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## Journal Article

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# BMJ Open Interruptions of biological and targeted synthetic disease-modifying antirheumatic drugs in rheumatoid arthritis: a descriptive cohort study assessing trends in patient characteristics in Switzerland

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## ABSTRACT

**Objectives** To identify differing patient characteristics at the time of stop and restart of biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in rheumatoid arthritis (RA), stratified by stop reason.

**Design** Explorative descriptive cohort study.

**Setting** Swiss Clinical Quality Management in Rheumatic Diseases (1999–2018).

**Participants** Patients with RA who stopped their first b/tsDMARD.

**Outcome measures** We assessed patient characteristics at b/tsDMARD stop and restart, stratified by stop reason (non-response, adverse event, remission, other).

**Results** Among 2526 eligible patients, most patients (38%) stopped their b/tsDMARD due to non-response. At treatment stop, most characteristics did not differ by stop reason, yet some differed significantly ( $p < 0.0001$ ), those stopping due to remission had lowest median Health Assessment Questionnaire measurements (0.1) and were least likely to use leflunomide combination therapy (3.9%) and to have fibromyalgia (6.7%). The majority of patients restarted b/tsDMARDs without changes in patient characteristics at restart. However, among the 48% of patients who restarted a b/tsDMARD after having previously stopped due to remission or other reasons, disease activity measurements were significantly worse compared with treatment stop date (mean disease activity score-erythrocyte sedimentation rate score of 2.0 at b/tsDMARD restart vs 3.5 at treatment stop ( $p < 0.0001$ )). Furthermore, we observed non-significant trends in several patient characteristics (eg, higher proportion of women (75% at b/tsDMARD restart vs 70% at treatment stop,  $p = 0.38$ ), patients with seropositivity (anti-citrullinated protein antibody positive 67% vs 58%,  $p = 0.25$ ), with family history of rheumatic diseases (24% vs 20%,  $p = 0.15$ ), osteoarthritis/arthroplasty (25% vs 20%,  $p = 0.34$ ) and the metabolic syndrome (11% vs 6%,  $p = 0.15$ )).

**Conclusion** Differences among patient characteristics across b/tsDMARD cessation strata were few. However, differences between stop and restart may have identified

## Strengths and limitations of this study

- The explorative nature of a large set of covariates in relation to biological or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) stopping and restarting is a strength of this study.
- Since we did not apply exclusion criteria, we assume our findings to be generalisable to most Caucasian patients with rheumatoid arthritis (RA).
- Our descriptive analyses of trends in patient characteristics among patients with RA stopping and restarting b/tsDMARDs do not claim causal findings but may be used to support existing evidence or generate hypotheses.
- Treatment start and stop of patients is manually entered by physicians into the database and may include random errors.
- Many variables had a high proportion of missingness, especially those with a predefined short look-back window (ie, RA disease activity measurements, health assessments).

an RA phenotype that is challenging to treat. Further research on identifying the patient characteristics predictive of successful drug holidays and the optimal time to initiate and stop a drug holiday is warranted.

## INTRODUCTION

The treatment of rheumatoid arthritis (RA) targets inflammatory processes and follows a stepwise approach.<sup>1</sup> The 2016 and 2019 RA treatment guidelines by the European Alliance of Associations for Rheumatology (EULAR) recommend adding a biological (b) or targeted synthetic (ts) disease-modifying antirheumatic drug (DMARD) to conventional synthetic (cs) DMARDs in patients who do not reach an acceptable level



of disease activity or present unfavourable prognostic markers such as anti-citrullinated peptide antibodies or early erosions.<sup>2 3</sup> However, individual b/tsDMARD therapy is frequently stopped due to non-response or partial response, with further stopping reasons including adverse events, remission or other (eg, a major surgery, breast feeding).<sup>4-7</sup> A registry study from seven European countries (including Switzerland) among 25 077 patients with RA assessed retention rates of bDMARDs (started in 2009) and variables associated with treatment cessation.<sup>8</sup> The study observed that 44.2% of patients stopped their treatment during follow-up and that RA disease activity was likely the most influential factor of treatment discontinuation. However, the study did not assess treatment restart, duration of cessation or potential changes in patient characteristics.

Thus, by following patients with RA from b/tsDMARD stop to restart, we aimed to compare patient characteristics and duration of treatment interruptions according to treatment stop reason and to identify patient characteristics related to b/tsDMARD restart. Furthermore, we aimed to describe time trends in interruptions from b/tsDMARDs to assess potential changes over time.

## METHODS

### Study design and data source

We conducted an explorative descriptive cohort study among patients with RA in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM). The SCQM is a nationwide longitudinal rheumatology registry and was established by the Swiss Society of Rheumatology in 1997.<sup>9</sup> Regulatory health authorities in Switzerland have recommended continuous monitoring with the SCQM system for all patients receiving b/tsDMARDs.<sup>10</sup> Patients come from a wide range of settings (ie, private practices as well as academic centres) and are usually enrolled prior to the initiation of therapy b/tsDMARD to allow for its nationwide monitoring.<sup>9</sup> RA diagnoses are made by a board-certified rheumatologist. The SCQM's protocol includes annual assessment of physical examination (ie, tender/swollen joint count, disease activity scores (eg, DAS28), laboratory tests (ie, erythrocyte sedimentation rate (ESR), rheumatoid factor) and several patient auto-evaluation questionnaires (eg, Health Assessment Questionnaire).<sup>9</sup> Thus, regular routine care of patients with RA is captured in SCQM. Moreover, clinical information is updated one to four times per year or every time a patient has a change in antirheumatic therapy (ie, b/tsDMARDs, csDMARDs, prednisone). Information on antirheumatic therapy is captured by the rheumatologists, who enter treatment with start and stop dates. When a treatment is stopped by the rheumatologist, the physician can choose the stop reason among the following: 'non-response', 'adverse event', 'remission' or 'other reason'. Treatment stop due to 'other reasons' is mainly due to patient preference. Further information captured in SCQM includes comorbidities and other medication use reported by the

patient (eg, osteoporosis (drugs), cardiovascular diseases and drugs, other analgesics/anti-inflammatory drugs). Thus, regular routine care of patients with RA is captured in SCQM.

### Study population

The study population comprised all patients with an RA diagnosis aged  $\geq 18$  years with a first-time b/tsDMARD (ie, abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, infliximab, golimumab, rituximab, sarilumab, tocilizumab, tofacitinib) while under observation in SCQM. We included patients who initiated a b/tsDMARD after or on their first visit in SCQM but not those who initiated a b/tsDMARD before their first visit in SCQM. Among eligible patients, we identified treatment stops using the recorded stop date of their first b/tsDMARD (referred to as the index date) between 1 January 1999 (no recorded treatment stops beforehand) and 31 December 2018. We disregarded treatment stops that had a treatment start of the same treatment on the same day since these reflect dose adjustments. An overview of the study conception is provided in [figure 1](#).

### Outcome

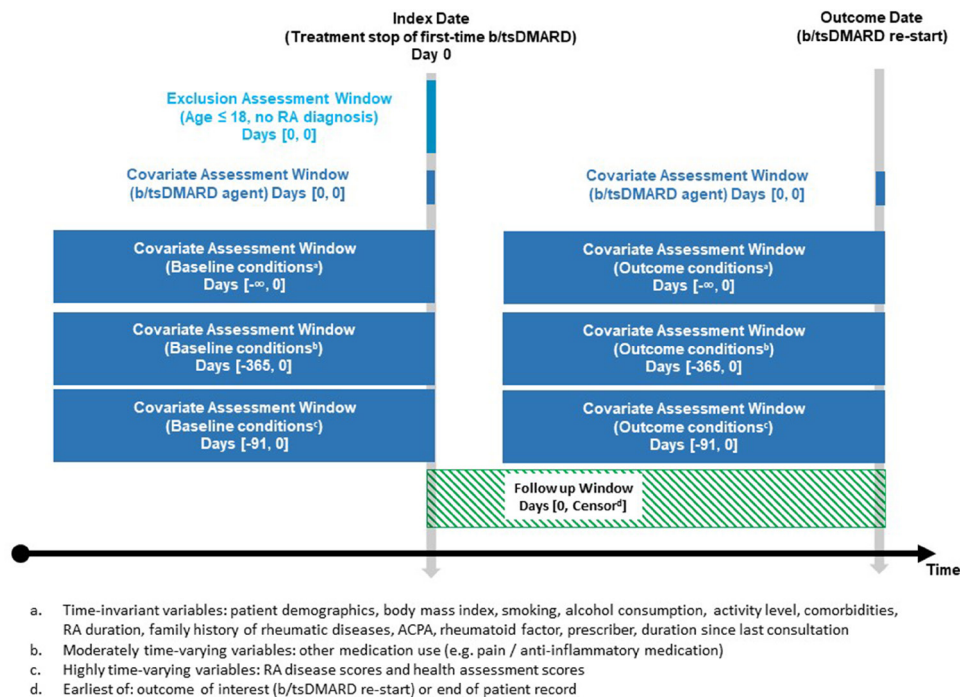
Our outcome was defined as the restart of the same or a new b/tsDMARD (ie, abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, infliximab, golimumab, rituximab, tocilizumab, tofacitinib). The date of restart is referred to as the outcome date.

### Follow-up

We followed all patients from first recorded stop date (ie, the index date) until the outcome date (ie, restart of a b/tsDMARD), censoring due to end of patient record, or end of available data (31 July 2019), whichever happened first. Thus, patients entering the study at the end of 2018 had the possibility of at least 7 months' follow-up.

### Covariates

Covariates were measured at index date, respectively, outcome date to assess changes therein, and included patient demographics, clinical information (eg, RA disease activity measures), and certain comorbidities such as cardiovascular disease or musculoskeletal disease. Missing information was handled using a *missing category*. However, to minimise missingness, we carried forward information from the nearest record within defined look-back windows (online supplemental file 1). For covariates that were not expected to change substantially over time such as chronic diseases (eg, cardiovascular disease) or lifestyle factors (eg, smoking), we used the last available information from an *ever before* lookback window. For other variables (eg, RA disease activity scores, other medication use, infections), we allowed a lookback window of 3 or 12 months depending on the assumed variability of the respective variable.



**Figure 1** Sketch of the study composition. ACPA, anti-citrullinated protein antibodies; b/tsDMARD, biological or targeted synthetic disease-modifying antirheumatic drug; RA, rheumatoid arthritis.

### Data analysis

We assessed annual proportions of patients stopping b/tsDMARDs to describe time trends of b/tsDMARD stops. All further analyses were carried out stratified by treatment cessation reasons which were recorded by the physician (ie, non-response, adverse event, remission, other reasons) or unknown reason if none was recorded. If more than one reason for treatment stop was recorded, homogenisation was conducted as indicated in online supplemental file 2.

To identify characteristics potentially related to different cessation reasons, we assessed patient characteristics at index date (ie, b/tsDMARD stop). Statistical assessment of differences among characteristics between groups was performed using two-sided statistical testing with a significance level of  $p < 0.000625$  (ie, analysis of variance for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables and  $X^2$  tests for categorical variables). The significance level of  $p < 0.000625$  was chosen given Bonferroni correction of the p value due to multiple testing (ie, by dividing the p value of 0.05 by the number of test carried out in this study (ie, 80 tests)).

We excluded the group ‘unknown reasons’ in statistical testing due to high variability among characteristics and high missingness. The population size per reason of b/tsDMARD stop was used as the denominator. Furthermore, we assessed the median duration of the first b/tsDMARD (ie, until index date) overall and stratified by cessation reason and by the combination of cessation reason and b/tsDMARD agent.

To assess differences in duration of b/tsDMARD interruptions following different cessation reasons, we

estimated Kaplan-Meier cumulative incidences of b/tsDMARD restart. Furthermore, to guide future investigators on the length of grace period to combine b/tsDMARD treatment as continuous spells, we provide the distribution of treatment-free days in the overall population. Finally, we assessed patient characteristics at outcome date (ie, b/tsDMARD restart) and compared them descriptively with the values at the index date. We also performed two-sided statistical testing with a significance level of  $p < 0.000625$  to assess statistical significance of differences in patient characteristics between the index and outcome date in the remission and other reasons strata only given observed findings. We performed two sample t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variables and  $X^2$  tests for categorical variables. We performed all analyses using SAS statistical software version V.9.4.

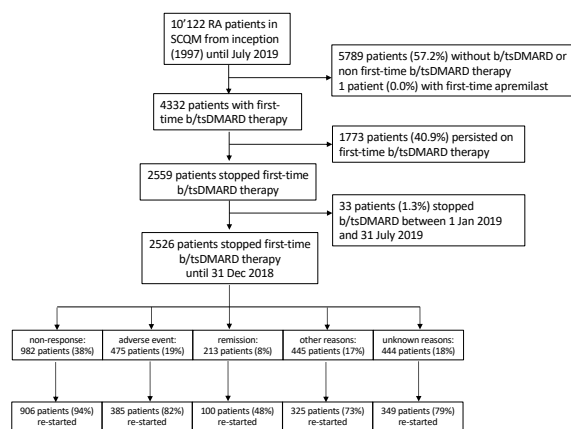
### Patient and public involvement

No patient involved.

### RESULTS

We identified 2526 patients who stopped their first-time b/tsDMARD in SCQM between 1999 and 2018 (flow chart can be seen in figure 2). Figure 3 shows the distribution of treatment stop reasons over time. From 1999 until 2010, the annual proportion of treatment stops due to unknown reasons dropped from 100% to nearly 0%. As of 2010, the proportions of treatment stop due to non-response and other reasons remained stable at around 45% and 20%, respectively. However, the proportions

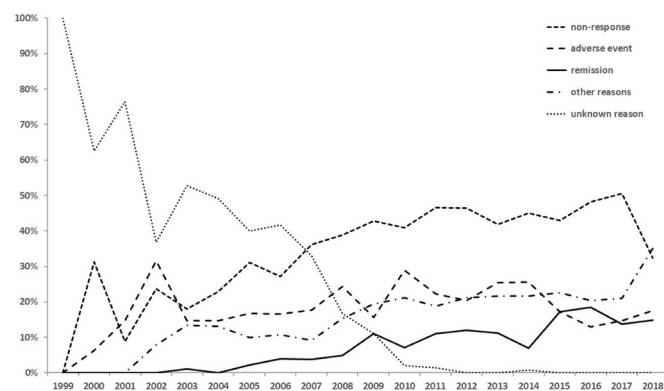




**Figure 2** Flow chart of the study population. b/tsDMARD, biological or targeted synthetic disease-modifying antirheumatic drug; RA, rheumatoid arthritis; SCQM, Swiss Clinical Quality Management in Rheumatic Diseases.

of treatment stop due to adverse events decreased (27% to 18% in 2018), while the proportions of treatment stops due to remission increased (7% to 13% in 2018). Corresponding numerical values are displayed in online supplemental file 3.

Table 1 displays selected patient characteristics stratified by treatment cessation reason. Among 2526 identified patients, 966 (38%), 470 (19%), 208 (8%), 438 (18%) and 444 (18%) patients stopped treatment due to non-response, an adverse event (majority: allergic reaction or infection), remission, other reasons (majority: patient preference) and unknown reasons, respectively. Overall, the majority of patients were women (78%) and the mean age of the study population was 56.3 years (SD: 13.5). No difference across cessation strata was observed for most patient characteristics including patient age, seropositivity, smoking status, setting, education and comorbidities such as cardiac disorders or osteoarthritis/arthroplasty. However, significant differences across cessation strata were observed. When compared with patients stopping their first b/tsDMARD due to non-response or an adverse event, patients in remission had better health



**Figure 3** Distribution of treatment cessation reasons over time.

assessment scores, and were less likely to use other RA treatment (eg, prednisone, csDMARDs especially leflunomide) and to have fibromyalgia. Moreover, while not statistically significant at the threshold of  $p < 0.000625$ , we observed the clinically relevant difference in the prevalence of recorded depression/anxiety which was least prevalent among patients stopping due to remission (7.7%) but most frequent among patients who stopped due to an adverse event (15.3%). A complete overview of all measurable patient characteristics at b/tsDMARD stop date can be found in online supplemental file 4.

We observed that the median treatment time of first-time b/tsDMARDs was 409 days overall ranging from 181 days among those stopping due to adverse events to 392 days among those stopping due to non-response, and to 891 days among those stopping due to remission (online supplemental file 5). Furthermore, the duration of first b/tsDMARD therapies as well as their proportions differed slightly between treatment cessation reasons. For example, tumour necrosis factor inhibitors (TNFi) overall had higher median treatment duration than non-TNFi bDMARDs or tsDMARDs. Among those patients who stopped due to non-response, the longest median treatment duration was observed with infliximab (514 days).

A total of 2065 (82%) patients restarted a b/tsDMARD; 906 (94%), 385 (82%), 100 (48%), 325 (74%) and 349 patients (79%) did so after having stopped due to non-response, adverse event, remission, other reasons and unknown reasons, respectively (flow chart in figure 2). The cumulative incidence of restarting b/tsDMARD therapy differed significantly between initial stop reasons (figure 4). The median time to restart (ie, median duration of treatment discontinuation) was shortest following a stop due to non-response (30 days) and longest after stopping due to remission (1597 days). Furthermore, the median duration of treatment discontinuation was 31, 98 and 212 days in patients who had stopped due to unknown reasons, adverse event and other reasons, respectively. When assessing the distribution of treatment-free days in the overall population, we observed that most patients restarted a (different) b/tsDMARD on the same day, followed by a restart on day 31 and day 1. The distribution of treatment-free days (by day) of a maximum of 100 days is provided in online supplemental file 6.

All patient characteristics at date of b/tsDMARD restart are displayed in online supplemental file 7. Patient characteristics have remained stable from date of treatment stop to restart in patients who stopped due to non-response or adverse events. However, this was not the case for patients who stopped b/tsDMARDs due to remission or other reasons. In comparison with the date of b/tsDMARD stop, RA disease activity (ie, DAS28-ESR, Rheumatoid Arthritis Disease Activity Index) was significantly worse at restart among those who stopped due to remission (table 2). Statistically non-significant trends at restart included increased proportions of women, patients with seropositivity, with family history of rheumatic diseases,

**Table 1** Selected patient characteristics at recorded stop date of b/tsDMARDs stratified by stop reason

| Patient characteristic at the index date | Non-response<br>n=966 (38%) | Adverse event<br>n=470 (19%) | Remission<br>n=208 (8%) | Other reasons<br>n=438 (17%) | P value |
|--|-----------------------------|------------------------------|-------------------------|------------------------------|---------|
| Mean age (years) (SD)                    | 56.3 (12.4)                 | 56.2 (13.5)                  | 57.8 (15.2)             | 56.1 (15.1)                  | 0.45    |
| Women (%)                                | 743 (76.9)                  | 392 (83.4)                   | 146 (70.2)              | 349 (79.7)                   | <0.001  |
| Men (%)                                  | 223 (23.1)                  | 78 (16.6)                    | 62 (29.8)               | 89 (20.3)                    |         |
| Smoker (%)                               | 212 (22.0)                  | 117 (24.9)                   | 51 (24.5)               | 97 (22.2)                    | 0.28    |
| Non-smoker (%)                           | 479 (49.6)                  | 219 (46.6)                   | 136 (65.4)              | 231 (52.7)                   |         |
| Missing smoking* (%)                     | 275 (28.5)                  | 134 (28.5)                   | 21 (10.1)               | 110 (25.1)                   |         |
| Median RA duration (IQR)                 | 6.2 (2.7–12.7)              | 6.1 (2.5–13.5)               | 5.1 (3.1–10.5)          | 7.4 (3.3–16.4)               | <0.01   |
| Missing RA duration* (%)                 | 20 (2.1)                    | 7 (1.5)                      | 5 (2.4)                 | 11 (2.5)                     |         |
| Compulsory schooling (%)                 | 254 (26.3)                  | 131 (27.9)                   | 60 (28.9)               | 115 (26.3)                   | 0.04    |
| Upper secondary level (%)                | 509 (52.7)                  | 237 (50.4)                   | 105 (50.5)              | 196 (44.8)                   |         |
| Tertiary education (%)                   | 101 (10.5)                  | 62 (13.2)                    | 31 (14.9)               | 72 (16.4)                    |         |
| Missing education* (%)                   | 102 (10.6)                  | 40 (8.5)                     | 12 (5.8)                | 55 (12.6)                    |         |
| University hospital (%)                  | 144 (14.9)                  | 61 (13.0)                    | 38 (18.3)               | 75 (17.1)                    | <0.01   |
| Other hospital (%)                       | 194 (20.1)                  | 104 (22.1)                   | 28 (13.5)               | 57 (13)                      |         |
| Office (%)                               | 623 (64.5)                  | 302 (64.3)                   | 142 (68.3)              | 303 (69.2)                   |         |
| Missing setting* (%)                     | 5 (0.5)                     | 3 (0.6)                      | 0 (0)                   | 3 (0.7)                      |         |
| Family history of rheum. dis.† (%)       | 234 (24.2)                  | 134 (28.5)                   | 42 (20.2)               | 116 (26.5)                   | 0.05    |
| No family history of rheum. dis.† (%)    | 532 (55.1)                  | 243 (51.7)                   | 125 (60.1)              | 214 (48.9)                   |         |
| Missing family history* (%)              | 200 (20.7)                  | 93 (19.8)                    | 41 (19.7)               | 108 (24.7)                   |         |
| Rheumatoid factor positive (%)           | 668 (69.2)                  | 325 (69.2)                   | 140 (67.3)              | 304 (69.4)                   | 0.92    |
| Rheumatoid factor negative (%)           | 274 (28.4)                  | 128 (27.2)                   | 60 (28.9)               | 116 (26.5)                   |         |
| Missing information* (%)                 | 24 (2.5)                    | 17 (3.6)                     | 8 (3.9)                 | 18 (4.1)                     |         |
| ACPA positive (%)                        | 512 (53)                    | 263 (56)                     | 120 (57.7)              | 256 (58.5)                   | 0.24    |
| ACPA negative (%)                        | 282 (29.2)                  | 132 (28.1)                   | 65 (31.3)               | 107 (24.4)                   |         |
| Missing information* (%)                 | 172 (17.8)                  | 75 (16)                      | 23 (11.1)               | 75 (17.1)                    |         |
| Mean DAS28-ESR (SD)                      | 3.8 (1.1)                   | 3.4 (1.3)                    | 2.0 (0.6)               | 3.1 (1.2)                    | <0.001  |
| Missing DAS28-ESR (%)                    | 700 (72.5)                  | 326 (69.4)                   | 135 (64.9)              | 331 (75.6)                   |         |
| Median HAQ score (IQR)                   | 0.9 (0.5–1.6)               | 0.8 (0.3–1.4)                | 0.1 (0–0.6)             | 0.8 (0.3–1.3)                | <0.0001 |
| Missing HAQ score (%)                    | 688 (71.2)                  | 288 (61.3)                   | 143 (68.8)              | 328 (74.9)                   |         |
| csDMARD use‡ (%)                         | 415 (43)                    | 221 (47)                     | 73 (35.1)               | 178 (40.6)                   | 0.03    |
| Methotrexate (%)                         | 258 (26.7)                  | 140 (29.8)                   | 59 (28.4)               | 126 (28.8)                   | 0.64    |
| Leflunomid (%)                           | 134 (13.9)                  | 71 (15.1)                    | 8 (3.9)                 | 39 (8.9)                     | <0.0001 |
| Prednisone use§ (%)                      | 379 (39.2)                  | 183 (38.9)                   | 30 (14.4)               | 132 (30.1)                   | <0.0001 |
| Other anti-inflammatory med.¶ (%)        | 413 (42.8)                  | 178 (37.9)                   | 72 (34.6)               | 182 (41.6)                   | 0.09    |
| Cardiac disorders (%)                    | 74 (7.7)                    | 37 (7.9)                     | 11 (5.3)                | 35 (8)                       | 0.63    |
| Metabolic syndrome** (%)                 | 46 (4.8)                    | 22 (4.7)                     | 13 (6.3)                | 24 (5.5)                     | 0.78    |
| Infections†† (%)                         | 26 (2.7)                    | 19 (4.0)                     | 8 (3.9)                 | 14 (3.2)                     | 0.54    |
| Injection site reaction†† (%)            | 0                           | 8 (1.7)                      | 0                       | 0                            | NA      |
| Cancer (%)                               | 27 (2.8)                    | 13 (2.8)                     | 11 (5.3)                | 18 (4.1)                     | 0.20    |
| Osteoarthritis or arthroplasty (%)       | 195 (20.2)                  | 93 (19.8)                    | 42 (20.2)               | 96 (21.9)                    | 0.86    |

Continued

Table 1 Continued

| Patient characteristic at the index date | Non-response<br>n=966 (38%) | Adverse event<br>n=470 (19%) | Remission<br>n=208 (8%) | Other reasons<br>n=438 (17%) | P value           |
|--|-----------------------------|------------------------------|-------------------------|------------------------------|-------------------|
| Fibromyalgia††                           | 178 (18.4)                  | 66 (14.0)                    | 14 (6.7)                | 43 (9.8)                     | <b>&lt;0.0001</b> |
| Other auto-immune disease§§ (%)          | 28 (2.9)                    | 14 (3.0)                     | 14 (6.7)                | 20 (4.6)                     | 0.03              |
| Depression/anxiety (%)                   | 105 (10.9)                  | 72 (15.3)                    | 16 (7.7)                | 51 (11.6)                    | 0.02              |

Percentages correspond to respective column totals.

All patient characteristics (including stop reason 'unknown') can be found in online supplemental file 4.

The significance level of  $p < 0.000625$  was chosen given Bonferroni correction of the p-value due to multiple testing (i.e., by dividing the p-value of 0.05 by the number of tests carried out in the study [i.e., 80 tests]) Values below this threshold are marked in bold.

\*Missing categories were not used to estimate p values per group.

†Family history includes RA, ankylosing spondylitis, psoriasis, psoriatic arthritis, chronic inflammatory bowel disease and other spondyloarthropathies (eg, reactive arthritis).

‡csDMARD use includes methotrexate, leflunomid, sulfasalazin, chloroquine, azathioprine, ciclosporin A, cyclophosphamide.

§Prednisone use includes systemic or intra-articular prednisone use.

¶Use of other pain/anti-inflammatory medications includes cyclo-oxygenase-2 inhibitors, other analgetics, conventional non-steroidal anti-inflammatory drugs, antidepressants, paracetamol, opiates, alternative treatments.

\*\*Metabolic syndrome defined as at least three out of the following four observations: hyperlipidaemia, hypertension, overweight (body mass index  $\geq 30 \text{ kg/m}^2$ ), diabetes type 1 or 2.

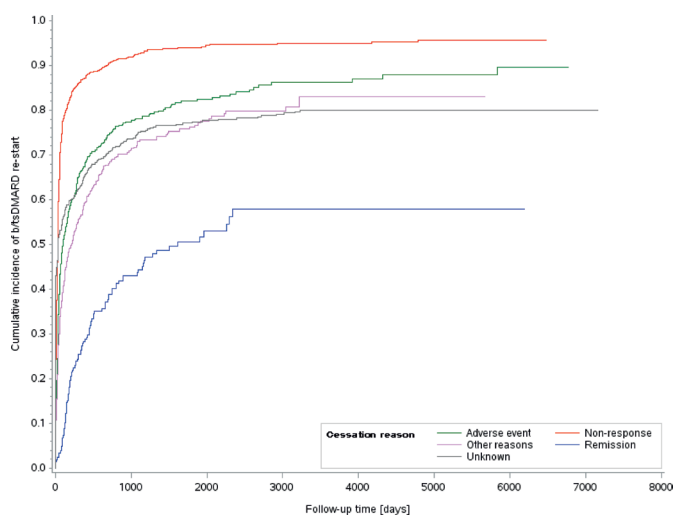
††infections and injection site reactions were captured in a 3-month lookback window only.

‡‡Fibromyalgia diagnoses include patients who have at least 10 more painful joints than swollen joints.

§§Other auto-immune diseases include Sjogren syndrome, systemic lupus erythematosus and other autoimmune diseases unspecified.

ACPA, anti-citrullinated protein antibodies; b/tsDMARD, biological or targeted synthetic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS, disease activity score; rheum. dis., rheumatic diseases; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IQR, Interquartile range; med., medication; NA, not applicable, data not shown; RA, rheumatoid arthritis; SD, Standard deviation.

recorded osteoarthritis, other auto-immune diseases, of prednisone or other anti-inflammatory drug use and of longer median RA duration in these two strata (ie, remission, other reasons). Missingness of covariates was generally lower at b/tsDMARD restart when compared with the date of treatment stop.



**Figure 4** Cumulative incidences of treatment restart stratified by cessation reasons. b/tsDMARD, biological or targeted synthetic disease-modifying antirheumatic drug.

## DISCUSSION

In this descriptive cohort study in the SCQM between 1999 and 2018, we observed 2526 patients with a recorded treatment stop of their first-time b/tsDMARD, with the majority stopping due to non-response (38%). Since 2010, trends of b/tsDMARD cessation depicted stable recordings of b/tsDMARD stops due to non-response and other reasons, a decrease in recordings of stops due to adverse events and an increase in recordings of remission. While the p values resulting from the statistical analysis reflect that patient characteristics such as health assessments, other RA treatment and prevalence of fibromyalgia differed significantly across some of the b/tsDMARD stop reasons, from a clinical perspective, the data suggest that patients who stopped due to different cessation reasons were rather similar. The majority of patients restarted b/tsDMARDs during our observation period, but only 48% of patients did so after having stopped due to remission. Time to restart of b/tsDMARDs was fastest when initially stopped due to non-response and slowest when initially stopped due to remission. At the date of treatment restart, compared with treatment stop, we observed significantly worse RA disease activity, and non-significant trends of various characteristics among patients who stopped due to remission or other reasons but not for those who stopped due to non-response or adverse events.

**Table 2** Selected patient characteristics at restart of b/tsDMARD compared with b/tsDMARD stop in patients who stopped due to remission or other reasons

| Patient characteristics               | Remission<br>n=208 | Remission<br>n=100 | P value           | Other reasons<br>n=438 | Other reasons<br>n=325 | P value |
|---------------------------------------|--------------------|--------------------|-------------------|------------------------|------------------------|---------|
|                                       | Index date         | Outcome date       |                   | Index date             | Outcome date           |         |
| Mean age (years) (SD)                 | 57.8 (15.2)        | 57.8 (15.7)        | 1.00              | 56.1 (15.1)            | 55.5 (14.8)            | 0.59    |
| Women (%)                             | 146 (70.2)         | 75 (75.0)          | 0.38              | 349 (79.7)             | 262 (80.6)             | 0.75    |
| Men (%)                               | 62 (29.8)          | 25 (25.0)          |                   | 89 (20.3)              | 63 (19.4)              |         |
| Smoker (%)                            | 51 (24.5)          | 25 (25.0)          | 0.04              | 97 (22.2)              | 65 (20)                | 0.08    |
| Non-smoker (%)                        | 136 (65.4)         | 73 (73.0)          |                   | 231 (52.7)             | 197 (60.6)             |         |
| Missing smoking (%)                   | 21 (10.1)          | 2 (2.0)            |                   | 110 (25.1)             | 63 (19.4)              |         |
| Median RA duration (IQR)              | 5.1 (3.1–10.5)     | 6.1 (3.8–11.7)     | 0.14              | 7.4 (3.3–16.4)         | 8.1 (3.5–17)           | 0.13    |
| Missing RA duration (%)               | 5 (2.4)            | 2 (2.0)            |                   | 11 (2.5)               | 7 (0.2)                |         |
| University hospital (%)               | 38 (18.3)          | 20 (20)            | 0.84              | 75 (17.1)              | 69 (21.2)              | 0.37    |
| Other hospital (%)                    | 28 (13.5)          | 15 (15)            |                   | 57 (13)                | 41 (12.6)              |         |
| Office (%)                            | 142 (68.3)         | 65 (65)            |                   | 303 (69.2)             | 214 (65.9)             |         |
| Missing setting* (%)                  | 0 (0)              | 0 (0)              |                   | 3 (0.7)                | 1 (0.3)                |         |
| Family history of rheum. dis.† (%)    | 42 (20.2)          | 24 (24.0)          | 0.15              | 116 (26.5)             | 89 (27.4)              | 0.54    |
| No family history of rheum. dis.† (%) | 125 (60.1)         | 65 (65.0)          |                   | 214 (48.9)             | 167 (51.4)             |         |
| Missing family history (%)            | 41 (19.7)          | 11 (11.0)          |                   | 108 (24.7)             | 69 (21.2)              |         |
| Rheumatoid factor positive (%)        | 140 (67.3)         | 72 (72)            | 0.57              | 304 (69.4)             | 235 (72.3)             | 0.66    |
| Rheumatoid factor negative (%)        | 60 (28.9)          | 26 (26)            |                   | 116 (26.5)             | 79 (24.3)              |         |
| Missing information (%)               | 8 (3.9)            | 2 (2)              |                   | 18 (4.1)               | 11 (3.4)               |         |
| ACPA positive (%)                     | 120 (57.7)         | 67 (67)            | 0.25              | 256 (58.5)             | 209 (64.3)             | 0.26    |
| ACPA negative (%)                     | 65 (31.3)          | 26 (26)            |                   | 107 (24.4)             | 68 (20.9)              |         |
| Missing information (%)               | 23 (11.1)          | 7 (7)              |                   | 75 (17.1)              | 48 (14.8)              |         |
| Mean DAS28-ESR (SD)                   | 2.0 (0.6)          | 3.5 (1.6)          | <b>&lt;0.0001</b> | 3.1 (1.2)              | 3.9 (1.4)              | <0.01   |
| Missing DAS28-ESR (%)                 | 135 (64.9)         | 53 (53.0)          |                   | 331 (75.6)             | 185 (56.9)             |         |
| Mean RADAI score (SD)                 | 1.4 (1.3)          | 3.5 (1.9)          | <b>&lt;0.0001</b> | 3.0 (2.1)              | 3.5 (2.2)              | 0.09    |
| Missing RADAI score (%)               | 150 (72.1)         | 72 (72.0)          |                   | 344 (78.5)             | 234 (72.2)             |         |
| Median HAQ score (IQR)                | 0.1 (0–0.6)        | 0.5 (0.1–1.0)      | 0.02              | 0.8 (0.3–1.3)          | 0.9 (0.3–1.5)          | 0.36    |
| Missing HAQ score (%)                 | 143 (68.8)         | 64 (64.0)          |                   | 328 (74.9)             | 221 (68.2)             |         |
| Median EuroQoL score (IQR)            | 77.9 (71.3–100)    | 69 (63.6–77.9)     | <0.001            | 69 (59.8–77.9)         | 68.7 (57.0–77.9)       | 0.04    |
| Missing EuroQoL score (%)             | 149 (71.6)         | 64 (64.0)          |                   | 359 (82.0)             | 241 (74.4)             |         |
| Mean SF-12 PC score (SD)              | 48.6 (7.8)         | 41.8 (9.9)         | <0.01             | 40.3 (10.3)            | 37.5 (10.2)            | 0.08    |
| Mean SF-12 MC score (SD)              | 51.5 (9.1)         | 48.6 (9.2)         | 0.20              | 47.5 (10.6)            | 45.6 (11.4)            | 0.25    |
| Missing SF-12 PC/MC score (%)         | 156 (75)           | 76 (76.0)          |                   | 352 (80.4)             | 242 (74.7)             |         |
| csDMARD use‡ (%)                      | 73 (35.1)          | 32 (32.0)          | 0.59              | 178 (40.6)             | 115 (35.4)             | 0.14    |
| Prednisone use§ (%)                   | 30 (14.4)          | 19 (19.0)          | 0.30              | 132 (30.1)             | 100 (30.8)             | 0.85    |
| Other anti-inflammatory med.¶ (%)     | 72 (34.6)          | 45 (45.0)          | 0.08              | 182 (41.6)             | 150 (46.2)             | 0.20    |
| Cardiac disorders (%)                 | 11 (5.3)           | 7 (7.0)            | 0.55              | 35 (8)                 | 28 (8.6)               | 0.76    |
| Metabolic syndrome** (%)              | 13 (6.3)           | 11 (11.0)          | 0.15              | 24 (5.5)               | 29 (8.9)               | 0.06    |
| Infections†† (%)                      | 8 (3.9)            | 5 (5.0)            | 0.63              | 14 (3.2)               | 17 (5.2)               | 0.16    |
| Osteoarthritis or arthroplasty (%)    | 42 (20.2)          | 25 (25.0)          | 0.34              | 96 (21.9)              | 78 (24.0)              | 0.50    |
| Cancer (%)                            | 11 (5.3)           | 4 (4.0)            | 0.62              | 18 (4.1)               | 15 (4.6)               | 0.73    |

Continued





Table 2 Continued

| Patient characteristics             | Remission<br>n=208 | Remission<br>n=100 | P value | Other reasons<br>n=438 | Other reasons<br>n=325 | P value |
|-------------------------------------|--------------------|--------------------|---------|------------------------|------------------------|---------|
|                                     | Index date         | Outcome date       |         | Index date             | Outcome date           |         |
| Fibromyalgia‡‡                      | 14 (6.7)           | 8 (8.0)            | 0.69    | 43 (9.8)               | 41 (12.6)              | 0.22    |
| Other auto-immune diseases§§<br>(%) | 14 (6.7)           | 8 (8.0)            | 0.69    | 20 (4.6)               | 21 (6.5)               | 0.25    |
| Depression/anxiety (%)              | 16 (7.7)           | 8 (8.0)            | 0.93    | 51 (11.6)              | 36 (11.1)              | 0.81    |

All patient characteristics can be found in online supplemental file 5.

\*Missing categories were not used to estimate p-values per group

†Family history includes RA, ankylosing spondylitis, psoriasis, psoriatic arthritis, chronic inflammatory bowel disease and other spondyloarthropathies (eg, reactive arthritis).

‡csDMARD use includes methotrexate, leflunomid, sulfasalazin, chloroquine, azathioprine, ciclosporin A, cyclophosphamide.

§Prednisone use includes systemic or intra-articular prednisone use.

¶Use of other pain/anti-inflammatory medications includes cyclo-oxygenase-2 inhibitors, other analgetics, conventional non-steroidal anti-inflammatory drugs, antidepressants, paracetamol, opiates, alternative treatments.

\*\*Metabolic syndrome defined as at least three out of the following four diagnoses: hyperlipidaemia, hypertension, overweight (body mass index  $\geq 30$  kg/m<sup>2</sup>), diabetes type 1 or 2.

††infections were captured in a 3-month lookback window only.

‡‡Fibromyalgia diagnoses include patients who have at least 10 more painful joints than swollen joints.

§§Other auto-immune diseases include Sjogren syndrome, systemic lupus erythematosus and other autoimmune diseases unspecified.

ACPA, anti-citrullinated protein antibodies; b/tsDMARD, biological or targeted synthetic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS, disease activity score; rheum. dis., rheumatic diseases; ESR, erythrocyte sedimentation rate; EuroQoL, a standardised instrument for measuring generic health status (EQ-5D); HAQ, Health Assessment Questionnaire; IQR, Interquartile range; MC, mental component; med, medication; PC, physical component; RA, rheumatoid arthritis; RADAI, Rheumatoid Arthritis Disease Activity Index; SD, Standard deviation; SF, short-form (health survey).

We observed that the median treatment time of first-time b/tsDMARDs—with the exception of stopping due to remission—fared below 2 years, which is a lot shorter than what was observed for methotrexate (around 4 years).<sup>11</sup> Furthermore, the individual first-time b/tsDMARD duration slightly differed across cessation strata. Our observation that TNFi had higher median treatment duration than non-TNFi bDMARDs is consistent with findings from RA cohorts in Switzerland, the USA and Japan, which reported higher retention rates with TNFi than with non-TNFi bDMARDs.<sup>4 7 12</sup> Among TNFi, a study performed in patients with RA in Denmark yielded increased rates of treatment response with adalimumab or etanercept within 6 or 12 months when compared with infliximab use.<sup>13</sup> However, we observed higher median treatment duration until cessation due to non-response with first-time infliximab (514 days) than with adalimumab or etanercept. Observed differences are likely due to our longer observation period also taking into account late secondary non-response.<sup>14</sup>

While we observed that most patient characteristics at treatment cessation date were not statistically different across cessation reasons, we note the clinical relevance. For example, we observed a significantly higher proportion of fibromyalgia among patients who stopped due to non-response and adverse events versus those who stopped due to remission. These findings are consistent with a recent review.<sup>15</sup> Moreover, we observed a higher

proportion of depression/anxiety among patients stopping b/tsDMARDs due to adverse events compared with those stopping due to remission. A potential association between depression/anxiety and treatment stop due to adverse events in rheumatology has not been reported to date and warrants further investigation. In particular, since there are other disease areas in which drug-related adverse events are perceived more severe in patients with depression and anxiety, for example, epilepsy.<sup>16</sup> Furthermore, the observation that leflunomide use at cessation was higher among patients with adverse events and lowest among patients in remission is partially consistent with the literature. A previous mono-centre study found that the discontinuation rate of leflunomide due to adverse drug reactions was higher compared with other csDMARDs.<sup>17</sup> However, while some studies have found a higher risk of hepatotoxicity and interstitial lung disease with leflunomide, large pharmacoepidemiological studies have failed to find an association and conclude that the observed association is likely due to channelling bias.<sup>18 19</sup> Channelling bias in this aspect means that those patient groups were rather prescribed leflunomide over other csDMARDs and that there is no causal association between hepatotoxicity and interstitial lung disease with leflunomide. While it may have been expected that university hospitals may be more likely to experiment with drug holidays than other settings, we did not observe this in our data. We neither observed the known association of higher

education and better RA outcomes.<sup>20</sup> These findings may be due to the uniqueness of Switzerland which affords an expensive healthcare system (third highest expenditure worldwide in 2019 in relation to the gross domestic product)<sup>21</sup> while the educational setting is slightly lower compared with other European countries. Only around 25% of people living in Switzerland in 2020 had tertiary education (15% of the study population).<sup>22</sup> We observed that Swiss rheumatologists follow EULAR RA treatment guidelines regarding b/tsDMARD cessation given a mean DAS28-ESR of 3.8 among those stopping due to non-response and a mean DAS28-ESR of 2.0 among those stopping due to remission.<sup>23</sup> Moreover, our results identifying that 38% of patients stopped b/tsDMARDs due to non-response and 19% due to adverse events were similar to RA cohorts in other countries.<sup>4 5 7 23</sup> Furthermore, a cohort study in SCQM suggested that bDMARDs were prescribed to patients earlier in Switzerland (ie, lower disease activity and fewer previous DMARD failures) than in other European countries.<sup>24</sup> Potentially, early b/tsDMARD therapy and wise use of treatment interruptions may give patients with RA in Switzerland a head start in RA progression prevention. Yet, missing guidance on when to restart b/tsDMARDs among those on treatment holidays is apparent when looking at a mean DAS28-ESR of 3.5 and 3.9 among those restarting after having stopped treatment due to remission and other treatment stop reasons, respectively. This observation further points towards a large discrepancy between a recommended treat-to-target strategy defined in clinical trials and translated into treatment guidance<sup>23</sup> and the real world on the other side.

The observed duration until median cumulative incidence of b/tsDMARD restart differed significantly between cessation strata with the shortest interruption among patients stopping due to non-response and adverse events and the longest among those with remission or other reasons as the stop reason. Moreover, only 48% of patients who stopped due to remission restarted a b/tsDMARD during the observation period, suggesting that >50% of patients likely achieved sustained b/tsDMARD-free remission following their first b/tsDMARD stop which indicates a tremendous success of Swiss rheumatologists.

Our findings identify patient-specific characteristics that may influence treatment restart after stopping due to remission or other reasons. Compared with date of b/tsDMARD stop, patients restarting a b/tsDMARD after an interruption due to remission or other reasons depicted an RA phenotype that is challenging to treat (statistically non-significant results). We observed non-significant trends towards a higher proportion of women, patients with seropositivity, with family history of rheumatic diseases, recorded osteoarthritis, metabolic syndrome, other auto-immune diseases, users of prednisone or other anti-inflammatory drugs, and with longer RA duration. Our findings are only partially consistent with a systematic review which suggested that patients less likely to relapse during treatment-free remission were women,

those who were younger and with shorter disease duration.<sup>25</sup> However, our results are consistent with the recent publication of the RETRO trial that assessed predictors of relapses (no comorbidities assessed).<sup>26</sup> While our observations in trends of patient characteristics were not statistically significant, they contribute towards identifying patients with RA who will experience a worsening of their RA activity in the absence of b/tsDMARDs. However, further research is needed to identify which patients are most likely to sustain remission during a treatment holiday.

Treatment holidays have been debated in rheumatology.<sup>27</sup> To date, EULAR recommends decreasing the b/tsDMARDs dose but not to stop them if a patient is in remission.<sup>3</sup> There remains substantial debate about stopping treatment after achieving remission should be recommended or avoided. This question is relevant because joint damage only visible in MRIs may continue in the absence of joint pain and swelling. To avoid worsening clinical outcomes and avoiding relapse, tapering therapy may be used. However, similar to stopping therapy, a tapering approach should weigh the benefits and risk. Not surprising, according to a systematic review, those stopping b/tsDMARDs completely are less likely to have adverse events compared with those only tapering the dose.<sup>25</sup> However, in terms of avoiding relapses, current literature seems to favour tapering the dose over stopping the treatment completely.<sup>26 28</sup> While we did not assess tapering of dosage, the proportion of patients stopping due to remission in Switzerland (8%) was similar to those in other countries such as Australia and Japan.<sup>4 11</sup> Moreover, as of 2010, we observed an increase in annual proportions of b/tsDMARD stops due to remission (up to 13% in 2018) and stable proportions of around 20% of b/tsDMARD stops due to other reasons. Moreover, the majority of patients who stopped due to other reasons indicated 'patient preference' and had generally fairly long treatment interruptions (>6 months) which may also indicate that the patient was doing well with low disease activity. This suggests that patients who stop b/tsDMARDs due to other reasons are an additional population of interest to. However, differences in patient characteristics at stop and restart were less profound than among those having stopped and restarted following remission. Given the long duration of discontinuation observed in our study as well as the frequent reporting of patients stopping b/tsDMARDs due to remission or patient/physician preference in our study and worldwide,<sup>4 5 7 23</sup> it seems important to develop a guideline on the use of drug holidays and the optimal time to initiate and stop them.

We assessed distribution of treatment-free periods to advise on grace periods for continuous treatment spells for future observational studies using b/tsDMARDs. Since treatment effect continues during short treatment-free periods, treatment recording may be slightly flawed due to manual entries, and most patients restarted b/tsDMARDs within 31 days, we suggest to allow a grace period of at least 1 month in future investigations and



to adapt this grace period depending on the treatment of interest to take into account half-lives and most used treatment intervals.

Strengths of this study include the explorative nature of a large set of covariates in relation to b/tsDMARD stopping and restarting. Furthermore, since we did not apply exclusion criteria, we assume our findings to be generalisable to most Caucasian patients with RA. While patient populations in selected European and US RA registries were shown to be comparable concerning demographics, there are differences regarding comorbidities, lifestyle factors and RA disease activity.<sup>29</sup> However, our results must be interpreted in the context of the following limitations. Our descriptive analyses of trends in patient characteristics among patients with RA stopping and restarting b/tsDMARDs do not claim causal findings but may be used to support existing evidence or generate hypotheses. Moreover, treatment start and stop of patients is manually entered by physicians into SCQM and may include random errors. Many variables had a high proportion of missingness, especially those with a predefined short lookback window (ie, RA disease activity measurements, health assessments). However, we assumed it more expedient to compare recent values of these variables of few patients than potentially outdated information of a larger proportion of patients. Finally, we likely may have missed important patient information that would have helped to better distinguish patients according to different cessation strata as well as when comparing characteristics at b/tsDMARD restart of patients. For example, we did not have imaging data to provide information on radiographic joint damage and the prevalence of depression/anxiety leading to patient distress was lower than reported in other studies in patients with RA, ranging from 8% to 35%.<sup>30</sup> Yet, we expect that data capturing between patient groups was likely non-differential yielding valid comparative results.

To conclude, this comprehensive study describes patients with RA experiencing an interruption in b/tsDMARD therapy. Increasing proportions of patients stopping b/tsDMARD therapy in recent years calls for recommendations on b/tsDMARD holidays. However, available research is scarce. Observed trends of various patient characteristics at the date of b/tsDMARD restart, in comparison with the date of treatment stop, suggest that patients with more severe RA and significant comorbidities—representing an RA phenotype that is difficult to treat—may experience a worsening of their RA activity in the absence of b/tsDMARDs. Further research on identifying the patient characteristics predictive of successful drug holidays and the optimal time to initiate and stop a drug holiday is warranted.

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