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Variation of SDAI during the dose-reduction phase is more relevant than predictive factors to evaluate the success of biologic withdrawal in rheumatoid arthritis patients in deep remission

Running head: prediction and predictability of relapse in RA patients undergoing spacing and withdrawal of biotherapy

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ABSTRACT

Objective - To determine clinical, biological and/or ultrasonographic (US) factors of relapse in rheumatoid arthritis (RA) patients in prolonged remission under biologics in a dose-reduction study.

Patients and methods - RA patients receiving the same biologic for more than 1 year, in SDAI remission for at least 1 year, were selected in an observational monocentric real-life study. The 18-months follow-up included spacing and withdrawal periods of biologic. Clinical, biological and 28 joint-US parameters were collected regularly. Relapse was defined by SDAI > 11.

Results - Fifty-three RA patients (mean age: 58 years; 72% women; median duration: 11 years) were enrolled. Forty-two received anti-cytokinic biologic targeting TNF (n = 39) or IL-6R (n = 3) and 11 were treated by abatacept. For 81%, it was the first BA. At month 18, 14 patients had completed follow-up; 2 had relapsed while 12 were still in remission. Median time to relapse was 11.8 months. In multivariate analysis, baseline factors predictive of relapse were corticosteroid intake, even at very low doses, female gender, longer disease duration and no methotrexate intake with biologic. Concerning the survival analysis, when taking also into account the factors of predictability, the main risk factor of relapse after discontinuation was an increase of SDAI > 0 during the spacing period (p = 0.03). US findings were not contributive.

Conclusion - In the context of RA in remission under biologics, variation of SDAI during the dose-reduction phase is more relevant than baseline parameters to predict success of drug withdrawal.

Key words: rheumatoid arthritis; biologic; withdrawal; spacing; remission; ultrasonography; prediction; predictability

Strengths and limitations of this study

Despite the limited size of the population studied, the originality of this prospective real-life multiparameter study using a well-defined procedure of gradual spacing and discontinuation of biologic agent (BA) in rheumatoid arthritis (RA) patients in SDAI remission for a period > 1 year is to take into account most BA available and to consider for the first time both predictive and predictable factors of relapse

Besides remission (SDAI < 3.3) for a long time (> 1 year), the present study confirms that the criteria of eligibility which are of importance for the success of biologic agent (BA) discontinuation are the combination with a synthetic DMARD, no corticosteroid intake, a short disease duration.

Deep remission based on the absence of PD-positive synovitis on US assessment of 28 joints prior to BA spacing appears to be insufficient to predict BA-free remission

The kinetic of SDAI during the spacing period seems to be more important than baseline values since the factor of predictability of relapse at BA withdrawal is a SDAI variation of > 0. In contrast, sequential assessment of joint activity by ultrasonography during the dose-reduction phase does not provide relevant information for RA management.

In the context of RA patients in SDAI remission under BA, undergoing therapeutic relief, a tight monitoring of disease activity during the dose-reduction phase of a BA appears to be relevant to identify potential relapsers; SDAI is an appropriate tool since slight variations are predictive of relapse. It seems better to consider factors of predictability during the dose-reduction phase than parameters collected just prior to this phase, regardless of their nature (clinical, biological or ultrasonographic). Thus, this study illustrates the importance to take into account the time factor rather than a single evaluation at a given time to manage remission in RA.

INTRODUCTION

In rheumatoid arthritis (RA), after achieving low disease activity (LDA) or remission (1), the goal of therapy is to maintain clinical, functional and structural remission (2). For some patients, this is possible even after the cessation of biological agent (BA)(3). The opportunity of discontinuing BA after achieving remission must be considered because of potential long-term safety issues and the economic burden associated with their expense. Furthermore, the disease can spontaneously evolve towards an inactive form. Multiple studies have investigated whether remission can be sustained after a BA is discontinued, namely, « biologic-free remission (BFR) »(3).

The European League Against Rheumatism (EULAR) 2012 guidelines (4) suggest that we can consider tapering BA. Determining the patient profile associated with a high chance of sustained remission after the cessation of BA is of great importance to avoid disease flares. For this purpose, two definitions of remission have been proposed, either the Boolean definition or a score of the Simplified Disease Activity Index (SDAI) < 3.3 (5, 6). However, the majority of studies did not use these definitions for eligibility to BA spacing or withdrawal. Indeed, in most reports, Disease Activity Score on 28 joints (DAS28) was used to select patients for withdrawal of BA in RA patients having achieved remission (7).

For patients with long-standing RA, the discontinuation of TNF-inhibitors after sustained remission has been shown to be possible in some cases. However, high flare rates have been documented in other studies. For these patients, biologic dose-reduction or spacing regimen followed by secondary withdrawal may be preferable instead of sudden discontinuation (3).

According to several studies, it appears that the criteria for spacing the administration of BA in RA patients in remission are not consensual and that we lack validated data. In this respect, a systematic review of studies addressing predictors of successful dose reduction or discontinuation of BA in RA shows that there is no consistent predictor (7).

To respect EULAR recommendations, we introduced standardized practices in our rheumatology department, in routine care, several years ago. Spacing and then discontinuation of BA is performed in RA patients in remission according to 2011 ACR-EULAR criteria (6).

The general objective of this real-life, prospective study was to define strict eligibility criteria for BA spacing/withdrawal in long-standing RA patients in remission. The specific objectives were (i) to define the rate of relapse during the spacing and withdrawal periods in a RA population; (ii) to identify predictive/predictable factors of relapse during the withdrawal phase of BA, and (iii) to determine whether duration and degree of clinical remission as well as US findings at time of BA spacing influenced the achievement of BA withdrawal.

PATIENTS AND METHODS

Study design

This prospective real life study comprised an inclusion visit and two phases (Figure 1).

Patients

In this study were enrolled all RA patients treated by biologic agent (BA) between 2012 and 2014, in the rheumatology department of Rouen University Hospital. BA were infliximab, etanercept, adalimumab, abatacept, certolizumab, and tocilizumab. Golimumab was not considered since it was introduced more recently. Rituximab was not relevant for such a strategy of spacing/withdrawal. Patients with subcutaneous treatment were selected at annual follow-up visits in the ambulatory care unit. Patients with intravenous BA were selected in the immunotherapy unit of the department.

Inclusion criteria

They comprised RA patients (older than 18 years), fulfilling ACR/EULAR 2010 criteria, in remission defined as a DAS28 < 2.6 for at least 12 months, and receiving the same BA for at least 1 year. Prior to initiation of spacing, a SDAI <3.3 was required (6). Patients taking prednisone (or equivalent) at a dose > 5mg/day or with structural evolution during the previous year were excluded.

Ethics

The agreement of both hospital and private rheumatologists was collected before BA spacing. All patients gave their consent for this procedure. The study (E2014-28) was approved by the ethics committee according to law n°2012-300

Schedule of visits and dose tapering

All visits were planned every 2 months during the spacing phase that lasted 6 or 7 months according to the BA used and then every 3 months during 1 year after discontinuation of the BA. Dose tapering was standardized for each drug during the spacing phase as shown in Figure 1.

Parameters studied

Inclusion visit

During this visit, the presence of all inclusion criteria was checked. The following parameters were collected: all data needed to calculate DAS28-ESR, DAS28-CRP and SDAI; completion of the Health Assessment Questionnaire (HAQ); laboratory tests (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factors (RF), and anti-cyclic citrullinated

peptide antibodies (anti-CCP). We also recorded the following data for each patient: demographic characteristics, RA duration, number of synthetic DMARDs, biologic agents received, and time on BA.

In addition, ultrasonographic examination of the 28 joints was carried out at baseline, using a MyLab 70 (Technos Esaote), by 3 operators (GA, MKM, JN) with long-standing experience in US evaluation of chronic inflammatory rheumatic diseases. They have already participated in several multicenter studies and the intra- and inter-observer reliability was similar to that reported in the study conducted by D'Agostino MA et al. (8). All sonographers were blinded to clinical information and laboratory data. A systematic multiplanar gray-scale (GS) and power-doppler (PD) ultrasound examination of the 28 joints included in the disease activity score (US-DAS28) was performed using a high-frequency (13.5 MHz) linear array transducer. Joints were evaluated using a semi-quantitative scoring system with a 0-3 scale for GS and PD according to the method developed by Szkudlarek et al (9). Findings were described using the definitions established by the OMERACT. The overall GS and PD scores for synovitis were measured and the global PDUS score (sum of total GS and PD scores) was calculated for each patient.

Spacing procedure

A visit was scheduled every 2/3 months according to the BA. At each visit, the parameters mentioned previously and ongoing treatments were recorded. An US evaluation of the 28 joints was carried out at month 7.

Spacing was defined for each BA. During this period, visits were performed at 3 time-points: months 2, 4 and 6 or 7. The inter-injection interval was increased at each visit in order to stop BA completely at month 7.

During the study period, all associated treatments were unmodified. The dose of conventional DMARDs and corticosteroids was stable.

Follow-up visits after biologic agent discontinuation

After discontinuation at month 7, patients were evaluated at 3-month intervals via physical examination, ESR and CRP determinations, SDAI and DAS28 computation, and 28 joint US examination.

Definition of relapse

Relapse was defined as SDAI > 11 which was determined by rheumatologists who were blinded to US findings.

In this dose-reduction phase, patients restarted their treatment with the previous scheme. After discontinuation, relapsing patients were immediately retreated with their previous BA, at the previous dosage, with no change in prednisone or synthetic DMARD dosage.

Statistical Analysis

Demographic characteristics, clinical and biological data were summarized by descriptive analysis. Student's t-tests and Fisher's tests were used for quantitative and qualitative variables, respectively. Relapse-free survival data were analyzed using the log-rank test. Qualitative variables were analysed directly; quantitative variables have been expressed as compared to normal values or median ; p-values lower than 0.10 were considered significant to be analysed in a multivariate model. In multivariate survival analysis, the Cox model was used. We used NCSS version 2007 for statistical analysis. P-values lower than 0.05 were considered significant.

Candidate predictors were: age, gender, disease duration, immunological status, number of previous biological DMARDs, type of BA, treatments combined to BA and their dose, disease activity scores at baseline and their kinetic during the spacing phase, US data at baseline and their outcome during the dose-reduction phase, HAQ at baseline and its kinetic during the tapering phase, ESR, CRP

Patient and public involvement

Patients were not involved in the design and the conduction of the present study

RESULTS

Baseline characteristics of the study population

Among the 378 RA patients treated with a BA between January 2012 and January 2013, 53 (14%) fulfilled our criteria for disease remission (SDAI < 3.3) and were selected for the spacing/discontinuation standardized procedure (figure 1). This cohort included 38 female and 15 male patients with a mean age of 58.5 years, a mean disease duration of 13 years (median 11 years; 4-32 years); 62% patients were rheumatoid factor positive and 62 % were anti-CCP positive; 49% were double-positive and 25% double negative; 85 % patients had at least one x-ray erosion. Among double negative RA patients, 85% had structural damage. At the inclusion visit, the mean values of DAS28-ESR, DAS28-CRP, SDAI and HAQ were 1.76, 1.6, 1.9 and 0.23, respectively.

Among the 53 patients, 6, 8, 24, 11, 1 and 3 were on infliximab, adalimumab, etanercept, abatacept, certolizumab and tocilizumab, respectively; 10 patients were switched to another BA: 1 switch (n = 5), 2 switches (n = 3), 3 switches (n=2). At the time of the study, 42 (79.2%) patients were taking methotrexate at a mean dose of 11.79 mg/week, and one patient was on leflunomide. Thus, 10 patients received BA in monotherapy. Only 4 patients were on prednisone (mean dose: 3.13 mg/day).

Results are also expressed in median (IQR) and summarized in Table 1.

Ultrasonographic data are shown in Table 2. The mean score of GS synovitis was 1.7 and that of PD synovitis was 0.7. The mean global score was 2.5, reflecting low disease activity. Among the 53 patients, 38 (72%) had a global score of 0. Global scores for GS and PD assessments were also expressed in a Boolean manner according to the definition used for the 4 items of the last remission criteria (< or = 1/28)(6). Each joint was graded 0 or 1. A value of 1 was considered when the grade was > 1 (2 or 3) for a given joint according to the Szkudlarek definition (7). Using this Boolean definition for US evaluation on 28 joints, three quarters of patients had a GS score < or = 1 and, more importantly, 89% had a PD score < or = 1 at baseline (Table 2).

Spacing and discontinuation periods

During the spacing period, 5 patients relapsed at month 4 and 14 at month 7

Thirty-four patients were able to stop their BA at month 7. At month 9, 7 patients relapsed, and 27 were able to continue treatment withdrawal. Ten patients relapsed at month 12, 2 at month 15 and 2 at month 18. At the end of the 18-month follow-up period, 14 patients had completed the visit; 2 had relapsed while 12 were still in remission. Among the 53 patients, 41 relapsed. Among those who relapsed, there were two patients in remission at their last visit who were lost to follow-up. Importantly, all patients on monotherapy (without combination with methotrexate) relapsed, as well as the 4 patients who received a low dose of corticosteroids.

Among the 12 non-relapsing patients, the mean DAS28 CRP was 2.14 (1.43-2.86; SD: 0.7) and the mean SDAI was 4.03 (0.37-7.7, SD: 3.66) at the last visit.

During the spacing and discontinuation phases, there were more patients with a global PD score > 1/28 according to the Boolean definition (Table 2).

Identification of predictive factors of relapse

The survival analysis of patients who relapsed found a median relapse time of 11.8 months (fig.2). There were a majority of women in the relapsing group: 79.5% versus 50% in non-relapsers (p = 0.066). The proportion of patients with disease duration longer than the median (11 years) was significantly higher in the relapsing group: 56.4% of relapsers versus 16.7% of non-relapsers (p = 0.022). Age, anti-CCP or RF positivity/titers were not significantly different between relapsers and non-relapsers. Clinical and US composite scores showed no significant difference. In this regard, while all patients with at least one PD-positive-US synovitis (grade > 1) were relapsers, those with a global score of 0 on sonography or satisfying the Boolean definition for GS or PD global scores could be relapsers or not.

Survival analysis between relapsers and non-relapsers showed that the following criteria: disease duration longer than the median (p = 0.032), previous biologic therapy (p = 0.068), and treatment with corticosteroids (p = 10-3), ESR> 10 (p = 0.098) were significantly (or tended to be) associated with relapse.

In multivariate analysis, relapse risk factors were corticosteroid use with a risk ratio of relapse at 13.78 (95%CI 3.95-48.08, p =0.001), disease duration longer than the median (11 years) with a risk ratio at 2.18 (95%CI: 1.08-4.39, p = 0.029).

Risk factors of relapse taking into account both factors of prediction and of predictability.

This analysis comprises both baseline parameters collected prior to dose-reduction phase (referred to as predictive factors) and kinetic of clinical, biological and US parameters during the tapering phase prior to discontinuation (labelled factors of predictability).

It has been carried out from patients that completed the tapering phase and underwent the discontinuation period.

Survival analysis during the withdrawal period, taking into account baseline parameters and the evolution of some of them during the spacing phase, was performed and included 32 patients. Median survival was 7.6 months (5.3-11.2) following the month 7 visit. There were 12 non-relapsing patients whereas 20 patients relapsed.

The univariate analysis showed that disease duration longer than the median (p = 0.021) was predictive of relapse after discontinuation of treatment. Before spacing, methotrexate intake (p = 0.140) was a potential protective factor during discontinuation of treatment.

The univariate survival analysis, taking into account the kinetics of parameters between M0 (baseline) and M7 (end of spacing phase) showed that variations of SDAI was significantly associated with relapse (Fig.3) in contrast to those of ultrasonographic scores (Table 3).

The multivariate analysis identified as relapse risk factors a SDAI increase > 0 between M0 and M7 with a risk ratio of 21.77 (95%CI 2.1-225.74, p = 0.03)(Fig 3). This point means that an increase of SDAI between two visits during the tapering phase was predictive of relapse defined by a SDAI > 11 after BA discontinuation. In contrast, methotrexate use was protective of relapse with a risk ratio of 0.07 (95%CI: 0.01-0.61, p = 0.016).

DISCUSSION

Our study has several strengths. This was a prospective real life study with a standardized procedure for spacing and discontinuation in accordance with international recommendations (4). Our analysis took into account all BA available except rituximab and JAK/STAT inhibitors (not available at the time of analysis), unlike other analyses that focused mainly on TNF-blocking agents or a single biologic agent (infliximab, etanercept, adalimumab, tocilizumab, abatacept). Even though the sample size for patients treated with abatacept and tocilizumab was low, we did not perform a specific analysis focused on TNF blockers since we consider that candidate predictors of relapse after discontinuation should be applied to any BA, whatever its mechanism of action. Moreover, although they target TNF, all TNF-antagonists have their own specificities concerning the mode of action.

Our study is one of the first to consider factors of predictability. However, one limitation of our study is the limited population size. These 53 patients in remission represented 14% of our population of 378 RA patients. This small percentage of patients in remission may be related to the strict definition of remission that we used (SDAI <3.3) whereas, when DAS28-ESR was considered (DAS 28 < 2.6), 142 (38%) patients were in remission, which is more in line with data reported in the literature. In addition, the majority of RA patients in our unit had longstanding disease. Finally, the tapering strategy was very rapid compared to those reported in the literature or done in daily practice but, to our knowledge, there is no consensus about the dose-reduction process for each BA. Nevertheless, this might alter the external validity of the present results.

The characteristics of our population are concordant with those observed in other reports such as PRESERVE, BEST, PRIZE, STRASS and that of Brocq et al (10-14).

Based on EULAR recommendations (4) and data from the literature, we performed spacing of BA rather than sudden discontinuation. Our scheme has the distinction of proposing gradual spacing and then discontinuation as in the STRASS study in which BA were represented by etanercept and adalimumab (14). Other studies (BeSt, PRESERVE, PRIZE) proposed dose reduction (9,10,13). In the present study and in the STRASS study (14), 35.8% and 26.5% of patients relapsed during the spacing period, respectively; then 64% and 37.5% of patients were able to stop BA and finally 77% and 81% relapsed, respectively.

Our study required very strict remission criteria compared to other studies and notably had a remission duration of at least one year compared to other studies which often selected patients with a remission duration of 6 months. In addition, we defined remission by SDAI < 3.3 (6) when other studies (RRR, PRESERVE) used DAS28 < 3.2 (10,15) or DAS28 < 2.6 (12, 13,14,16). In this respect, with low disease activity as criteria of selection (DAS28 < 3.2), RRR and PRESERVE had a lower BA-free remission rate (43 and 42%) than PRIZE and BeSt (53 and 80%). Thus, it seems better to use BA withdrawal only in patients with deep remission as reported by Tanaka et al who found that a DAS-28 ESR < 2.2 was associated with maintenance of drug-free remission (15).Those data led us to retain a SDAI < 3.3 as a criterion of eligibility for BA spacing. Such a level of clinical and biological remission is close to US remission as observed in a previous study (17) and in ours in which three quarters of patients had a global (GS plus PD) US score of 0 based on the assessment of 28 joints. Moreover, the duration of remission appears to be an important prerequisite to consider BA relief. Indeed, subclinical joint activity is long-lasting in RA joints in clinical remission. Even though there is attenuation over time, the mean time (+/- SD) since last clinical swelling and positive sonographic assessment was significantly shorter in patients showing high GS or PD signals compared with lower-grade GS or PD signals (18). Since subclinical disease activity may persist several years in clinically inactive joints and US PD positive synovitis is related to subsequent flare (19-21), deep remission based on US DAS28 findings is also required.

Nevertheless, deep remission based on the absence of PD-positive synovitis (89% in the present study) and on US assessment of 28 joints seems insufficient to predict BFR since a large proportion of patients with a global US score of 0 were relapsers. We can postulate that

a single evaluation prior to BA relief is not relevant enough and thus sequential assessment at regular intervals during a period that needs to be defined should be performed to confirm that US remission is persistent before initiating BA dose-reduction. In this respect, in the study conducted by Alivernini et al, the selection of patients was based on US-findings in a cohort of 42 consecutive patients with longstanding RA in clinical remission (DAS < 1.6 for at least 6 months) and receiving combination therapy with methotrexate and TNF-blocking agents (adalimumab or etanercept). Despite serial PD-negative findings during the tapering and discontinuation phases, 38% of patients relapsed after 12-month follow-up after discontinuation (22).

Since characteristics of remission prior to BA relief are unable to predict BA-free remission, the question arose as to whether other parameters, before BA discontinuation as well as during the spacing phase, were potential risk factors of relapse after BA withdrawal.

One of the predictive factors of relapse was long-standing RA with disease duration longer than the median (11 years). In fact, most studies (10,11,13,15) focused on more recent RA with a disease duration less than 6 years. The populations closest to ours were those of the Brocq and STRASS (12,14) in which the mean disease duration was 11 and 9 years, respectively. These 2 studies analyzed non-naive BA patients and the remission rate at one year was 24% and 37.5%, respectively, which was closer to that of our cohort (23%) but lower than that observed in studies with shorter disease duration that included naive BA RA (PRESERVE: 42%, BeSt: 80%, PRIZE: 50%, RRR: 43%)(10,11,13,15). Thus, our results are in line with data in the literature since a disease duration longer the threshold of 5 years is a factor of relapse. In the same way, use of previous BA is a risk factor of relapse.

Low dose glucocorticoid, less than 5 mg per day, was still associated with relapse after treatment discontinuation. Spacing or discontinuation could not be initiated in patients with glucocorticoids, even at a very low dose (3 mg/d in the present study). RRR and STRASS studies allowed corticosteroids at a dose less than 5 mg/day (14,15), PRESERVE tolerated up to 10 mg / day with 60% of patients on prednisone (10). These studies did not observe a correlation between relapse and long-term corticosteroid. For EULAR, in patients in long-term remission, the first step is to reduce corticosteroids and in case of persistent remission the next step is to decrease BA.

Pertinently, the combination with a synthetic DMARD is of importance for the success of BA discontinuation. Indeed, methotrexate combination with BA is a protective factor of relapse. While Brocq et al. did not find it, BeSt reported a protective effect of methotrexate (11,12). The same findings were stated in the PRESERVE and PRIZE studies (10,13). In a meta-analysis (23), a combination of methotrexate with BA achieved low disease activity more quickly and ensured the maintenance of remission after discontinuation of BA, more likely in case of monotherapy. In a meta-analysis of randomized controlled trials on stopping DMARDs in monotherapy, relapse was observed in 46% of RA patients after discontinuation of DMARDs (3). There are no consensual guidelines for BA discontinuation. NICE recommends a prudent decrease in the dose of DMARDs with a recovery to previous dose in case of relapse (24). EULAR recommends that BA tapering can be considered if a patient is

in persistent remission after glucocorticoid tapering, especially if this treatment is combined with conventional DMARDs such as methotrexate (4). For EULAR, spacing treatment or decreasing the dosage is quite similar. Those guidelines corroborate our results.

Although data from the RETRO, BeSt, HIT-HARD and POET studies suggest that anti-CCP status has an influence on relapse with a lower chance of maintaining remission in the presence of anti-CCP (25), positivity and/or levels of markers reflecting systemic inflammation or autoimmunity (RF and anti-CCP) were not predictive of relapse in the present study. Only composite biomarker testing including acute phase reactants, cytokines and metalloproteinases were suggested to be relevant in the RETRO study (26).

While there was no difference between a DAS28 <2.6 or a SDAI ≤ 3.3 on relapse after stopping treatment, a fluctuation of > 0 in SDAI during spacing was significantly associated with relapse. There are no data in the literature on the influence of DAS28 or SDAI fluctuations on relapse during the spacing period. However, although SDAI at baseline showed no difference, we consider this score to be more robust than DAS28 and our analysis shows that a worsening of this score was associated with relapse. This analysis provides new criteria for tapering BA. Given our results, only patients with decreased SDAI score in relief can stop BA, other patients with increased SDAI should continue BA at the last dose or injection interval. Thus, the kinetic of SDAI during the spacing period seems to be more important than baseline values.

In conclusion, we propose spacing of BA for patients with RA of limited duration, in both clinical and US deep remission of at least one year, on conventional DMARDs, especially methotrexate and after tapering corticosteroids. Therefore, we suggest withdrawal of BA only if the SDAI or DAS do not worsen during the spacing period.

Other studies are needed to confirm the relevance of these predictive and predictable factors of relapse when considering BA alleviation/discontinuation in RA patients in remission under BA.

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Contributors
OV, SD, TL, GA were involved in the conception and the design of this study; OV, SD, SP, TL were involved in the acquisition of clinical data; MKM, JN, PR, NS performed the ultrasonographic assessments; OV, GA were involved in the statistical analysis; OV, SD, TL, GA were involved in the analysis and interpretation of the data; All authors were involved in the drafting and revision of the manuscript

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Ethics approval - The study (E2014-28) was approved by the ethics committee according to law n°2012-300

Data sharing: no additional data available

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Table 1. Demographic, clinical, biological, and drug chracteristics of the study population at baseline and according to the occurrence of relapse during the spacing and discontinuation phases

Parameter		Spacing phase			Discontinuation phase		
	Total (n = 53)	Non-relapser (n = 34)	Relapser (n = 19)	p	Non-relapser (n = 13)	Relapsers (n = 38)	p
Gender, Female n (%)	38 (72)	20 (59)	18 (95)	0.009	7 (54)	30 (79)	0.14
Age, mean +/- SD (in years)	56.8 +/- 11.8	57.5 +/-13	55.5 +/- 9.4	0.56	55.9 +/-12.6	57.4 +/- 11.7	0.52
Disease duration, mean +/- SD (in years)	13 +/- 10.3	13 +/- 11.9	13.1 +/- 7	0.23	13.1 +/-13.9	13.4 +/- 9.1	0.29
BA duration, mean +/- SD (in years)	5.3 +/- 2.9	4.7 +/- 2.8	6.3 +/- 2.8	0.07	4.8 +/- 2.7	5.6 +/- 2.9	0.38
DAS 28 ESR, median (IDR)	1.8 (1.4 – 2.1)	1.7 (1.4 – 2.1)	2 (1.4 – 2.2)	0.62	1.5 (1.3 – 1.9)	2 (1.5 – 2.2)	0.11
DAS 28 CRP, median (IQR)	1.6 (1.2 – 1.9)	1.6 (1.2 – 1.9)	1.6 (1.4 – 1.8)	0.93	1.7 (1.5 – 1.9)	1.6 (1.2 – 1.8)	0.18
SDAI, median (IQR)	2 (1 – 3)	1.6 (0.8 – 3)	2 (1 – 3.1)	0.28	2.4 (2 – 3)	1 (1 – 2.9)	0.13
HAQ (0-3), median (IQRR)	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.85	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.84
RF positivity (> 20 IU/ml), n (%)	33 (62)	19 (56)	14 (74)	0.25	8 (62)	24 (63)	1
Anti-CCP positivity (> 10 UA/ml), n (%)	33 (62)	24 (71)	9 (47)	0.14	9 (69)	22 (58)	0.52
GS score, median (IQR)	0 (0 – 2)	0 (0 – 2)	0 (0 – 0)	0.39	0 (0 – 0)	0 (0 – 2)	0.37
PD score, median (IQR)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.59	0 (0 – 0)	0 (0 – 0)	0.5
Biologic agent							
Certolizumab, n (%)	1 (2)	1 (3)	0 (0)	0.87	0 (0)	0 (0)	0.22
Etanercept, n (%)	24 (45)	13 (38)	11 (58)		5 (38)	18 (47)	
Adalimumab, n (%)	8 (15)	6 (18)	2 (11)		1 (8)	7 (18)	
Abatacept, n (%)	11 (21)	8 (24)	3 (16)		2 (15)	9 (24)	
Infliximab, n (%)	6 (11)	4 (12)	2 (11)		3 (23)	3 (8)	
Tocilizumab, n (%)	3 (6)	2 (6)	1 (5)		2 (15)	1 (3)	
Methotrexate							
N (%)	42 (79)	28 (82)	14 (74)		12 (92)	28 (74)	0.25
Dose, median (IQR)	15 (7.5 – 15)	15 (7.5 – 16.9)	10 (8.8 – 15)	0.47	15 (10 -25)	10 (5.6 – 15)	0.24
Prednisone							
N (%)	4 (8)	2 (6)	2 (11)		0 (0)	4 (11)	0.56
Dose, median, IQR	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.53	0 (0 – 0)	0 (0 – 0)	0.23

Table 2. Ultrasonographic data at baseline and over the 18-months follow-up period using a Boolean definition

Sonography	Baseline		Month 6 -7		Month 9		Month 12		Month 15		Month 18	
Number of patients	53		42		30		20		15		12	
Mode	GS	PD	GS	PD	GS	PD	GS	PD	GS	PD	GS	PD
Score = 0	20 (38)	36 (68)	15 (36)	26 (62)	6 (20)	14 (47)	7 (25)	13 (65)	3 (20)	8 (53)	2 (17)	7 (58)
Score = 1	19 (36)	11 (21)	11 (26)	7 (17)	8 (27)	6 (20)	0 (0)	2 (10)	5 (33)	0 (0)	5 (42)	2 (17)
Score < or = 1	39 (74)	47 (89)	26 (62)	33 (79)	14 (47)	20 (67)	7 (25)	15 (75)	8 (53)	8 (53)	7 (59)	9 (75)
Score > 1	14 (26)	6 (11)	16 (38)	9 (21)	16 (53)	10 (33)	13 (75)	5 (25)	7 (47)	7 (47)	5 (41)	3 (25)

Results are expressed as number (%)

Abbreviations - GS: gray-scale; PD: power-doppler

Table 3. Analysis of kinetic of composite indexes and ultrasonographic data during the spacing phase as potential predictable factors of relapse after biologic agent withdrawal

Population	All	Relapser	Non-relapser	p
Composite indexes				
Delta DAS 28 ESR > 0, %	77	82.4	66.7	0.18
Delta DAS 28 ESR, mean (SD)	0.4 (0.56)	0.56 (0.57)	0.19 (0.49)	0.07
Delat DAS 28 CRP > 0, %	48	52.9	37.5	0.149
Delta DAS 28 CRP, mean (SD)	0.1 (0.62)	0.22 (0.66)	-0.07 (0.5)	0.582
Delta SDAI > 0, %	60	70.6	37.5	0.03
Delta SDAI, mean (SD)	0.8 (2.87)	1.39 (3.17)	-0.34 (1.69)	0.03
Ultrasonographic data				
Delta GS score > 0, %	17.4	12.5	28.6	0.55
Delta GS score, mean (SD)	0 (0.98)	-0.19 (0.98)	0.29 (0.95)	0.39
Delta PD score > 0, %	30.4	31.3	28.6	1
Delta PD score, mean (SD)	0.1 (1.01)	0.06 (1.06)	0.29 (0.95)	0.68
Delta global score > 0, %	21.7	18.8	28.6	0.62
Delta global score, mean (SD)	- 0.4 (5.01)	-1.06 (5.8)	1.14 (1.95)	0.16

Abbreviations - DAS: Disease Activity Score; SDAI: Simplified Disease Activity Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; GS: Gray-Scale; PD: Power Doppler; SD: Standard Deviation

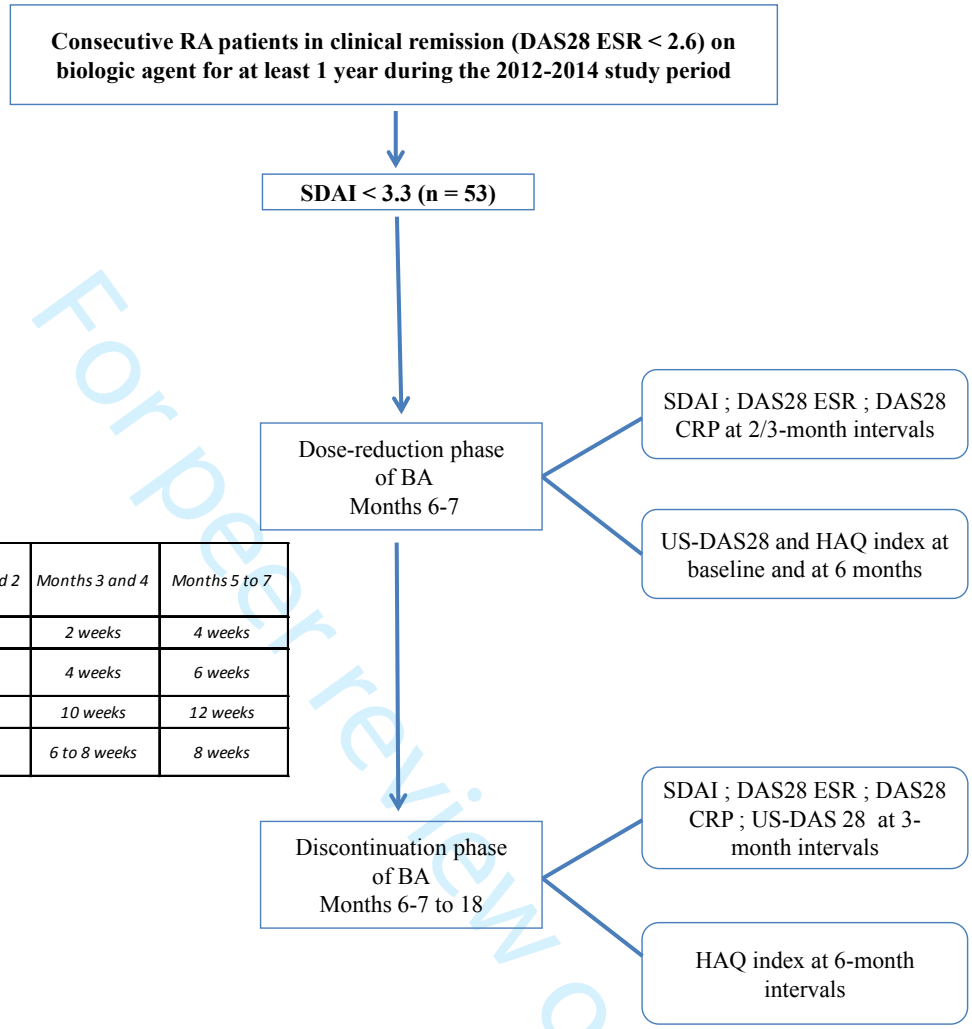
Figure legends

Figure 1. Study design

Figure.2 Global survival curve of biologic agent-free remission

Figure 3. Survival curve showing that a SDAI increase > 0 during the spacing phase was significantly associated to a higher risk of relapse. Survival curve of Delta SDAI> 0 (dotted line) and Delta SDAI ≤ 0 (full line)

Figure 1



Injection interval	*Months 1 and 2*	*Months 3 and 4*	*Months 5 to 7*
ETANERCEPT	*10 days*	*2 weeks*	*4 weeks*
ADALIMUMAB CERTOLIZUMAB	*3 weeks*	*4 weeks*	*6 weeks*
INFLIXIMAB	*8 weeks*	*10 weeks*	*12 weeks*
ABATACEPT TOCILIZUMAB	*6 weeks*	*6 to 8 weeks*	*8 weeks*

Abbreviations: RA : rheumatoid arthritis ; SDAI : Simplified Disease Activity Index ; DAS28 : Disease Activity Score on 28 joints ; ESR : Erythrocyte Sedimentation Rate ; CRP : C-Reactive Protein ; US : UltraSonography; BA : Biologic agent ; HAQ : Health Assessment Questionnaire

Figure 2

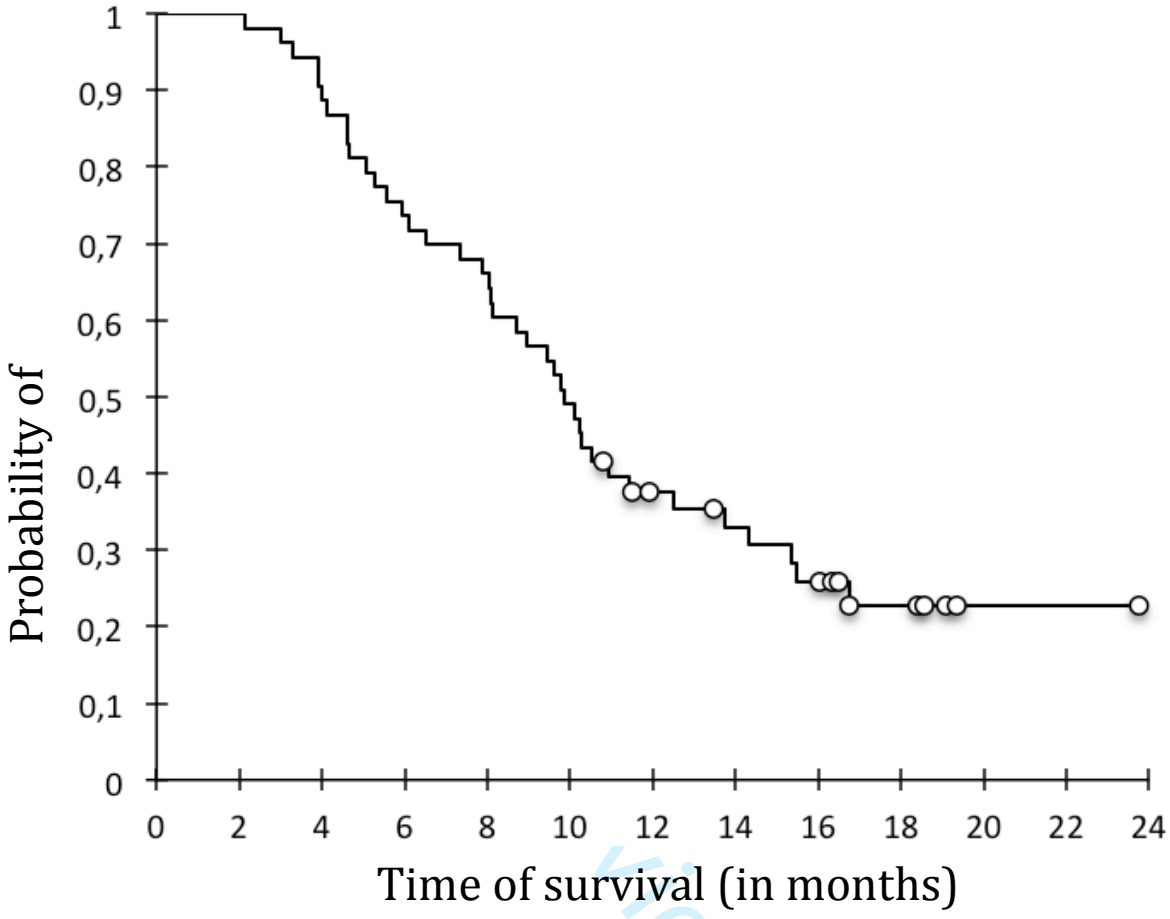
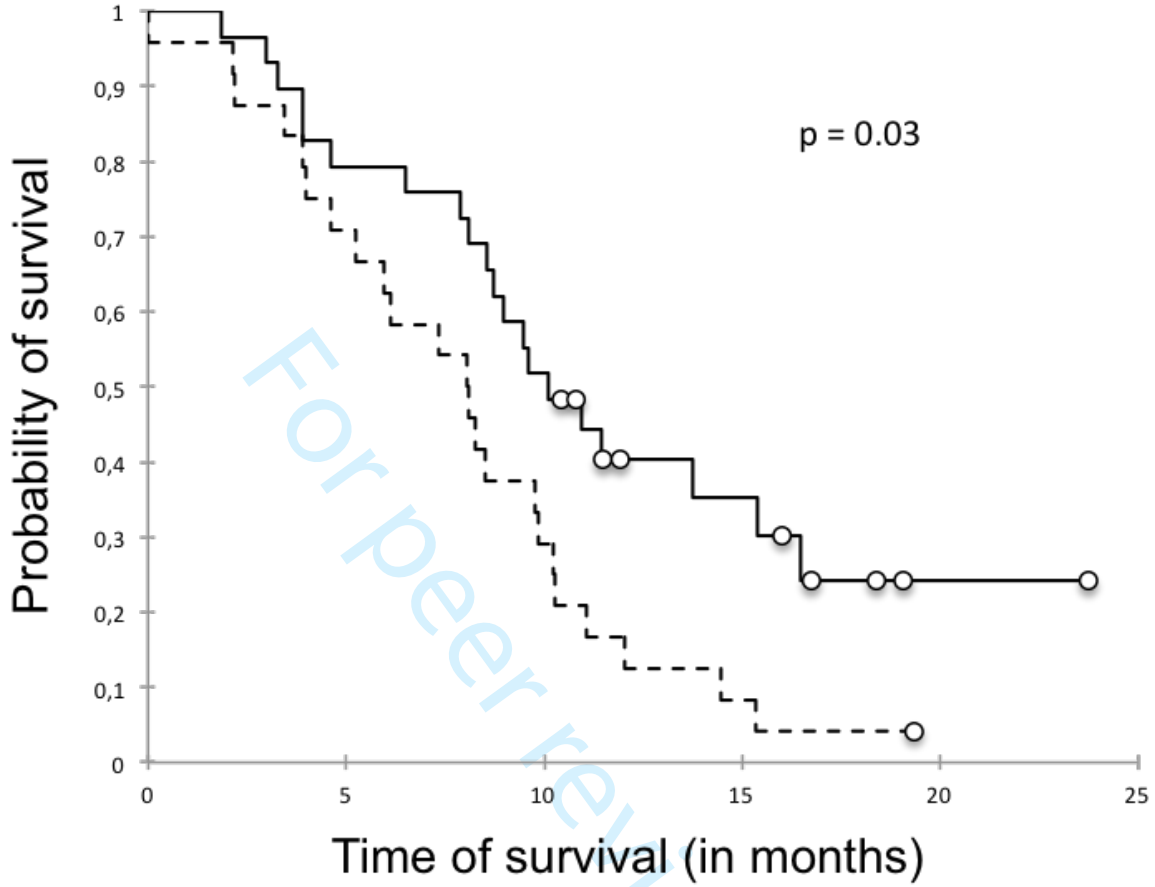


Figure 3



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5,6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5,6*
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	7,8
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1,p16
		(b) Indicate number of participants with missing data for each variable of interest	7,8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7,8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7,8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Variation of SDAI during the dose-reduction phase is more relevant than predictive factors to evaluate the success of biologic withdrawal in rheumatoid arthritis patients in clinical remission

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Variation of SDAI during the dose-reduction phase is more relevant than predictive factors to evaluate the success of biologic withdrawal in rheumatoid arthritis patients in clinical remission

Running head: prediction and predictability of relapse in RA patients undergoing spacing and withdrawal of biotherapy

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ABSTRACT

Objective - To determine predictive factors of relapse in rheumatoid arthritis (RA) patients undergoing bDMARD dose-reduction/discontinuation.

Patients and methods - RA patients receiving the same bDMARD for more than 1 year, in SDAI remission, were selected in an observational monocentric real-life study. The 18-months follow-up included spacing (6 months) and withdrawal (12 months) periods of bDMARD. Clinical, biological and ultrasonographic (US) parameters were collected regularly. Relapse was defined by SDAI > 11.

Results - Fifty-three RA patients (mean age: 58 years; 72% women; median duration: 11 years) were enrolled. Forty-two received anti-cytokinic bDMARD targeting TNF (n = 39) or IL-6R (n = 3) and 11 were treated by abatacept. For 81%, it was the first bDMARD. The numbers of relapses during the spacing and discontinuation periods were 19 and 20 respectively. After 18 months of follow-up, 12/53 maintained bDMARD-free remission, 39/53 had relapsed and 2 were lost of follow-up. Median time to relapse was 11.8 months. In multivariate analysis, baseline factors predictive of relapse were corticosteroid intake, female gender, longer disease duration and no methotrexate intake with bDMARD. Concerning the survival analysis, when taking also into account the factors of predictability, the main risk factor of relapse after discontinuation was an increase of SDAI > 0 during the spacing period (p = 0.03). US findings were not contributive.

Conclusion - In the context of RA in remission under bDMARDs, variation of SDAI during the dose-reduction phase is more relevant than baseline parameters to predict success of drug withdrawal.

Key words: rheumatoid arthritis; bDMARD; withdrawal; spacing; remission; ultrasonography; prediction; predictability

Strengths and limitations of this study

Despite the limited size of the population studied, the originality of this prospective real-life multiparameter study using a well-defined procedure of gradual spacing and discontinuation of biological DMARD (bDMARD) in rheumatoid arthritis (RA) patients in SDAI remission for a period > 1 year is to take into account most bDMARD available and to consider for the first time both predictive and predictable factors of relapse

Besides remission (SDAI < 3.3) for a long time (> 1 year), the present study confirms that the criteria of eligibility which are of importance for the success of bDMARD discontinuation are the combination with a synthetic DMARD, no corticosteroid intake, a short disease duration.

Deep remission based on the absence of PD-positive synovitis on US assessment of 28 joints prior to bDMARD spacing appears to be insufficient to predict bDMARD-free remission

The kinetic of SDAI during the spacing period seems to be more important than baseline values since the factor of predictability of relapse at bDMARD withdrawal is a SDAI variation of > 0. In contrast, sequential assessment of joint activity by ultrasonography during the dose-reduction phase does not provide relevant information for RA management.

In the context of RA patients in SDAI remission under bDMARD, undergoing therapeutic relief, a tight monitoring of disease activity during the dose-reduction phase of a bDMARD appears to be relevant to identify potential relapsers; SDAI is an appropriate tool since slight variations are predictive of relapse. It seems better to consider factors of predictability during the dose-reduction phase than parameters collected just prior to this phase, regardless of their nature (clinical, biological or ultrasonographic). Thus, this study illustrates the importance to take into account the time factor rather than a single evaluation at a given time to manage remission in RA.

INTRODUCTION

In rheumatoid arthritis (RA), after achieving low disease activity (LDA) or remission (1), the goal of therapy is to maintain clinical, functional and structural remission (2). For some patients, this is possible even after the cessation of biological DMARD (bDMARD)(3). The opportunity of discontinuing bDMARD after achieving remission must be considered because of potential long-term safety issues and the economic burden associated with their expense. Furthermore, the disease can spontaneously evolve towards an inactive form. Multiple studies have investigated whether remission can be sustained after a bDMARD is discontinued, namely, « biologic-free remission (BFR) »(3).

The European League Against Rheumatism (EULAR) 2012 guidelines (4) suggest that we can consider tapering bDMARD. Determining the patient profile associated with a high chance of sustained remission after the cessation of bDMARD is of great importance to avoid disease flares. For this purpose, two definitions of remission have been proposed, either the Boolean definition or a score of the Simplified Disease Activity Index (SDAI) < 3.3 (5, 6). However, the majority of studies did not use these definitions for eligibility to bDMARD spacing or withdrawal. Indeed, in most reports, Disease Activity Score on 28 joints (DAS28) was used to select patients for withdrawal of bDMARD in RA patients having achieved remission (7).

For patients with long-standing RA, the discontinuation of TNF-inhibitors after sustained remission has been shown to be possible in some cases. However, high flare rates have been documented in other studies. For these patients, bDMARD dose-reduction or spacing regimen followed by secondary withdrawal may be preferable instead of sudden discontinuation (3).

According to several studies, it appears that the criteria for spacing the administration of bDMARD in RA patients in remission are not consensual and that we lack validated data. In this respect, a systematic review of studies addressing predictors of successful dose reduction or discontinuation of bDMARD in RA shows that there is no consistent predictor (7).

To respect EULAR recommendations, we introduced standardized practices in our rheumatology department, in routine care, several years ago. Spacing and then discontinuation of bDMARD is performed in RA patients in remission according to 2011 ACR-EULAR criteria (6).

The general objective of this real-life, prospective study was to define strict eligibility criteria for bDMARD spacing/withdrawal in long-standing RA patients in remission. The specific objectives were (i) to define the rate of relapse during the spacing and withdrawal periods in a RA population; (ii) to identify predictive/predictable factors of relapse during the withdrawal phase of bDMARD, and (iii) to determine whether duration and degree of clinical remission as well as US findings at time of bDMARD spacing influenced the achievement of bDMARD withdrawal.

PATIENTS AND METHODS

Study design

This prospective real life study comprised an inclusion visit and two phases (Figure 1).

Patients

In this study were enrolled all RA patients treated by bDMARD between 2012 and 2014, in the rheumatology department of Rouen University Hospital. bDMARDs were infliximab, etanercept, adalimumab, abatacept, certolizumab, and tocilizumab. Golimumab was not considered since it was introduced more recently. Rituximab was not relevant for such a strategy of spacing/withdrawal. Patients with subcutaneous treatment were selected at annual follow-up visits in the ambulatory care unit. Patients with intravenous bDMARD were selected in the immunotherapy unit of the department.

Inclusion criteria

They comprised RA patients (older than 18 years), fulfilling ACR/EULAR 2010 criteria, in remission defined as a DAS28 < 2.6 for at least 12 months, and receiving the same bDMARD for at least 1 year. Prior to initiation of spacing, a SDAI <3.3 was required (6). Patients taking prednisone (or equivalent) at a dose > 5mg/day or with structural evolution during the previous year were excluded.

Ethics

The agreement of both hospital and private rheumatologists was collected before bDMARD spacing. All patients gave their consent for this procedure. The study (E2014-28) was approved by the ethics committee according to law n°2012-300

Schedule of visits and dose tapering

All visits were planned every 2 months during the spacing phase that lasted 6 or 7 months according to the bDMARD used and then every 3 months during 1 year after discontinuation of the bDMARD. Dose tapering was standardized for each drug during the spacing phase as shown in Figure 1.

Parameters studied

Inclusion visit

During this visit, the presence of all inclusion criteria was checked. The following parameters were collected: all data needed to calculate DAS28-ESR, DAS28-CRP and SDAI; completion of the Health Assessment Questionnaire (HAQ); laboratory tests (erythrocyte sedimentation

rate (ESR), C-reactive protein (CRP), rheumatoid factors (RF), and anti-cyclic citrullinated peptide antibodies (anti-CCP). We also recorded the following data for each patient: demographic characteristics, RA duration, number of synthetic DMARDs, bDMARDs received, and time on BA.

In addition, ultrasonographic examination of the 28 joints was carried out at baseline, using a MyLab 70 (Technos Esaote), by 4 operators (MKM, JN, PR, NS) with long-standing experience in US evaluation of chronic inflammatory rheumatic diseases. They have already participated in several multicenter studies and the intra- and inter-observer reliability was similar to that reported in the study conducted by D'Agostino MA et al. (8). All sonographers were blinded to clinical information and laboratory data. A systematic multiplanar gray-scale (GS) and power-doppler (PD) ultrasound examination of the 28 joints included in the disease activity score (US-DAS28) was performed using a high-frequency (13.5 MHz) linear array transducer. Joints were evaluated using a semi-quantitative scoring system with a 0-3 scale for GS and PD according to the method developed by Szkudlarek et al (9). Findings were described using the definitions established by the OMERACT. The overall GS and PD scores for synovitis were measured and the global PDUS score (sum of total GS and PD scores) was calculated for each patient.

Spacing procedure

A visit was scheduled every 2/3 months according to the bDMARD. At each visit, the parameters mentioned previously and ongoing treatments were recorded. An US evaluation of the 28 joints was carried out at month 7.

Spacing was defined for each bDMARD. During this period, visits were performed at 3 time-points: months 2, 4 and 6 or 7. The inter-injection interval was increased at each visit in order to stop bDMARD completely at month 7.

During the study period, all associated treatments were unmodified. The dose of conventional DMARDs and corticosteroids was stable.

Follow-up visits after bDMARD discontinuation

After discontinuation at month 7, patients were evaluated at 3-month intervals via physical examination, ESR and CRP determinations, SDAI and DAS28 computation, and 28 joint US examination.

Definition of relapse

Relapse was defined as SDAI > 11 which was determined by rheumatologists who were blinded to US findings.

In this dose-reduction phase, patients restarted their treatment with the previous scheme. After discontinuation, relapsing patients were immediately retreated with their previous BbDMARD, at the previous dosage, with no change in prednisone or synthetic DMARD dosage.

Statistical Analysis

Demographic characteristics, clinical and biological data were summarized by descriptive analysis. Student's t-tests and Fisher's tests were used for quantitative and qualitative variables, respectively. Relapse-free survival data were analyzed using the log-rank test. Qualitative variables were analysed directly; quantitative variables have been expressed as compared to normal values or median ; p-values lower than 0.10 were considered significant to be analysed in a multivariate model. In multivariate survival analysis, the Cox model was used. We used NCSS version 2007 for statistical analysis. P-values lower than 0.05 were considered significant.

Candidate predictors were: age, gender, disease duration, immunological status, number of previous bDMARDs, type of bDMARD, treatments combined to bDMARD and their dose, disease activity scores at baseline and their kinetic during the spacing phase, US data at baseline and their outcome during the dose-reduction phase, HAQ at baseline and its kinetic during the tapering phase, ESR, CRP

Two types of analysis were performed. For the first one, the primary outcome was relapse versus no relapse either during the dose-reduction phase or over the discontinuation period. The second one, which was the more relevant, was focused on time to relapse. Concerning the two patients in remission at their last visit who were lost of follow-up, they have been censored at the time of their last visit. Thus, they have been included in the remission group for the survival analysis but excluded from the binary outcome analysis of relapse vs no-relapse.

Patient and public involvement

Patients were not involved in the design and the conduction of the present study

RESULTS

Baseline characteristics of the study population

Among the 378 RA patients treated with a bDMARD between January 2012 and January 2013, 53 (14%) fulfilled our criteria for disease remission (SDAI < 3.3) and were selected for the spacing/discontinuation standardized procedure (figure 1). This cohort included 38 female and 15 male patients with a mean age of 58.5 years, a mean disease duration of 13 years (median 11 years; 4-32 years); 62% patients were rheumatoid factor positive and 62 % were anti-CCP positive; 49% were double-positive and 25% double negative; 85 % patients had at least one x-ray erosion. Among double negative RA patients, 85% had structural damage. At the inclusion visit, the mean values of DAS28-ESR, DAS28-CRP, SDAI and HAQ were 1.76, 1.6, 1.9 and 0.23, respectively.

Among the 53 patients, 6, 8, 24, 11, 1 and 3 were on infliximab, adalimumab, etanercept, abatacept, certolizumab and tocilizumab, respectively; 10 patients were switched to another bDMARD: 1 switch (n = 5), 2 switches (n = 3), 3 switches (n=2). At the time of the study, 42 (79.2%) patients were taking methotrexate at a mean dose of 11.79 mg/week, and one patient was on leflunomide. Thus, 10 patients received bDMARD in monotherapy. Only 4 patients were on prednisone (mean dose: 3.13 mg/day).

Results are also expressed in median (IQR) and summarized in Table 1.

Ultrasonographic data are shown in Table 2. The mean score of GS synovitis was 1.7 and that of PD synovitis was 0.7. The mean global score was 2.5, reflecting low disease activity. Among the 53 patients, 38 (72%) had a global score of 0. Global scores for GS and PD assessments were also expressed in a Boolean manner according to the definition used for the 4 items of the last remission criteria (< or = 1/28)(6). Each joint was graded 0 or 1. A value of 1 was considered when the grade was > 1 (2 or 3) for a given joint according to the Szkudlarek definition (7). Using this Boolean definition for US evaluation on 28 joints, three quarters of patients had a GS score < or = 1 and, more importantly, 89% had a PD score < or = 1 at baseline (Table 2).

Spacing and discontinuation periods

During the spacing period, 5 patients relapsed at month 4 and 14 at month 7

Thirty-four patients were able to stop their bDMARD at month 7. At month 9, 7 patients relapsed, and 27 were able to continue treatment withdrawal. Ten patients relapsed at month 12, 2 at month 15 and 2 at month 18. At the end of the 18-month follow-up period, 14 patients had completed the visit; 2 had relapsed while 12 were still in remission. Among the 53 patients, 41 relapsed. Among those who relapsed, there were two patients in remission at their last visit who were lost to follow-up. Importantly, all patients on monotherapy (without combination with methotrexate) relapsed, as well as the 4 patients who received a low dose of corticosteroids.

Among the 12 non-relapsing patients, the mean DAS28 CRP was 2.14 (1.43-2.86; SD: 0.7) and the mean SDAI was 4.03 (0.37-7.7, SD: 3.66) at the last visit. Ten had a DAS-28 CRP < 2.6 and 7 a SDAI < 3.3 at all visits. Thus, according to the SDAI definition of remission, only 7 patients had a sustained deep remission (i.e., a SDAI < 3.3 at all time-points)

During the spacing and discontinuation phases, there were more patients with a global PD score > 1/28 according to the Boolean definition (Table 2).

Identification of predictive factors of relapse

The survival analysis of patients who relapsed found a median relapse time of 11.8 months (fig.2). There were a majority of women in the relapsing group: 79.5% versus 50% in non-relapsers (p = 0.066). The proportion of patients with disease duration longer than the median (11 years) was significantly higher in the relapsing group: 56.4% of relapsers versus 16.7% of non-relapsers (p = 0.022). Age, anti-CCP or RF positivity/titers were not significantly

different between relapsers and non-relapsers. Indeed, the number of non-relapsers who were seronegative and without erosions was limited to 1 patient. Clinical and US composite scores showed no significant difference. In this regard, while all patients with at least one PD-positive-US synovitis (grade > 1) were relapsers, those with a global score of 0 on sonography or satisfying the Boolean definition for GS or PD global scores could be relapsers or not.

Survival analysis between relapsers and non-relapsers showed that the following criteria: disease duration longer than the median (p = 0.032), previous biologic therapy (p = 0.068), and treatment with corticosteroids (p = 10-3), ESR> 10 (p = 0.098) were significantly (or tended to be) associated with relapse.

In multivariate analysis, relapse risk factors were corticosteroid use with a risk ratio of relapse at 13.78 (95%CI 3.95-48.08, p =0.001), disease duration longer than the median (11 years) with a risk ratio at 2.18 (95%CI: 1.08-4.39, p = 0.029).

Risk factors of relapse taking into account both factors of prediction and of predictability.

This analysis comprises both baseline parameters collected prior to dose-reduction phase (referred to as predictive factors) and kinetic of clinical, biological and US parameters during the tapering phase prior to discontinuation (labelled factors of predictability).

It has been carried out from patients that completed the tapering phase and underwent the discontinuation period.

Survival analysis during the withdrawal period, taking into account baseline parameters and the evolution of some of them during the spacing phase, was performed and included 32 patients. Median survival was 7.6 months (5.3-11.2) following the month 7 visit. There were 12 non-relapsing patients whereas 20 patients relapsed.

The univariate analysis showed that disease duration longer than the median (p = 0.021) was predictive of relapse after discontinuation of treatment. Before spacing, methotrexate intake (p = 0.140) was a potential protective factor during discontinuation of treatment.

The univariate survival analysis, taking into account the kinetics of parameters between M0 (baseline) and M7 (end of spacing phase) showed that variations of SDAI was significantly associated with relapse (Fig.3) in contrast to those of ultrasonographic scores (Table 3).

The multivariate analysis identified as relapse risk factors a SDAI increase > 0 between M0 and M7 with a risk ratio of 21.77 (95%CI 2.1-225.74, p = 0.03)(Fig 3). This point means that an increase of SDAI between two visits during the tapering phase was predictive of relapse defined by a SDAI > 11 after bDMARD discontinuation. In contrast, methotrexate use was protective of relapse with a risk ratio of 0.07 (95%CI: 0.01-0.61, p = 0.016). After exclusion of the 4 patients who received low doses (1, 2.5, 4 and 5 mg per day) of corticosteroids, the same findings were obtained (data not shown).

DISCUSSION

Our study has several strengths. This was a prospective real life study with a standardized procedure for spacing and discontinuation in accordance with international recommendations (4). Our analysis took into account all bDMARD available except rituximab and JAK/STAT inhibitors (not available at the time of analysis), unlike other analyses that focused mainly on TNF-blocking agents or a single bDMARD (infliximab, etanercept, adalimumab, tocilizumab, abatacept). Even though the sample size for patients treated with abatacept and tocilizumab was low, we did not perform a specific analysis focused on TNF blockers since we consider that candidate predictors of relapse after discontinuation should be applied to any bDMARD, whatever its mechanism of action. Moreover, although they target TNF, all TNF-antagonists have their own specificities concerning the mode of action.

Our study is one of the first to consider factors of predictability. However, one limitation of our study is the limited population size. These 53 patients in remission represented 14% of our population of 378 RA patients. This small percentage of patients in remission may be related to the strict definition of remission that we used (SDAI <3.3) whereas, when DAS28-ESR was considered (DAS 28 < 2.6), 142 (38%) patients were in remission, which is more in line with data reported in the literature. In addition, the majority of RA patients in our unit had longstanding disease. Moreover, the tapering strategy was very rapid compared to those reported in the literature or done in daily practice but, to our knowledge, there is no consensus about the dose-reduction process for each bDMARD. Nevertheless, this might alter the external validity of the present results. Finally, we have not investigated molecular and cellular biomarkers likely to reflect an immunological remission.

The characteristics of our population are concordant with those observed in other reports such as PRESERVE, BEST, PRIZE, STRASS and that of Brocq et al (10-14).

Based on EULAR recommendations (4) and data from the literature, we performed spacing of bDMARD rather than sudden discontinuation. Our scheme has the distinction of proposing gradual spacing and then discontinuation as in the STRASS study in which bDMARD were represented by etanercept and adalimumab (14). Other studies (BeSt, PRESERVE, PRIZE) proposed dose reduction (9,10,13). In the present study and in the STRASS study (14), 35.8% and 26.5% of patients relapsed during the spacing period, respectively; then 64% and 37.5% of patients were able to stop BA and finally 77% and 81% relapsed, respectively.

Our study required very strict remission criteria compared to other studies and notably had a remission duration of at least one year compared to other studies which often selected patients with a remission duration of 6 months. In addition, we defined remission by SDAI < 3.3 (6) when other studies (RRR, PRESERVE) used DAS28 < 3.2 (10,15) or DAS28 < 2.6 (12, 13,14,16). In this respect, with low disease activity as criteria of selection (DAS28 < 3.2), RRR and PRESERVE had a lower bDMARD-free remission rate (43 and 42%) than PRIZE

and BeSt (53 and 80%). Thus, it seems better to use bDMARD withdrawal only in patients with deep remission as reported by Tanaka et al who found that a DAS-28 ESR < 2.2 was associated with maintenance of DFR (15).Those data led us to retain a SDAI < 3.3 as a criterion of eligibility for bDMARD spacing. Such a level of clinical and biological remission is close to US remission as observed in a previous study (17) and in ours in which three quarters of patients had a global (GS plus PD) US score of 0 based on the assessment of 28 joints. Moreover, the duration of remission appears to be an important prerequisite to consider bDMARD relief. Indeed, subclinical joint activity is long-lasting in RA joints in clinical remission. Even though there is attenuation over time, the mean time (+/- SD) since last clinical swelling and positive sonographic assessment was significantly shorter in patients showing high GS or PD signals compared with lower-grade GS or PD signals (18). Since subclinical disease activity may persist several years in clinically inactive joints and US PD positive synovitis is related to subsequent flare (19-21), deep remission based on US DAS28 findings is also required.

Nevertheless, deep remission based on the absence of PD-positive synovitis (89% in the present study) and on US assessment of 28 joints seems insufficient to predict BFR since a large proportion of patients with a global US score of 0 were relapsers. We can postulate that a single evaluation prior to bDMARD relief is not relevant enough and thus sequential assessment at regular intervals during a period that needs to be defined should be performed to confirm that US remission is persistent before initiating bDMARD dose-reduction. In this respect, in the study conducted by Alivernini et al, the selection of patients was based on US-findings in a cohort of 42 consecutive patients with longstanding RA in clinical remission (DAS < 1.6 for at least 6 months) and receiving combination therapy with methotrexate and TNF-blocking agents (adalimumab or etanercept). Despite serial PD-negative findings during the tapering and discontinuation phases, 38% of patients relapsed after 12-month follow-up after discontinuation (22).

Since characteristics of remission prior to bDMARD relief are unable to predict BFR, the question arose as to whether other parameters, before bDMARD discontinuation as well as during the spacing phase, were potential risk factors of relapse after bDMARD withdrawal.

One of the predictive factors of relapse was long-standing RA with disease duration longer than the median (11 years). In fact, most studies (10,11,13,15) focused on more recent RA with a disease duration less than 6 years. The populations closest to ours were those of the Brocq and STRASS (12,14) in which the mean disease duration was 11 and 9 years, respectively. These 2 studies analyzed non-naive bDMARD patients and the remission rate at one year was 24% and 37.5%, respectively, which was closer to that of our cohort (23%) but lower than that observed in studies with shorter disease duration that included naive bDMARD RA (PRESERVE: 42%, BeSt: 80%, PRIZE: 50%, RRR: 43%)(10,11,13,15). Thus, our results are in line with data in the literature since a disease duration longer the threshold of 5 years is a factor of relapse. In the same way, use of previous bDMARD is a risk factor of relapse.

Low dose glucocorticoid, less than 5 mg per day, was still associated with relapse after treatment discontinuation. Spacing or discontinuation could not be initiated in patients with glucocorticoids, even at a very low dose (3 mg/d in the present study). RRR and STRASS studies allowed corticosteroids at a dose less than 5 mg/day (14,15), PRESERVE tolerated up to 10 mg / day with 60% of patients on prednisone (10). These studies did not observe a correlation between relapse and long-term corticosteroid. For EULAR, in patients in long-term remission, the first step is to reduce corticosteroids and in case of persistent remission the next step is to decrease bDMARD.

Pertinently, the combination with a synthetic DMARD is of importance for the success of bDMARD discontinuation. Indeed, methotrexate combination with bDMARD is a protective factor of relapse. While Brocq et al. did not find it, BeSt reported a protective effect of methotrexate (11,12). The same findings were stated in the PRESERVE and PRIZE studies (10,13). In a meta-analysis (23), a combination of methotrexate with bDMARD achieved low disease activity more quickly and ensured the maintenance of remission after discontinuation of bDMARD, more likely in case of monotherapy. In a meta-analysis of randomized controlled trials on stopping DMARDs in monotherapy, relapse was observed in 46% of RA patients after discontinuation of DMARDs (3). There are no consensual guidelines for bDMARD discontinuation. NICE recommends a prudent decrease in the dose of DMARDs with a recovery to previous dose in case of relapse (24). EULAR recommends that bDMARD tapering can be considered if a patient is in persistent remission after glucocorticoid tapering, especially if this treatment is combined with conventional DMARDs such as methotrexate (4). For EULAR, spacing treatment or decreasing the dosage is quite similar. Those guidelines corroborate our results.

Although data from the RETRO, BeSt, HIT-HARD and POET studies suggest that anti-CCP status has an influence on relapse with a lower chance of maintaining remission in the presence of anti-CCP (25), positivity and/or levels of markers reflecting systemic inflammation or autoimmunity (RF and anti-CCP) were not predictive of relapse in the present study. Only composite biomarker testing including acute phase reactants, cytokines and metalloproteinases were suggested to be relevant in the RETRO study (26).

While there was no difference between a DAS28 <2.6 or a SDAI $\leq$ 3.3 on relapse after stopping treatment, a fluctuation of > 0 in SDAI during spacing was significantly associated with relapse. There are no data in the literature on the influence of DAS28 or SDAI fluctuations on relapse during the spacing period. However, although SDAI at baseline showed no difference, we consider this score to be more robust than DAS28 and our analysis shows that a worsening of this score was associated with relapse. This analysis provides new criteria for tapering bDMARD. Given our results, only patients with decreased SDAI score in relief can stop bDMARD, other patients with increased SDAI should continue bDMARD at the last dose or injection interval. Thus, the kinetic of SDAI during the spacing period seems to be more important than baseline values.

In conclusion, we propose spacing of bDMARD for patients with RA of limited duration, in both clinical and US deep remission of at least one year, on conventional DMARDs,

especially methotrexate and after tapering corticosteroids. Therefore, we suggest withdrawal of bDMARD only if the SDAI or DAS do not worsen during the spacing period.

Other studies are needed to confirm the relevance of these predictive and predictable factors of relapse when considering bDMARD alleviation/discontinuation in RA patients in remission under bDMARD and to evaluate the interest of a panel of molecular and cellular biomarkers that could help to personalize DMARD withdrawal as suggested by recent works using composite scores or multi-omics approaches to define molecular remission (27,28)

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Contributors
OV, SD, TL, GA were involved in the conception and the design of this study; OV, SD, SP, TL were involved in the acquisition of clinical data; MKM, JN, PR, NS performed the ultrasonographic assessments; OV, GA were involved in the statistical analysis; OV, SD, TL, GA were involved in the analysis and interpretation of the data; All authors were involved in the drafting and revision of the manuscript

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Table 1. Demographic, clinical, biological, and drug chracteristics of the study population at baseline and according to the occurrence of relapse during the spacing and discontinuation phases

Parameter		Spacing phase			Discontinuation phase		
	Total (n = 53)	Non-relapser (n = 34)	Relapser (n = 19)	p	Non-relapser (n = 13)	Relapsers (n = 38)	p
Gender, Female n (%)	38 (72)	20 (59)	18 (95)	0.009	7 (54)	30 (79)	0.14
Age, median (IDR)	58 (49-63)	58 (50-63)	56 (48,5-61)	0.56	52 (47-62)	58 (50-63)	0.52
Disease duration, median (IDR)	11 (6-15)	10 (6.3-12.8)	12 (7-16)	0.23	9 (8-11)	12 (6.3-15)	0.29
bDMARD duration, median (IDR)	5 (3-8)	4 (3-7)	7 (3.5-8)	0.07	4 (3-7)	5.5 (3-8)	0.38
DAS 28 ESR, median (IQR)	1.8 (1.4 – 2.1)	1.7 (1.4 – 2.1)	2 (1.4 – 2.2)	0.62	1.5 (1.3 – 1.9)	2 (1.5 – 2.2)	0.11
DAS 28 CRP, median (IQR)	1.6 (1.2 – 1.9)	1.6 (1.2 – 1.9)	1.6 (1.4 – 1.8)	0.93	1.7 (1.5 – 1.9)	1.6 (1.2 – 1.8)	0.18
SDAI, median (IQR)	2 (1 – 3)	1.6 (0.8 – 3)	2 (1 – 3.1)	0.28	2.4 (2 – 3)	1 (1 – 2.9)	0.13
HAQ (0-3), median (IQRR)	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.85	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.84
RF positivity (> 20 IU/ml), n (%)	33 (62)	19 (56)	14 (74)	0.25	8 (62)	24 (63)	1
Anti-CCP positivity (> 10 UA/ml), n (%)	33 (62)	24 (71)	9 (47)	0.14	9 (69)	22 (58)	0.52
GS score, median (IQR)	0 (0 – 2)	0 (0 – 2)	0 (0 – 0)	0.39	0 (0 – 0)	0 (0 – 2)	0.37
PD score, median (IQR)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.59	0 (0 – 0)	0 (0 – 0)	0.5
bDMARD							
Certolizumab, n (%)	1 (2)	1 (3)	0 (0)	0.87	0 (0)	0 (0)	0.22
Etanercept, n (%)	24 (45)	13 (38)	11 (58)		5 (38)	18 (47)	
Adalimumab, n (%)	8 (15)	6 (18)	2 (11)		1 (8)	7 (18)	
Abatacept, n (%)	11 (21)	8 (24)	3 (16)		2 (15)	9 (24)	
Infliximab, n (%)	6 (11)	4 (12)	2 (11)		3 (23)	3 (8)	
Tocilizumab, n (%)	3 (6)	2 (6)	1 (5)		2 (15)	1 (3)	
Methotrexate							
N (%)	42 (79)	28 (82)	14 (74)		12 (92)	28 (74)	0.25
Dose, median (IQR)	15 (7.5 – 15)	15 (7.5 – 16.9)	10 (8.8 – 15)	0.47	15 (10 -25)	10 (5.6 – 15)	0.24
Prednisone							
N (%)	4 (8)	2 (6)	2 (11)		0 (0)	4 (11)	0.56
Dose, median, IQR	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.53	0 (0 – 0)	0 (0 – 0)	0.23

Table 2. Ultrasonographic data at baseline and over the 18-months follow-up period using a Boolean definition

Sonography	Baseline		Month 6 -7		Month 9		Month 12		Month 15		Month 18	
Number of patients	53		42		30		20		15		12	
Mode	GS	PD	GS	PD	GS	PD	GS	PD	GS	PD	GS	PD
Score = 0	20 (38)	36 (68)	15 (36)	26 (62)	6 (20)	14 (47)	7 (25)	13 (65)	3 (20)	8 (53)	2 (17)	7 (58)
Score = 1	19 (36)	11 (21)	11 (26)	7 (17)	8 (27)	6 (20)	0 (0)	2 (10)	5 (33)	0 (0)	5 (42)	2 (17)
Score < or = 1	39 (74)	47 (89)	26 (62)	33 (79)	14 (47)	20 (67)	7 (25)	15 (75)	8 (53)	8 (53)	7 (59)	9 (75)
Score > 1	14 (26)	6 (11)	16 (38)	9 (21)	16 (53)	10 (33)	13 (75)	5 (25)	7 (47)	7 (47)	5 (41)	3 (25)

Results are expressed as number (%)

Abbreviations - GS: gray-scale; PD: power-doppler

Table 3. Analysis of kinetic of composite indexes and ultrasonographic data during the spacing phase as potential predictable factors of relapse after biologic agent withdrawal

Population	All	Relapser	Non-relapser	p
Composite indexes				
Delta DAS 28 ESR > 0, %	77	82.4	66.7	0.18
Delta DAS 28 ESR, mean (SD)	0.4 (0.56)	0.56 (0.57)	0.19 (0.49)	0.07
Delat DAS 28 CRP > 0, %	48	52.9	37.5	0.149
Delta DAS 28 CRP, mean (SD)	0.1 (0.62)	0.22 (0.66)	-0.07 (0.5)	0.582
Delta SDAI > 0, %	60	70.6	37.5	0.03
Delta SDAI, mean (SD)	0.8 (2.87)	1.39 (3.17)	-0.34 (1.69)	0.03
Ultrasonographic data				
Delta GS score > 0, %	17.4	12.5	28.6	0.55
Delta GS score, mean (SD)	0 (0.98)	-0.19 (0.98)	0.29 (0.95)	0.39
Delta PD score > 0, %	30.4	31.3	28.6	1
Delta PD score, mean (SD)	0.1 (1.01)	0.06 (1.06)	0.29 (0.95)	0.68
Delta global score > 0, %	21.7	18.8	28.6	0.62
Delta global score, mean (SD)	- 0.4 (5.01)	-1.06 (5.8)	1.14 (1.95)	0.16

Abbreviations - DAS: Disease Activity Score; SDAI: Simplified Disease Activity Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; GS: Gray-Scale; PD: Power Doppler; SD: Standard Deviation

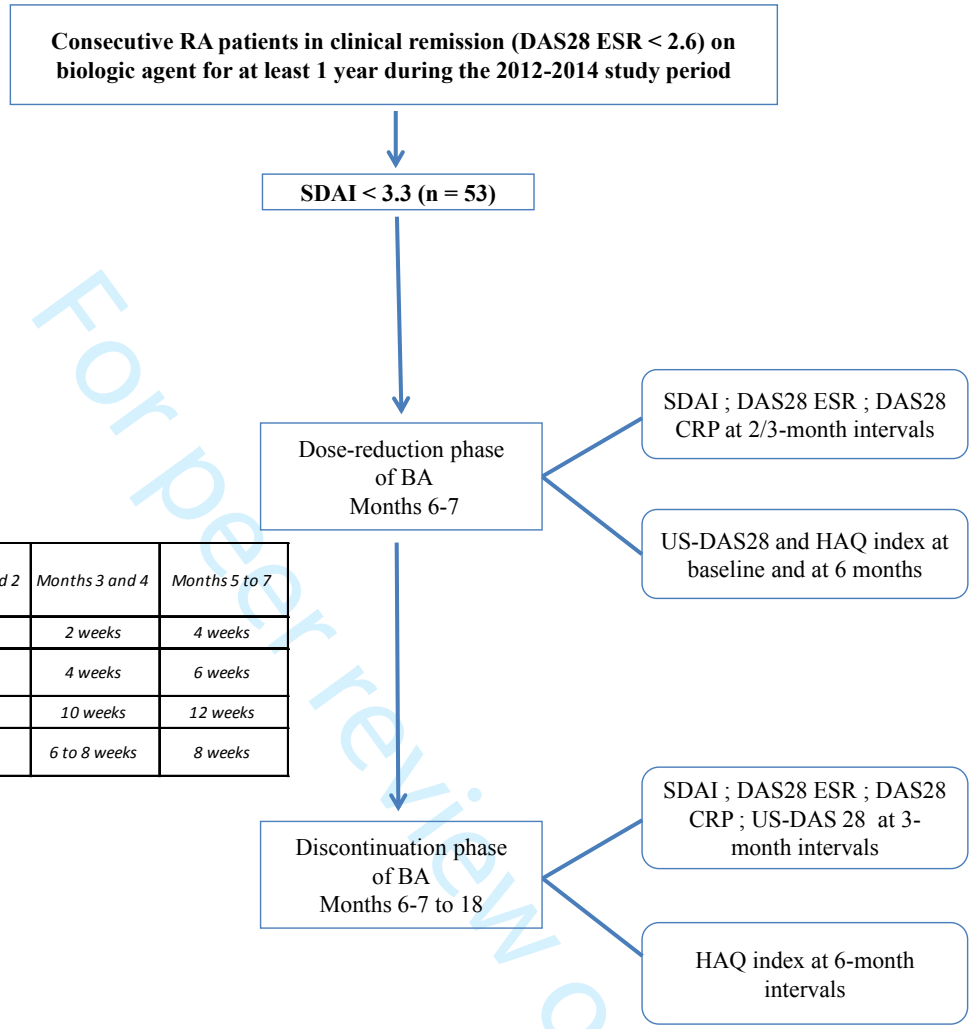
Figure legends

Figure 1. Study design

Figure.2 Global survival curve of biologic agent-free remission

Figure 3. Survival curve showing that a SDAI increase > 0 during the spacing phase was significantly associated to a higher risk of relapse. Survival curve of Delta SDAI> 0 (dotted line) and Delta SDAI ≤ 0 (full line)

Figure 1



Injection interval	*Months 1 and 2*	*Months 3 and 4*	*Months 5 to 7*
ETANERCEPT	*10 days*	*2 weeks*	*4 weeks*
ADALIMUMAB CERTOLIZUMAB	*3 weeks*	*4 weeks*	*6 weeks*
INFLIXIMAB	*8 weeks*	*10 weeks*	*12 weeks*
ABATACEPT TOCILIZUMAB	*6 weeks*	*6 to 8 weeks*	*8 weeks*

Abbreviations: RA : rheumatoid arthritis ; SDAI : Simplified Disease Activity Index ; DAS28 : Disease Activity Score on 28 joints ; ESR : Erythrocyte Sedimentation Rate ; CRP : C-Reactive Protein ; US : UltraSonography; BA : Biologic agent ; HAQ : Health Assessment Questionnaire

Figure 2

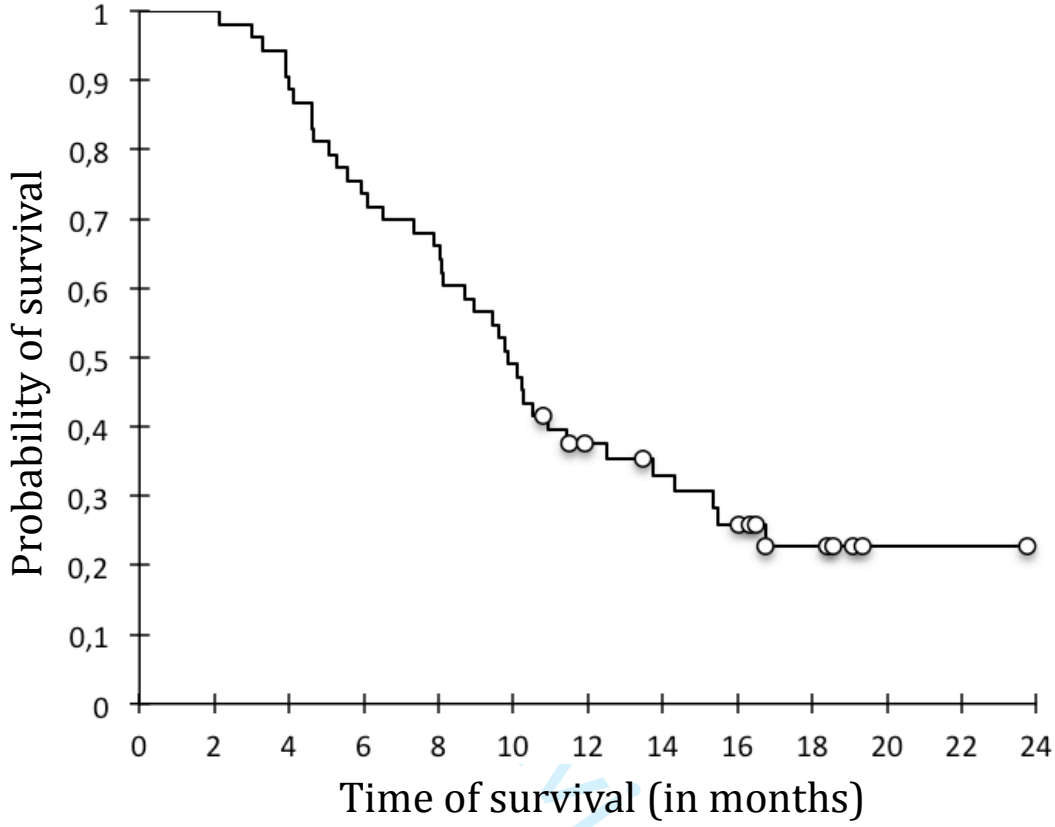
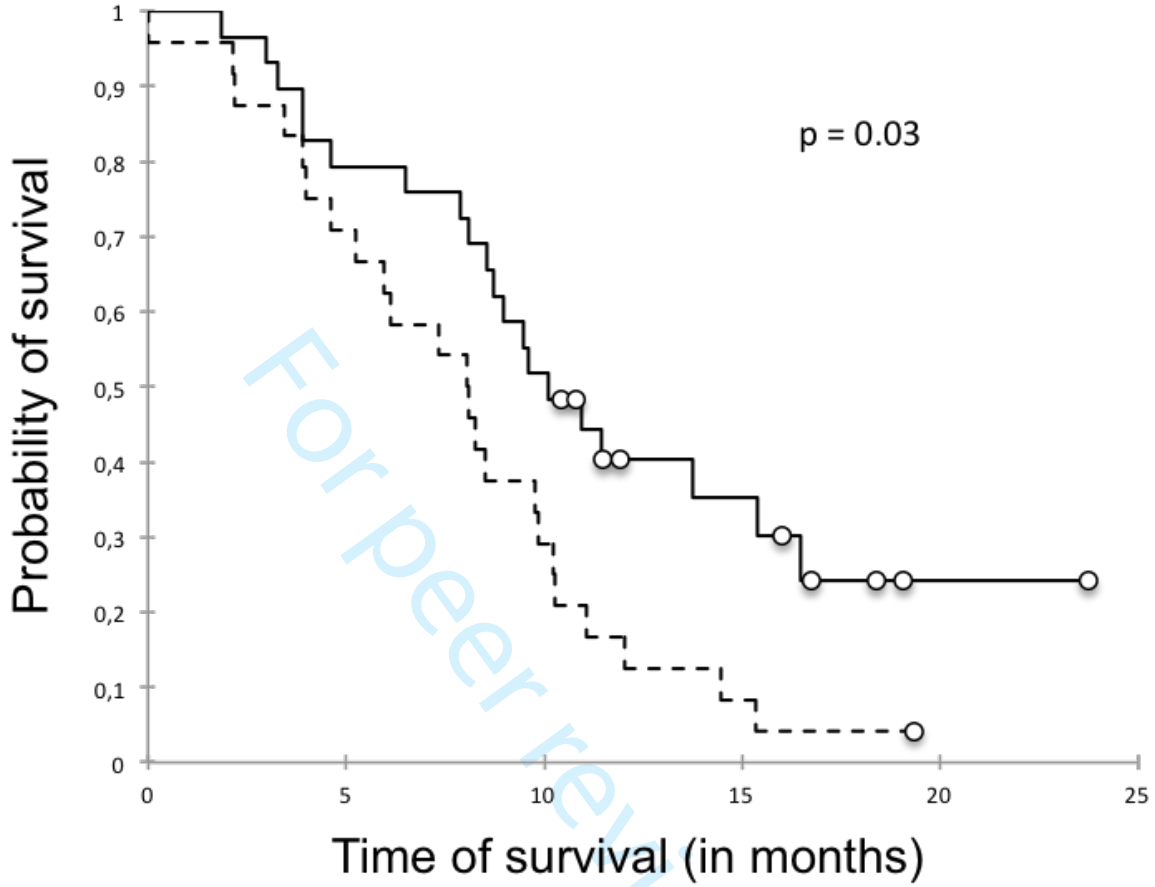


Figure 3



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5,6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5,6*
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	7,8
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1,p16
		(b) Indicate number of participants with missing data for each variable of interest	7,8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7,8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7,8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Relapse in rheumatoid arthritis patients undergoing dose-reduction and withdrawal of biologics: are predictable factors more relevant than predictive parameters? An observational prospective real-life study

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Keywords:	RHEUMATOLOGY, rheumatoid arthritis, ULTRASONOGRAPHY, discontinuation, prediction

Relapse in rheumatoid arthritis patients undergoing dose-reduction and withdrawal of biologics: are predictable factors more relevant than predictive parameters? An observational prospective real-life study

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ABSTRACT

Objective - To determine predictive/predictable factors of relapse in rheumatoid arthritis (RA) patients undergoing biologic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) dose-reduction/discontinuation.

Patients and methods - RA patients receiving the same bDMARD for more than 1 year, in SDAI (Simplified Disease Activity Index) remission, were selected in an observational monocentric real-life study. The 18-months follow-up included spacing (6 months) and withdrawal (12 months) periods of bDMARD. Clinical, biological and ultrasonographic (US) parameters were collected regularly. Relapse was defined by SDAI > 11.

Results - Fifty-three RA patients (mean age: 58 years; 72% women; median duration: 11 years) were enrolled. Forty-two received anti-cytokinic bDMARD targeting TNF (n = 39) or IL-6R (n = 3) and 11 were treated by abatacept. The numbers of relapses during the spacing and discontinuation periods were 19 and 20 respectively. After 18 months of follow-up, 12/53 maintained bDMARD-free remission, 39/53 had relapsed and 2 were lost of follow-up. Median time to relapse was 11.8 months. In multivariate analysis, baseline factors predictive of relapse were corticosteroid intake, female gender, longer disease duration and no methotrexate intake with bDMARD. Concerning the survival analysis, when taking also into account the factors of predictability, the main risk factor of relapse after discontinuation was an increase of SDAI > 0 during the spacing period (p = 0.03). US findings were not contributive.

Conclusion - In the context of RA in remission under bDMARDs, variation of SDAI during the dose-reduction phase is more relevant than baseline parameters to predict success of drug withdrawal.

Key words: rheumatoid arthritis; biologic DMARD; withdrawal; spacing; remission; ultrasonography; prediction; predictability

Strengths and limitations of this study

This prospective real-life multiparameter study used a well-defined procedure of gradual dose-reduction and discontinuation of biologic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) in rheumatoid arthritis (RA) patients in remission for at least 1 year

Very strict remission criteria based on clinical and ultrasonographic data were required to consider dose-reduction of bDMARDs

Both factors of prediction (collected just prior to therapeutic relief) and predictability (related to kinetic of parameters during the dose-reduction phase) were considered as potential predictors of relapse

Almost all bDMARDs were taken into account to identify candidate predictors of relapse after discontinuation that could be applied to any drug

The main weakness of the study is the limited population size

INTRODUCTION

In rheumatoid arthritis (RA), after achieving low disease activity (LDA) or remission (1), the goal of therapy is to maintain clinical, functional and structural remission (2). For some patients, this is possible even after the cessation of biologic DMARD (bDMARD)(3). The opportunity of discontinuing bDMARD after achieving remission must be considered because of potential long-term safety issues and the economic burden associated with their expense. Furthermore, the disease can spontaneously evolve towards an inactive form. Multiple studies have investigated whether remission can be sustained after a bDMARD is discontinued, namely, « biologic-free remission (BFR) »(3).

The European League Against Rheumatism (EULAR) 2012 guidelines (4) suggest that we can consider tapering bDMARD. Determining the patient profile associated with a high chance of sustained remission after the cessation of bDMARD is of great importance to avoid disease flares. For this purpose, two definitions of remission have been proposed, either the Boolean definition or a score of the Simplified Disease Activity Index (SDAI) < 3.3 (5, 6). However, the majority of studies did not use these definitions for eligibility to bDMARD spacing or withdrawal. Indeed, in most reports, Disease Activity Score on 28 joints (DAS28) was used to select patients for withdrawal of bDMARD in RA patients having achieved remission (7).

For patients with long-standing RA, the discontinuation of TNF-inhibitors after sustained remission has been shown to be possible in some cases. However, high flare rates have been documented in other studies. For these patients, bDMARD dose-reduction or spacing regimen followed by secondary withdrawal may be preferable instead of sudden discontinuation (3).

According to several studies, it appears that the criteria for spacing the administration of bDMARD in RA patients in remission are not consensual and that we lack validated data. In this respect, a systematic review of studies addressing predictors of successful dose reduction or discontinuation of bDMARD in RA shows that there is no consistent predictor (7).

To respect EULAR recommendations, we introduced standardized practices in our rheumatology department, in routine care, several years ago. Spacing and then discontinuation of bDMARD is performed in RA patients in remission according to 2011 ACR-EULAR criteria (6).

The general objective of this real-life, prospective study was to define strict eligibility criteria for bDMARD spacing/withdrawal in long-standing RA patients in remission. The specific objectives were (i) to define the rate of relapse during the spacing and withdrawal periods in a RA population; (ii) to identify predictive/predictable factors of relapse during the withdrawal phase of bDMARD, and (iii) to determine whether duration and degree of clinical remission as well as US findings at time of bDMARD spacing influenced the achievement of bDMARD withdrawal.

PATIENTS AND METHODS

Study design

This prospective real life study comprised an inclusion visit and two phases (Figure 1).

Patients

In this study were enrolled all RA patients treated by bDMARD between 2012 and 2014, in the rheumatology department of Rouen University Hospital. bDMARDs were infliximab, etanercept, adalimumab, abatacept, certolizumab and tocilizumab. Golimumab was not considered since it was introduced more recently. Rituximab was not relevant for such a strategy of spacing/withdrawal. Patients with subcutaneous treatment were selected at annual follow-up visits in the ambulatory care unit. Patients with intravenous bDMARD were selected in the immunotherapy unit of the department.

Inclusion criteria

They comprised RA patients (older than 18 years), fulfilling ACR/EULAR 2010 criteria, in remission defined as a DAS28 < 2.6 for at least 12 months, and receiving the same bDMARD for at least 1 year. Prior to initiation of spacing, a SDAI <3.3 was required (6). Patients taking prednisone (or equivalent) at a dose > 5mg/day or with structural evolution during the previous year were excluded.

Ethics

The agreement of both hospital and private rheumatologists was collected before bDMARD spacing. All patients gave their consent for this procedure. The study (E2014-28) was approved by the local institutional review board (named Ethics Committee for Non-Interventional Research) according to law n°2012-300.

Schedule of visits and dose tapering

All visits were planned every 2 months during the spacing phase that lasted 6 or 7 months according to the bDMARD used and then every 3 months during 1 year after discontinuation of the bDMARD. Dose tapering was standardized for each drug during the spacing phase as shown in Figure 1.

Parameters studied

Inclusion visit

During this visit, the presence of all inclusion criteria was checked. The following parameters were collected: all data needed to calculate DAS28-ESR, DAS28-CRP and SDAI; completion of the Health Assessment Questionnaire (HAQ); laboratory tests (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factors (RF), and anti-cyclic citrullinated peptide antibodies (anti-CCP). We also recorded the following data for each patient: demographic characteristics, RA duration, number of synthetic DMARDs, bDMARDs received, and time on bDMARD.

In addition, ultrasonographic examination of the 28 joints was carried out at baseline, using a MyLab 70 (Technos Esaote), by 4 operators (MKM, JN, PR, NS) with long-standing experience in US evaluation of chronic inflammatory rheumatic diseases. They have already participated in several multicenter studies and the intra- and inter-observer reliability was similar to that reported in the study conducted by D'Agostino MA et al. (8). All sonographers were blinded to clinical information and laboratory data. A systematic multiplanar gray-scale (GS) and power-doppler (PD) ultrasound examination of the 28 joints included in the disease activity score (US-DAS28) was performed using a high-frequency (13.5 MHz) linear array transducer. Joints were evaluated using a semi-quantitative scoring system with a 0-3 scale for GS and PD according to the method developed by Szkudlarek et al (9). Findings were described using the definitions established by the OMERACT. The overall GS and PD scores for synovitis were measured and the global PDUS score (sum of total GS and PD scores) was calculated for each patient.

Spacing procedure

A visit was scheduled every 2/3 months according to the bDMARD. At each visit, the parameters mentioned previously and ongoing treatments were recorded. An US evaluation of the 28 joints was carried out at month 7.

Spacing was defined for each bDMARD. During this period, visits were performed at 3 time-points: months 2, 4 and 6 or 7. The inter-injection interval was increased at each visit in order to stop bDMARD completely at month 7.

During the study period, all associated treatments were unmodified. The dose of conventional DMARDs and corticosteroids was stable.

Follow-up visits after bDMARD discontinuation

After discontinuation at month 7, patients were evaluated at 3-month intervals via physical examination, ESR and CRP determinations, SDAI and DAS28 computation, and 28 joint US examination.

Definition of relapse

Relapse was defined as SDAI > 11 which was determined by rheumatologists who were blinded to US findings.

In this dose-reduction phase, patients restarted their treatment with the previous scheme. After discontinuation, relapsing patients were immediately retreated with their previous bDMARD, at the previous dosage, with no change in prednisone or synthetic DMARD dosage.

Statistical Analysis

Demographic characteristics, clinical and biological data were summarized by descriptive analysis. Student's t-tests and Fisher's tests were used for quantitative and qualitative variables, respectively. Relapse-free survival data were analyzed using the log-rank test. Qualitative variables were analysed directly; quantitative variables have been expressed as

compared to normal values or median ; p-values lower than 0.10 were considered significant to be analysed in a multivariate model. In multivariate survival analysis, the Cox model was used. We used NCSS version 2007 for statistical analysis. P-values lower than 0.05 were considered significant.

Candidate predictors were: age, gender, disease duration, immunological status, number of previous bDMARDs, type of bDMARD, treatments combined to bDMARD and their dose, disease activity scores at baseline and their kinetic during the spacing phase, US data at baseline and their outcome during the dose-reduction phase, HAQ at baseline and its kinetic during the tapering phase, ESR, CRP

Two types of analysis were performed. For the first one, the primary outcome was relapse versus no relapse either during the dose-reduction phase or over the discontinuation period. The second one, which was the more relevant, was focused on time to relapse. Concerning the two patients in remission at their last visit who were lost of follow-up, they have been censored at the time of their last visit. Thus, they have been included in the remission group for the survival analysis but excluded from the binary outcome analysis of relapse versus no-relapse.

Patient and public involvement

Patients were not involved in the design and the conduction of the present study

RESULTS

Baseline characteristics of the study population

Among the 378 RA patients treated with a bDMARD between January 2012 and January 2013, 53 (14%) fulfilled our criteria for disease remission (SDAI < 3.3) and were selected for the spacing/discontinuation standardized procedure (figure 1). This cohort included 38 female and 15 male patients with a mean age of 58.5 years, a mean disease duration of 13 years (median 11 years; 4-32 years); 62% patients were rheumatoid factor positive and 62 % were anti-CCP positive; 49% were double-positive and 25% double negative; 85 % patients had at least one x-ray erosion. Among double negative RA patients, 85% had structural damage. At the inclusion visit, the mean values of DAS28-ESR, DAS28-CRP, SDAI and HAQ were 1.76, 1.6, 1.9 and 0.23, respectively.

Among the 53 patients, 6, 8, 24, 11, 1 and 3 were on infliximab, adalimumab, etanercept, abatacept, certolizumab and tocilizumab, respectively; 10 patients were switched to another bDMARD: 1 switch (n = 5), 2 switches (n = 3), 3 switches (n=2). At the time of the study, 42 (79.2%) patients were taking methotrexate at a mean dose of 11.79 mg/week, and one patient was on leflunomide. Thus, 10 patients received bDMARD in monotherapy. Only 4 patients were on prednisone (mean dose: 3.13 mg/day).

Results are also expressed in median (IQR) and summarized in Table 1.

Ultrasonographic data are shown in Table 2. The mean score of GS synovitis was 1.7 and that of PD synovitis was 0.7. The mean global score was 2.5, reflecting low disease activity. Among the 53 patients, 38 (72%) had a global score of 0. Global scores for GS and PD assessments were also expressed in a Boolean manner according to the definition used for the 4 items of the last remission criteria (< or = 1/28)(6). Each joint was graded 0 or 1. A value of 1 was considered when the grade was > 1 (2 or 3) for a given joint according to the Szkudlarek definition (7). Using this Boolean definition for US evaluation on 28 joints, three quarters of patients had a GS score < or = 1 and, more importantly, 89% had a PD score < or = 1 at baseline (Table 2).

Spacing and discontinuation periods

During the spacing period, 5 patients relapsed at month 4 and 14 at month 7

Thirty-four patients were able to stop their bDMARD at month 7. At month 9, 7 patients relapsed, and 27 were able to continue treatment withdrawal. Ten patients relapsed at month 12, 2 at month 15 and 2 at month 18. At the end of the 18-month follow-up period, 14 patients had completed the visit; 2 had relapsed while 12 were still in remission. Among the 53 patients, 41 relapsed. Among those who relapsed, there were two patients in remission at their last visit who were lost to follow-up. Importantly, all patients on monotherapy (without combination with methotrexate) relapsed, as well as the 4 patients who received a low dose of corticosteroids.

Among the 12 non-relapsing patients, the mean DAS28 CRP was 2.14 (1.43-2.86; SD: 0.7) and the mean SDAI was 4.03 (0.37-7.7, SD: 3.66) at the last visit. Ten had a DAS-28 CRP < 2.6 and 7 a SDAI < 3.3 at all visits. Thus, according to the SDAI definition of remission, only 7 patients had a sustained deep remission (i.e., a SDAI < 3.3 at all time-points)

During the spacing and discontinuation phases, there were more patients with a global PD score > 1/28 according to the Boolean definition (Table 2).

Identification of predictive factors of relapse

The survival analysis of patients who relapsed found a median relapse time of 11.8 months (fig.2). There were a majority of women in the relapsing group: 79.5% versus 50% in non-relapsers (p = 0.066). The proportion of patients with disease duration longer than the median (11 years) was significantly higher in the relapsing group: 56.4% of relapsers versus 16.7% of non-relapsers (p = 0.022). Age, anti-CCP or RF positivity/titers were not significantly different between relapsers and non-relapsers. Indeed, the number of non-relapsers who were seronegative and without erosions was limited to 1 patient. Clinical and US composite scores showed no significant difference. In this regard, while all patients with at least one PD-positive-US synovitis (grade > 1) were relapsers, those with a global score of 0 on sonography or satisfying the Boolean definition for GS or PD global scores could be relapsers or not.

Survival analysis between relapsers and non-relapsers showed that the following criteria: disease duration longer than the median (p = 0.032), previous biologic therapy (p = 0.068),

and treatment with corticosteroids (p = 10-3), ESR> 10 (p = 0.098) were significantly (or tended to be) associated with relapse.

In multivariate analysis, relapse risk factors were corticosteroid use with a risk ratio of relapse at 13.78 (95%CI 3.95-48.08, p =0.001), disease duration longer than the median (11 years) with a risk ratio at 2.18 (95%CI: 1.08-4.39, p = 0.029).

Risk factors of relapse taking into account both factors of prediction and of predictability.

This analysis comprises both baseline parameters collected prior to dose-reduction phase (referred to as predictive factors) and kinetic of clinical, biological and US parameters during the tapering phase prior to discontinuation (labelled factors of predictability).

It has been carried out from patients that completed the tapering phase and underwent the discontinuation period.

Survival analysis during the withdrawal period, taking into account baseline parameters and the evolution of some of them during the spacing phase, was performed and included 32 patients. Median survival was 7.6 months (5.3-11.2) following the month 7 visit. There were 12 non-relapsing patients whereas 20 patients relapsed.

The univariate analysis showed that disease duration longer than the median (p = 0.021) was predictive of relapse after discontinuation of treatment. Before spacing, methotrexate intake (p = 0.140) was a potential protective factor during discontinuation of treatment.

The univariate survival analysis, taking into account the kinetics of parameters between M0 (baseline) and M7 (end of spacing phase) showed that variations of SDAI was significantly associated with relapse (Fig.3) in contrast to those of ultrasonographic scores (Table 3).

The multivariate analysis identified as relapse risk factors a SDAI increase > 0 between M0 and M7 with a risk ratio of 21.77 (95%CI 2.1-225.74, p = 0.03)(Fig 3). This point means that an increase of SDAI between two visits during the tapering phase was predictive of relapse defined by a SDAI > 11 after bDMARD discontinuation. In contrast, methotrexate use was protective of relapse with a risk ratio of 0.07 (95%CI: 0.01-0.61, p = 0.016). After exclusion of the 4 patients who received low doses (1, 2.5, 4 and 5 mg per day) of corticosteroids, the same findings were obtained (data not shown).

DISCUSSION

Our study has several strengths. This was a prospective real life study with a standardized procedure for spacing and discontinuation in accordance with international recommendations (4). Our analysis took into account all bDMARD available except rituximab and JAK/STAT inhibitors (not available at the time of analysis), unlike other analyses that focused mainly on TNF-blocking agents or a single bDMARD (infliximab, etanercept, adalimumab, tocilizumab, abatacept). Even though the sample size for patients treated with abatacept and tocilizumab was low, we did not perform a specific analysis focused on TNF blockers since we consider

that candidate predictors of relapse after discontinuation should be applied to any bDMARD, whatever its mechanism of action. Moreover, although they target TNF, all TNF-antagonists have their own specificities concerning the mode of action.

Our study is one of the first to consider factors of predictability. However, one limitation of our study is the limited population size. These 53 patients in remission represented 14% of our population of 378 RA patients. This small percentage of patients in remission may be related to the strict definition of remission that we used (SDAI <3.3) whereas, when DAS28-ESR was considered (DAS 28 < 2.6), 142 (38%) patients were in remission, which is more in line with data reported in the literature. In addition, the majority of RA patients in our unit had longstanding disease. Moreover, the tapering strategy was very rapid compared to those reported in the literature or done in daily practice but, to our knowledge, there is no consensus about the dose-reduction process for each bDMARD. Nevertheless, this might alter the external validity of the present results. Finally, we have not investigated molecular and cellular biomarkers likely to reflect an immunological remission.

The characteristics of our population are concordant with those observed in other reports such as PRESERVE, BEST, PRIZE, STRASS and that of Brocq et al (10-14).

Based on EULAR recommendations (4) and data from the literature, we performed spacing of bDMARD rather than sudden discontinuation. Our scheme has the distinction of proposing gradual spacing and then discontinuation as in the STRASS study in which bDMARD were represented by etanercept and adalimumab (14). Other studies (BeSt, PRESERVE, PRIZE) proposed dose reduction (9,10,13). In the present study and in the STRASS study (14), 35.8% and 26.5% of patients relapsed during the spacing period, respectively; then 64% and 37.5% of patients were able to stop BA and finally 77% and 81% relapsed, respectively.

Our study required very strict remission criteria compared to other studies and notably had a remission duration of at least one year compared to other studies which often selected patients with a remission duration of 6 months. In addition, we defined remission by SDAI < 3.3 (6) when other studies (RRR, PRESERVE) used DAS28 < 3.2 (10,15) or DAS28 < 2.6 (12, 13,14,16). In this respect, with low disease activity as criteria of selection (DAS28 < 3.2), RRR and PRESERVE had a lower bDMARD-free remission rate (43 and 42%) than PRIZE and BeSt (53 and 80%). Thus, it seems better to use bDMARD withdrawal only in patients with deep remission as reported by Tanaka et al who found that a DAS-28 ESR < 2.2 was associated with maintenance of DFR (15).Those data led us to retain a SDAI < 3.3 as a criterion of eligibility for bDMARD spacing. Such a level of clinical and biological remission is close to US remission as observed in a previous study (17) and in ours in which three quarters of patients had a global (GS plus PD) US score of 0 based on the assessment of 28 joints. Moreover, the duration of remission appears to be an important prerequisite to consider bDMARD relief. Indeed, subclinical joint activity is long-lasting in RA joints in clinical remission. Even though there is attenuation over time, the mean time (+/- SD) since last clinical swelling and positive sonographic assessment was significantly shorter in patients showing high GS or PD signals compared with lower-grade GS or PD signals (18). Since subclinical disease activity may persist several years in clinically inactive joints and US PD

positive synovitis is related to subsequent flare (19-21), deep remission based on US DAS28 findings is also required.

Nevertheless, deep remission based on the absence of PD-positive synovitis (89% in the present study) and on US assessment of 28 joints seems insufficient to predict BFR since a large proportion of patients with a global US score of 0 were relapsers. We can postulate that a single evaluation prior to bDMARD relief is not relevant enough and thus sequential assessment at regular intervals during a period that needs to be defined should be performed to confirm that US remission is persistent before initiating bDMARD dose-reduction. In this respect, in the study conducted by Alivernini et al, the selection of patients was based on US-findings in a cohort of 42 consecutive patients with longstanding RA in clinical remission (DAS < 1.6 for at least 6 months) and receiving combination therapy with methotrexate and TNF-blocking agents (adalimumab or etanercept). Despite serial PD-negative findings during the tapering and discontinuation phases, 38% of patients relapsed after 12-month follow-up after discontinuation (22).

Since characteristics of remission prior to bDMARD relief are unable to predict BFR, the question arose as to whether other parameters, before bDMARD discontinuation as well as during the spacing phase, were potential risk factors of relapse after bDMARD withdrawal.

One of the predictive factors of relapse was long-standing RA with disease duration longer than the median (11 years). In fact, most studies (10,11,13,15) focused on more recent RA with a disease duration less than 6 years. The populations closest to ours were those of the Brocq and STRASS (12,14) in which the mean disease duration was 11 and 9 years, respectively. These 2 studies analyzed non-naive bDMARD patients and the remission rate at one year was 24% and 37.5%, respectively, which was closer to that of our cohort (23%) but lower than that observed in studies with shorter disease duration that included naive bDMARD RA (PRESERVE: 42%, BeSt: 80%, PRIZE: 50%, RRR: 43%)(10,11,13,15). Thus, our results are in line with data in the literature since a disease duration longer the threshold of 5 years is a factor of relapse. In the same way, use of previous bDMARD is a risk factor of relapse.

Low dose glucocorticoid, less than 5 mg per day, was still associated with relapse after treatment discontinuation. Spacing or discontinuation could not be initiated in patients with glucocorticoids, even at a very low dose (3 mg/d in the present study). RRR and STRASS studies allowed corticosteroids at a dose less than 5 mg/day (14,15), PRESERVE tolerated up to 10 mg / day with 60% of patients on prednisone (10). These studies did not observe a correlation between relapse and long-term corticosteroid. For EULAR, in patients in long-term remission, the first step is to reduce corticosteroids and in case of persistent remission the next step is to decrease bDMARD.

Pertinently, the combination with a synthetic DMARD is of importance for the success of bDMARD discontinuation. Indeed, methotrexate combination with bDMARD is a protective factor of relapse. While Brocq et al. did not find it, BeSt reported a protective effect of methotrexate (11,12). The same findings were stated in the PRESERVE and PRIZE studies

(10,13). In a meta-analysis (23), a combination of methotrexate with bDMARD achieved low disease activity more quickly and ensured the maintenance of remission after discontinuation of bDMARD, more likely in case of monotherapy. In a meta-analysis of randomized controlled trials on stopping bDMARDs in monotherapy, relapse was observed in 46% of RA patients after discontinuation of bDMARDs (3). There are no consensual guidelines for bDMARD discontinuation. NICE recommends a prudent decrease in the dose of bDMARDs with a recovery to previous dose in case of relapse (24). EULAR recommends that bDMARD tapering can be considered if a patient is in persistent remission after glucocorticoid tapering, especially if this treatment is combined with conventional DMARDs such as methotrexate (4). For EULAR, spacing treatment or decreasing the dosage is quite similar. Those guidelines corroborate our results.

Although data from the RETRO, BeSt, HIT-HARD and POET studies suggest that anti-CCP status has an influence on relapse with a lower chance of maintaining remission in the presence of anti-CCP (25), positivity and/or levels of markers reflecting systemic inflammation or autoimmunity (RF and anti-CCP) were not predictive of relapse in the present study. Only composite biomarker testing including acute phase reactants, cytokines and metalloproteinases were suggested to be relevant in the RETRO study (26).

While there was no difference between a DAS28 <2.6 or a SDAI ≤ 3.3 on relapse after stopping treatment, a fluctuation of > 0 in SDAI during spacing was significantly associated with relapse. There are no data in the literature on the influence of DAS28 or SDAI fluctuations on relapse during the spacing period. However, although SDAI at baseline showed no difference, we consider this score to be more robust than DAS28 and our analysis shows that a worsening of this score was associated with relapse. This analysis provides new criteria for tapering bDMARD. Given our results, only patients with decreased SDAI score in relief can stop bDMARD, other patients with increased SDAI should continue bDMARD at the last dose or injection interval. Thus, the kinetic of SDAI during the spacing period seems to be more important than baseline values.

CONCLUSION

We propose spacing of bDMARD for patients with RA of limited duration, in both clinical and US deep remission of at least one year, on conventional DMARDs, especially methotrexate and after tapering corticosteroids. Therefore, we suggest withdrawal of bDMARD only if the SDAI or DAS do not worsen during the spacing period.

Other studies are needed to confirm the relevance of these predictive and predictable factors of relapse when considering bDMARD alleviation/discontinuation in RA patients in remission under bDMARD and to evaluate the interest of a panel of molecular and cellular biomarkers that could help to personalize DMARD withdrawal as suggested by recent works using composite scores or multi-omics approaches to define molecular remission (27,28)

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Contributors
OV, SD, TL, GA were involved in the conception and the design of this study; OV, SD, SP, TL were involved in the acquisition of clinical data; MKM, JN, PR, NS performed the ultrasonographic assessments; OV, GA were involved in the statistical analysis; OV, SD, TL, GA were involved in the analysis and interpretation of the data; All authors were involved in the drafting and revision of the manuscript

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Competing interests – The authors declare that they have no conflict of interest with regard to this work

Ethics approval - The study (E2014-28) was approved by the local institutional review board (named Ethics Committee for Non-Interventional Research) according to law n°2012-300

Data sharing: data are available upon request.

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Table 1. Demographic, clinical, biological, and drug chracteristics of the study population at baseline and according to the occurrence of relapse during the spacing and discontinuation phases

Parameter		Spacing phase			Discontinuation phase		
	Total (n = 53)	Non-relapser (n = 34)	Relapser (n = 19)	p	Non-relapser (n = 13)	Relapsers (n = 38)	p
Gender, Female n (%)	38 (72)	20 (59)	18 (95)	0.009	7 (54)	30 (79)	0.14
Age, median (IDR)	58 (49-63)	58 (50-63)	56 (48,5-61)	0.56	52 (47-62)	58 (50-63)	0.52
Disease duration, median (IDR)	11 (6-15)	10 (6.3-12.8)	12 (7-16)	0.23	9 (8-11)	12 (6.3-15)	0.29
bDMARD duration, median (IDR)	5 (3-8)	4 (3-7)	7 (3.5-8)	0.07	4 (3-7)	5.5 (3-8)	0.38
DAS 28 ESR, median (IQR)	1.8 (1.4 – 2.1)	1.7 (1.4 – 2.1)	2 (1.4 – 2.2)	0.62	1.5 (1.3 – 1.9)	2 (1.5 – 2.2)	0.11
DAS 28 CRP, median (IQR)	1.6 (1.2 – 1.9)	1.6 (1.2 – 1.9)	1.6 (1.4 – 1.8)	0.93	1.7 (1.5 – 1.9)	1.6 (1.2 – 1.8)	0.18
SDAI, median (IQR)	2 (1 – 3)	1.6 (0.8 – 3)	2 (1 – 3.1)	0.28	2.4 (2 – 3)	1 (1 – 2.9)	0.13
HAQ (0-3), median (IQRR)	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.85	0.1 (0 – 0.3)	0.1 (0 – 0.3)	0.84
RF positivity (> 20 IU/ml), n (%)	33 (62)	19 (56)	14 (74)	0.25	8 (62)	24 (63)	1
Anti-CCP positivity (> 10 UA/ml), n (%)	33 (62)	24 (71)	9 (47)	0.14	9 (69)	22 (58)	0.52
GS score, median (IQR)	0 (0 – 2)	0 (0 – 2)	0 (0 – 0)	0.39	0 (0 – 0)	0 (0 – 2)	0.37
PD score, median (IQR)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.59	0 (0 – 0)	0 (0 – 0)	0.5
bDMARD							
Certolizumab, n (%)	1 (2)	1 (3)	0 (0)	0.87	0 (0)	0 (0)	0.22
Etanercept, n (%)	24 (45)	13 (38)	11 (58)		5 (38)	18 (47)	
Adalimumab, n (%)	8 (15)	6 (18)	2 (11)		1 (8)	7 (18)	
Abatacept, n (%)	11 (21)	8 (24)	3 (16)		2 (15)	9 (24)	
Infliximab, n (%)	6 (11)	4 (12)	2 (11)		3 (23)	3 (8)	
Tocilizumab, n (%)	3 (6)	2 (6)	1 (5)		2 (15)	1 (3)	
Methotrexate							
N (%)	42 (79)	28 (82)	14 (74)		12 (92)	28 (74)	0.25
Dose, median (IQR)	15 (7.5 – 15)	15 (7.5 – 16.9)	10 (8.8 – 15)	0.47	15 (10 -25)	10 (5.6 – 15)	0.24
Prednisone							
N (%)	4 (8)	2 (6)	2 (11)		0 (0)	4 (11)	0.56
Dose, median, IQR	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.53	0 (0 – 0)	0 (0 – 0)	0.23

Table 2. Ultrasonographic data at baseline and over the 18-months follow-up period using a Boolean definition

Sonography	Baseline		Month 6 -7		Month 9		Month 12		Month 15		Month 18	
Number of patients	53		42		30		20		15		12	
Mode	GS	PD	GS	PD	GS	PD	GS	PD	GS	PD	GS	PD
Score = 0	20 (38)	36 (68)	15 (36)	26 (62)	6 (20)	14 (47)	7 (25)	13 (65)	3 (20)	8 (53)	2 (17)	7 (58)
Score = 1	19 (36)	11 (21)	11 (26)	7 (17)	8 (27)	6 (20)	0 (0)	2 (10)	5 (33)	0 (0)	5 (42)	2 (17)
Score < or = 1	39 (74)	47 (89)	26 (62)	33 (79)	14 (47)	20 (67)	7 (25)	15 (75)	8 (53)	8 (53)	7 (59)	9 (75)
Score > 1	14 (26)	6 (11)	16 (38)	9 (21)	16 (53)	10 (33)	13 (75)	5 (25)	7 (47)	7 (47)	5 (41)	3 (25)

Results are expressed as number (%)

Abbreviations - GS: gray-scale; PD: power-doppler

Table 3. Analysis of kinetic of composite indexes and ultrasonographic data during the spacing phase as potential predictable factors of relapse after biologic agent withdrawal

Population	All	Relapser	Non-relapser	p
Composite indexes				
Delta DAS 28 ESR > 0, %	77	82.4	66.7	0.18
Delta DAS 28 ESR, mean (SD)	0.4 (0.56)	0.56 (0.57)	0.19 (0.49)	0.07
Delat DAS 28 CRP > 0, %	48	52.9	37.5	0.149
Delta DAS 28 CRP, mean (SD)	0.1 (0.62)	0.22 (0.66)	-0.07 (0.5)	0.582
Delta SDAI > 0, %	60	70.6	37.5	0.03
Delta SDAI, mean (SD)	0.8 (2.87)	1.39 (3.17)	-0.34 (1.69)	0.03
Ultrasonographic data				
Delta GS score > 0, %	17.4	12.5	28.6	0.55
Delta GS score, mean (SD)	0 (0.98)	-0.19 (0.98)	0.29 (0.95)	0.39
Delta PD score > 0, %	30.4	31.3	28.6	1
Delta PD score, mean (SD)	0.1 (1.01)	0.06 (1.06)	0.29 (0.95)	0.68
Delta global score > 0, %	21.7	18.8	28.6	0.62
Delta global score, mean (SD)	- 0.4 (5.01)	-1.06 (5.8)	1.14 (1.95)	0.16

Abbreviations - DAS: Disease Activity Score; SDAI: Simplified Disease Activity Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; GS: Gray-Scale; PD: Power Doppler; SD: Standard Deviation

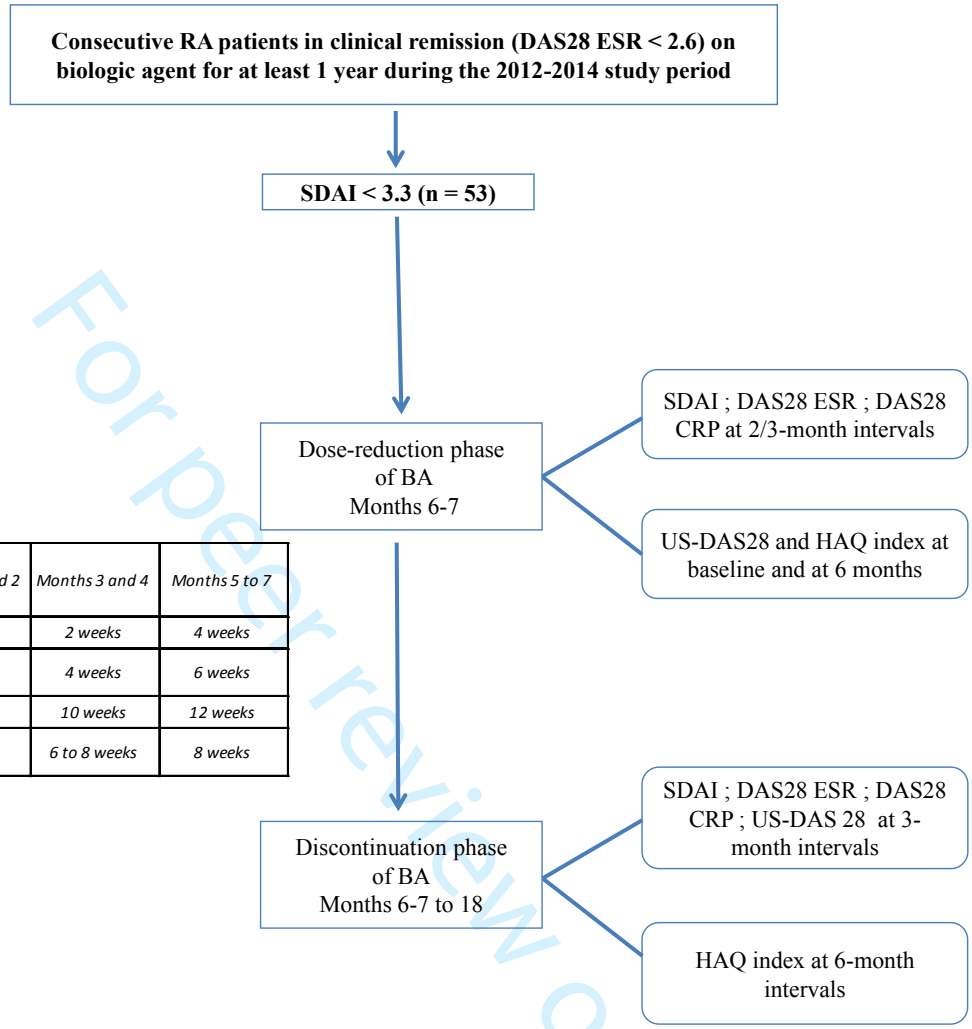
Figure legends

Figure 1. Study design

Figure.2 Global survival curve of biologic free remission

Figure 3. Survival curve showing that a SDAI increase > 0 during the spacing phase was significantly associated to a higher risk of relapse. Survival curve of Delta SDAI> 0 (dotted line) and Delta SDAI ≤ 0 (full line)

Figure 1



Injection interval	*Months 1 and 2*	*Months 3 and 4*	*Months 5 to 7*
ETANERCEPT	*10 days*	*2 weeks*	*4 weeks*
ADALIMUMAB CERTOLIZUMAB	*3 weeks*	*4 weeks*	*6 weeks*
INFLIXIMAB	*8 weeks*	*10 weeks*	*12 weeks*
ABATACEPT TOCILIZUMAB	*6 weeks*	*6 to 8 weeks*	*8 weeks*

Abbreviations: RA : rheumatoid arthritis ; SDAI : Simplified Disease Activity Index ; DAS28 : Disease Activity Score on 28 joints ; ESR : Erythrocyte Sedimentation Rate ; CRP : C-Reactive Protein ; US : UltraSonography; BA : Biologic agent ; HAQ : Health Assessment Questionnaire

Figure 2

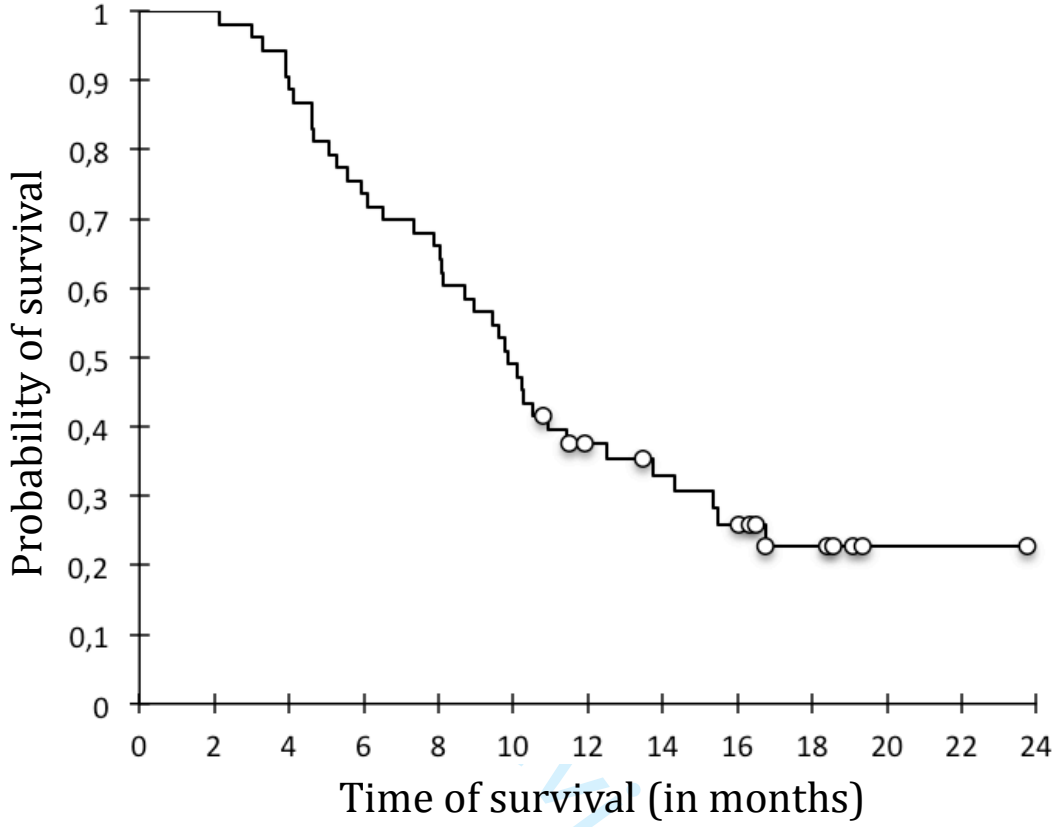
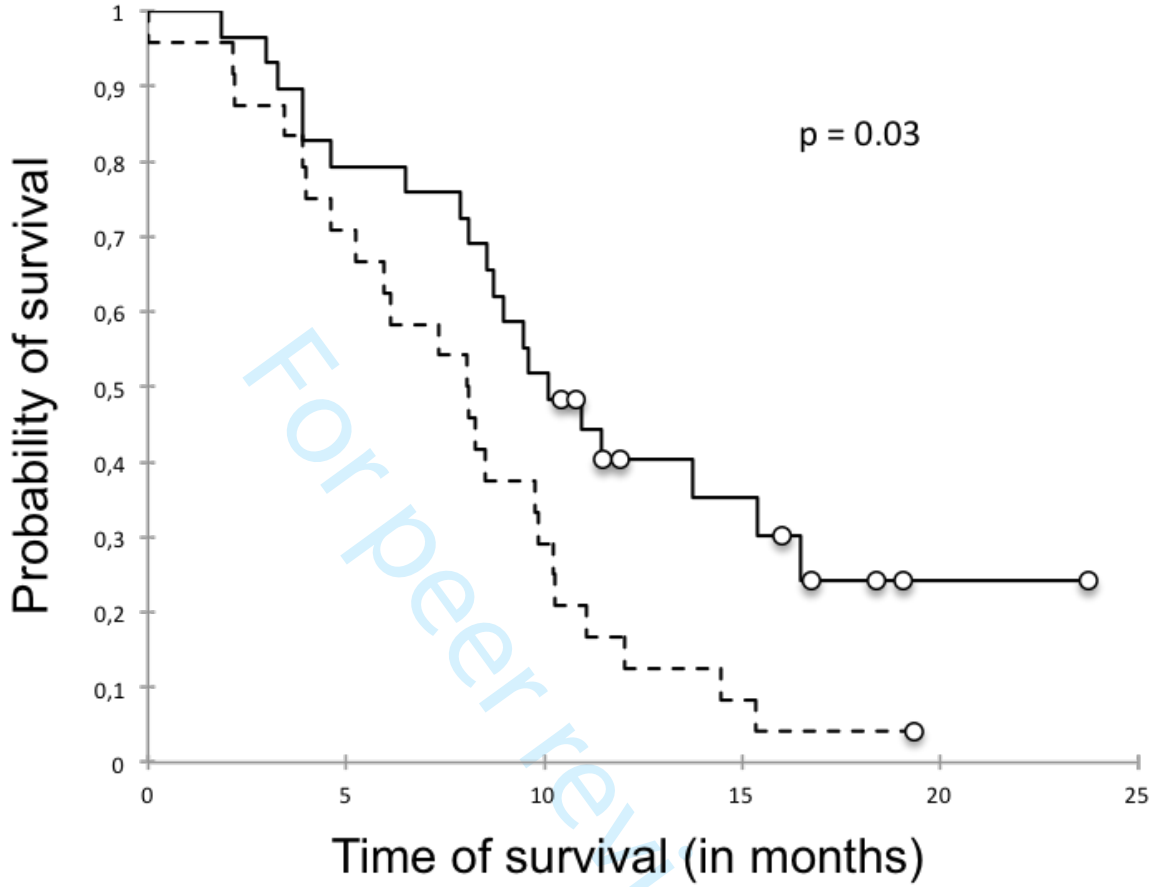


Figure 3



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5,6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5,6*
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	7,8
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1,p16
		(b) Indicate number of participants with missing data for each variable of interest	7,8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7,8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7,8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.