| **bDMARD withdrawal** | 28         | 8          | 0.001   |

| **AEs** | **SAEs** | **Discontinuations due to SAEs** | **AEs of special interest** |
|---------|----------|-------------------------------|---------------------------|
| 12 (14.6%) | 1 (1.2%) | 0 (0%)                        | 0 (0%)                    |
| 15 (18.1%) | 1 (1.2%) | 0 (0%)                        | 0 (0%)                    |
| 16 (20.0%) | 1 (1.2%) | 0 (0%)                        | 0 (0%)                    |
| 16 (20.0%) | 1 (1.2%) | 0 (0%)                        | 0 (0%)                    |

| **Number of patients** | **Number of events** |
|------------------------|----------------------|
| 81                     | 12 (14.8%)           |
| 186                    | 15 (8.1%)            |
| 69                     | 2 (0.9%)             |
| 75                     | 1 (0.5%)             |

| **Death** | **Number of patients** | **Number of events** |
|-----------|------------------------|----------------------|
| 1 (1.2%)  | 1 (0.5%)               | 0 (0%)               |

| **AEs of special interest** | **Number of patients** | **Number of events** |
|-----------------------------|------------------------|----------------------|
| Malignancy                  | 0                      | 0 (0%)               |
| Autoimmune events           | 2                      | 1 (0.5%)             |
| Infections                  | 16                     | 4 (0.9%)             |

| **AEs of special interest** | **Number of patients** | **Number of events** |
|-----------------------------|------------------------|----------------------|
| Death                       | 1                      | 0 (0%)               |

Number of patients; bNumber of events; AEs: adverse events; bDMARDs: biological disease-modifying antirheumatic drug; SAEs: serious adverse events.
that de-escalation of MTX, rather than bDMARD, was the preferred option selected by RA patients who showed sustained remission in response to MTX/ bDMARD, based on physician/patient shared decision-making. We plan to apply the same tapering strategy in the treatment of patients with other rheumatic diseases.

Acknowledgement

The authors thank all the medical staff in all participating institutions for providing the data, especially Ms Chizuko Ishihara and Hiroko Yoshida for the excellent data management in the FREE-J registry. We also thank Dr Kazuyoshi Saito at Tobata General Hospital; Dr Kentaro Hanami and Dr Shunsuke Fukuyo at Wakamatsu Hospital of the University of Occupational and Environmental Health; Dr Keisuke Nakatsuka at Fukuoka Yutaka Hospital, and all staff members at Kitakyushu General Hospital and Shimonoseki Saiseikai Hospital for their engagement in data collection of the FIRST registry. All authors were involved in the drafting and critical revision of the manuscript, and all authors approved the final version to be published. Y.T. and A.Y. had full access to all of the data in the study and Y.T. unified the study and version to be published. Y.T. and A.Y. had full access to all of the data in the study Y.T. and A.Y. takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: Y.T. and A.Y. Acquisition of data: all authors. Analysis and interpretation of data: Y.T. and A.Y. Acquisition of data: all authors. Analysis and interpretation of data: Y.T. and A.Y.

Funding: This work was supported in part by a Grant-In-Aid for Japan Agency for Medical Research and Development [#15ek0410016h0002].

Disclosure statement: Y.T. has received speaking fees and/or honoraria from Gilead Sciences Co. Ltd; Abbvie GK, Behringer-Ingelheim Co. Ltd; Eli Lilly Co. Ltd; Astellas Co. Ltd; Bristol-Myers Squibb Co. Ltd; GlaxoSmithKline K.K.; Chugai Pharmaceutical Co., Ltd; Mitsubishi Tanabe Pharma Co., Ltd; Daiichi Sankyo Co., Ltd; Chugai Pharmaceutical Co., Ltd; and Astra-Zeneca Co., Ltd, and has received research grants from Asahi-Kasei Pharma Co., Ltd; Abbvie GK, Chugai Pharmaceutical Co., Ltd; Mitsubishi-Tanabe Pharma Co., Ltd; Eisai Co., Ltd; Takeda Pharmaceutical Co., Ltd; Corona Co., Ltd; and Daiichi-Sankyo Co., Ltd; Kowa Co., Ltd; Behringer-Ingelheim Co., Ltd.

Y.K. has received speaking fees and/or honoraria from Gilead Sciences Co. Ltd; Abbvie GK, Behringer-Ingelheim Co. Ltd; Eli Lilly Co. Ltd; Mitsubishi-Tanabe Pharma Co., Ltd; Chugai Pharmaceutical Co., Ltd; Eisai Co., Ltd; Astellas Co. Ltd; Bristol-Myers Co. Ltd; and Astra-Zeneca Co., Ltd, and has received research grants from Asahi-Kasei Pharma Co., Ltd; Abbvie GK, Chugai Pharmaceutical Co., Ltd; Mitsubishi-Tanabe Pharma Co., Ltd; Eisai Co., Ltd; Takeda Pharmaceutical Co., Ltd; Corona Co., Ltd; Daiichi-Sankyo Co., Ltd; Kowa Co., Ltd; Behringer-Ingelheim Co., Ltd.

T.T. has received research grants from Asahi Kasei Pharma Corp., AbbVie GK, AYUMI Pharmaceutical Corporation, Eisai Co., Ltd, Ono Pharma Co., Ltd, Mitsubishi Tanabe Pharma Co., Diaichi Sankyo Co., Ltd, Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan K.K, Nippon Kayaku Co., Behringer-Ingelheim Co., Ltd, UCBI Japan; DNA Chip Research Inc.; and received speaking fees from AbbVie GK., Eisai Co., Ltd, Gilead Sciences, Inc., Mitsubishi Tanabe Pharma Co., Diaichi Sankyo Co., Ltd, Chugai Pharmaceutical Co, Ltd, Eli Lilly Japan K.K, Bristol-Myers K.K, Novartis Pharma K.K., Pfizer Japan Inc., SRL, Inc., AYUMI Pharma. Co, Janssen Pharmaceutical K.K., UCB Japan, Sanofi. K.K.; and consultancy fees from Astellas Pharma Inc., AbbVie GK., Gilead Sciences, Inc., Glaxo SimthKline K.K., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co, Ltd, Pfizer Japan Inc., Eli Lilly Japan K.K, Novartis Pharma K.K., Janssen Pharmaceutical K.K.

K.A. has received speaking fees and/or honoraria from Abbvieve GK, Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd, Eli Lilly Co. Ltd, Eisai Co. Ltd, Gilead Sciences Co. Ltd, GlaxoSmithKline K.K., Janssen Pharmaceutical K.K., Novartis Pharma K.K., Pfizer Japan Inc., and has received research grants from Asahi-Kasei Pharma Co. Ltd and Chugai Pharmaceutical Co. Ltd.

A.K. has received grants from AbbVie, Actelion, Asahi Kasei, Astellas, AYUMI, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Kyowa Hakko Kirin, MSD, Neopharma, Novartis, ONO, Sanofi, Taisho, Takeda Science Foundation, and Teijin and speaking fees from AbbVie, Actelion, Asahi Kasei, Astellas, Boehringer Ingelheim, Celltrion, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, GSK, Janssen, Kowa, MedPeer, Mitsubishi Tanabe, Novartis, ONO, Pfizer, Taisho, and Takeda.

M.M. has received personal fees from Chugai Pharmaceutical, grants from Chugai Pharmaceutical and grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

N.N. has received grants and personal fees from Chugai, and Eisai, personal fees from Mitsubishi Tanabe, AbbVie GK, Novartis, Astellas, Eli Lilly, and patents for tocilizumab with royalties paid by Chugai.

T.A. has received research grants and/or honoraria from Gilead Sciences Inc., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd, Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd, Pfizer Inc., AbbVie Inc., Eisai Co. Ltd, Daiichi-Sankyo Co. Ltd, Bristol-Myers Squibb Co., UCB Japan Co. Ltd, Eli Lilly Japan K.K, Otsuka Pharmaceutical Co., Ltd, AstraZeneca plc, Novartis Pharma K.K., Nippon Boehringer Ingelheim Co., Ltd, Alexion Inc.

T.S. has received speaking fees and/or honoraria from AbbVie GK, Behringer-Ingelheim Co. Ltd; Eli Lilly Co. Ltd; Mitsubishi-Tanabe Pharma Co. Ltd; Chugai Pharmaceutical Co. Ltd; Eisai Co. Ltd; Astellas Co. Ltd; Bristol-Myers Co. Ltd; and has received research grants from Asahi-Kasei Pharma Co. Ltd; Chugai Pharmaceutical Co. Ltd; Mitsubishi-Tanabe Pharma Co. Ltd; Astellas Co. Ltd; and Bristol-Myers Co. Ltd.
K.O. has received research grants and/or speaker’s fee from AbbVie, Actelion, Asahi-Kasei Pharma, Astellas, AYUMI, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Janssen, JB, Mitsubishi Tanabe, Nippon Kayaku, Nippon Shinyaku, Novartis, Sanofi and Takeda.

K.F. has received speaking fees and/or honoraria from Gilead Sciences Co. Ltd; Abbvie GK, Behringer-Ingelheim Co. Ltd; Eli Lilly Co. Ltd; Mitsubishi-Tanabe Pharma Co. Ltd; Chugai Pharmaceutical Co. Ltd; Amgen Co. Ltd; Eisai Co. Ltd; Astellas Co. Ltd; Bristol-Myers Co. Ltd and has received research grants from Asahi-Kasei Pharma Co. Ltd; Abbvie GK, Chugai Pharmaceutical Co. Ltd; Mitsubishi-Tanabe Pharma Co. Ltd; Eisai Co. Ltd; Tsumura Co. Ltd; Bristol-Myers Co. Ltd; Eli Lilly Co. Ltd.

Y.F. has received consultant fees from NTT date MSE Co., occupational physician fee from The Loft Co. Ltd, Asahi Shimbun Co., conference participation fee from Sompo Health Support Inc, Chugai, Asahi-Kasei, IBEC, Mitsubishi Res Ins., speaking fee from Astra Zeneca KK, Pfizer Japan Inc., research grants from Saibugas Co. Ltd, Nippon Steel Co., Hitachi System Ltd.

K.N. has received speaking fees from Bristol-Myers, Sanofi, AbbVie, Eisai, Eli Lilly, Chugai, Pfizer, Takeda and Mitsubishi-Tanabe, and research grants from Mitsubishi-Tanabe and Eisai.

S.H. has received speaking fees, consultancy fees and/or research grant from AbbVie, Asahi-Kasei Pharma, Astellas, Ayumi, Celgene, Chugai, Eisai, Gilead, GlaxoSmithKline, Janssen, Kyorin, Eli Lilly, Novartis, Pfizer, Sanofi, Tanabe-Mitsubishi, UCB.

S.N. has received speaking fees, and/or honoraria from Bristol-Myers, GlaxoSmithKline, Chugai, Sanofi, Pfizer, Astellas, Asahi-kasei, Boehringer Ingelheim and has received research grants from Mitsubishi-Tanabe, Novartis and MSD. The other authors have declared no conflict of interest.

Data availability statement
Data cannot be shared for ethical/privacy reasons.

Supplementary data
Supplementary data are available at Rheumatology online.

References
1 Smolen JS, Aletaha D, Barton A et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.
2 Smolen JS, Landewé RBM, Bijlsma JWJ et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–99.
3 Tanaka Y. Rheumatoid arthritis. Inflamm Regen 2020;40:20–8.
4 Weinblatt ME, Bathon JM, Kremer JM et al. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and longstanding rheumatoid arthritis. Arthritis Care Res 2011;63:373–82.
5 Keystone EC, Breedveld FC, van der Heijde D et al. Long-term effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. J Rheumatol 2014;41:5–14.
6 Tanaka Y. Next stage of RA treatment: TNF-inhibitor-free remission will be a possible treatment goal? Ann Rheum Dis 2013;72:i124–i127.
7 Tanaka Y, Hirata S, Saleem B, Emery P. Discontinuation of biologics in patients with rheumatoid arthritis. Clin Exp Rheumatol 2013;31(4 Suppl 78):S22–7.
8 Tanaka Y. Stopping tumour necrosis factor-targeted biological DMARDs in rheumatoid arthritis. Rheumatology 2016;55:ii15–ii22.
9 Tanaka Y. Rheumatoid arthritis: DMARD de-escalation – let the patient guide you. Nat Rev Rheumatol 2017;13:637–8.
10 Tanaka Y, Takeuchi T, Mimori T et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis, RRR (remission induction by remicade in RA) study. Ann Rheum Dis 2010;69:1286–91.
11 Tanaka Y, Hirata S, Kubo S et al. Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. Ann Rheum Dis 2015;74:389–95.
12 Atsumi T, Tanaka Y, Yamamoto K et al. Clinical benefit of 1-year certolizumab pegol (CZP) add-on therapy to methotrexate treatment in patients with early rheumatoid arthritis was observed following CZP discontinuation: 2-year results of the C-OPERA study, a phase III randomised trial. Ann Rheum Dis 2017;76:1348–56.
13 Bouman CA, van Herwaarden N, van den Hoogen FH et al. Long-term outcomes after disease activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-year data of the DRESS study - a randomised controlled pragmatic non-inferiority strategy trial. Ann Rheum Dis 2017;76:1716–22.
14 den Broeder N, Bouman CAM, Kievit W et al. van der Maas A, den Broeder AA. Three-year cost-effectiveness analysis of the DRESS study: protocolised tapering is key. Ann Rheum Dis 2019;78:141–2.
15 Edwards CJ, Fautrel B, Schulze-Koops H, Huizinga TWJ, Kruger K. Dosing down with biologic therapies: a systematic review and clinicians’ perspective. Rheumatology 2017;56:1847–56.
16 Cavalli G, Favalli EG. Biologic discontinuation strategies and outcomes in patients with rheumatoid arthritis. Expert Rev Clin Immunol 2019;15:1313–22.
17 Tanaka Y, Smolen JS, Jones H et al. The effect of deep or sustained remission on maintenance of remission after...
dose reduction or withdrawal of etanercept in patients with rheumatoid arthritis. Arthritis Res Ther 2019;21:164.

18 Schett G, Emery P, Tanaka Y et al. Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. Ann Rheum Dis 2016;75:1428–37.

19 van Mulligen E, de Jong PHP, Kuijper TM et al. Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: first-year results of the randomised controlled TARA study. Ann Rheum Dis 2019;78:746–53.

20 Friedman B, Cronstein B. Methotrexate mechanism in treatment of rheumatoid arthritis. Joint Bone Spine 2019;86:301–7.

21 Sherbini AA, Sharma SD, Gwinnutt JM, Hyrich KL, Verstappen SMM. Prevalence and predictors of adverse events with methotrexate mono- and combination-therapy for rheumatoid arthritis: a systematic review. Rheumatology 2021;60:4001–17.

22 Elwyn G, Frosch D, Thomson R et al. Shared decision making: a model for clinical practice. J Gen Intern Med 2012;27:1361–7.

23 Smolen JS, Landewé R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–50.

24 Schoemaker CG, de Wit MPT. Treat-to-target from the patient perspective is bowling for a perfect strike. Arthritis Rheumatol 2021;73:9–11.

25 Sidiropoulos P, Bounas A, Athanassiou P et al. Correlation of patient preferences to treatment outcomes in patients with rheumatoid arthritis treated with tumour necrosis factor inhibitors in Greece. Clin Rheumatol 2020;39:3643–52.

26 Barton JL, Décary S. New galaxies in the universe of shared decision-making and rheumatoid arthritis. Curr Opin Rheumatol 2020;32:273–8.

27 Desai SP, Leatherwood C, Forman M et al. Treat-to-target approach in rheumatoid arthritis: a quality improvement trial. Arthritis Care Res 2021;73:207–14.

28 Bartlett SJ, De Leon E, Orbai AM et al. Patient-reported outcomes in RA care improve patient communication, decision-making, satisfaction and confidence: qualitative results. Rheumatology 2020;59:1662–70.

29 Hazlewood GS, Loyola-Sanchez A, Bykerk V et al. Patient and rheumatologist perspectives on tapering DMARDs in rheumatoid arthritis: a qualitative study. Rheumatology 2021;60:5484.

30 Strand V, Goncalves J, Isaacs JD. Immunogenicity of biologic agents in rheumatology. Nat Rev Rheumatol 2021;17:81–97.

31 Schett G, Tanaka Y, Isaacs JD. Why remission is not enough: underlying disease mechanisms in RA that prevent cure. Nat Rev Rheumatol 2021;17:135–44.