PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	vittecoq, olivier; desouches, sandra; kozyreff, marie; nicolau, julia; Pouplin, Sophie; Rottenberg, Pascal; sens, nicolas; Lequerre, Thierry; avenel, gilles

VERSION 1 – REVIEW

REVIEWER	Professor Paul Emery Leeds Institute of Rheumatic and Musculoskeletal Medicine, United Kingdom
REVIEW RETURNED	07-Aug-2019

GENERAL COMMENTS	This is a paper that looks at an important area i.e. tapering and stopping bDMARDs. The title is not ideal as a predictive factor would be more relevant than a change after starting to withdraw bDMARD, also it is not clear that the numbers of patients in this study allow this conclusion. Furthermore, there is a discussion on whether they actually have deep remission. It is perhaps premature to report the findings of the study when only 14 patients had completed follow up (as stated in abstract, but not clear if that is correct). In the abstract, the timing of withdrawal and the stopping should be spelt out. The numbers of relapses during the spacing period should be included in the abstract. The standard abbreviation is bDMARD rather than DA. Importantly 41 of 53 patients relapsed - this again needs to be made clear in the abstract. Points to address • The patients without methotrexate should be considered separately and patients who are taking corticosteroid steroid would not normally be considered as being in remission and should be excluded. • The finding that a deterioration in clinical signs and symptoms predicts relapse, is a new finding, but perhaps not surprising, • I am unsure whether the distinction between predictive and predictability is valid. • It would be interesting to know how many patients had been in sustained deep remission. • The heterogeneity of therapy is an issue, and individual drugs should be analysed separately. • The fact that 25% patients were double negatives (CCP/RF) and 15% had no erosions suggests these are very mild patients possibly different pathogenesis. The numbers of survivors without

	relapse who were seronegative and without erosions needs to be included. • The SDAI of non-relapse of 2.4 was higher than that of relapsers, needs comment. • The authors have split the disease duration to show longer duration was predictive of relapse. Yet in the table there is no difference in duration, if they are going to do this for disease duration they apply the same principle of above/below median to the other parameters. • Sonography scores are extremely difficult to interpret as it unknown whether patients had relapsed or not at the time points indicated.

REVIEWER	Dr Kenneth Baker Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University I am named as an inventor on a patent application relating to biomarkers of drug-free remission in rheumatoid arthritis
REVIEW RETURNED	21-Aug-2019

GENERAL COMMENTS	Vittecoq et al present a prospective single-centre study of 53 patients with established rheumatoid arthritis in sustained remission (DAS28<2.6 for ≥12 months and SDAI<3.3 at point of enrolment) attempting biologic spacing to eventual discontinuation. Patients taking a variety of biologic agents (mainly anti-TNF drugs) with or without concomitant conventional synthetic DMARDs are included. They aimed to compare rates of disease relapse (SDAI>11) based on baseline variables versus longitudinal changes in disease activity as measured by SDAI and 28-joint ultrasound assessment. Baseline factors predictive of relapse versus no-relapse were female sex and longer disease duration, baseline factors predictive of time-to-relapse were steroid use and disease duration. Longitudinal analyses demonstrate that an increase in SDAI relative to baseline at visits following commencement of biologic spacing is also predictive of relapse. Ultrasound variables were not predictive of relapse (either at baseline or longitudinally). Overall the quality of the study is good and should be of interest to a wide clinical audience. I have a few minor comments: 1. I am a little confused as to what the primary outcome measure was for the study analysis – is it relapse vs. no-relapse (i.e. binary outcome) or time-to-relapse? Outcomes for both measures appear to be presented in the manuscript, and it is potentially confusing for the reader. For example – female sex was predictive of relapse vs. no-relapse, but then is not mentioned in the survival analysis section, suggesting it is not predictive of time-to-relapse? 2. In the abstract: “At month 18, 14 patients had completed follow-up; 2 had relapsed while 12 were still in remission” is a bit confusing and suggests that the remainder had been lost to follow-up (rather than the intended meaning: dropped out of the study due to relapse). It would perhaps be clearer to state: “After 18 months of follow-up, 12/53 (23%) maintained biologic-free remission, 39/53 (74%) had relapsed and 2 (4%) were lost to follow-up” (if I have understood the numbers correctly). 3. Page 8: “among those who relapsed, there were two patients in remission at their last visit who were lost to follow-up” – I am not sure what is meant by this statement? I would suggest that these

	two patients are censored at the time of last visit and included in the remission group for the purposes of survival analysis, and excluded from binary outcome analyses of relapse vs. no-relapse – how these drop-out patients were handled in the analysis does need to be stated. 4. I like the discussion, which links nicely to the published literature. However, I do feel that the overall conclusion of the study is perhaps overstated in that the authors only examined baseline variables/demographics that are routinely collected in clinical practice. It is thus possible that other experimental laboratory biomarkers (e.g. circulating cytokines/chemokines, immunological cellular phenotype, peripheral blood gene expression etc) may be predictive of successful biologic tapering (publications do exist to suggest this). The authors may wish to consider adding a comment about this to the limitations of the study.

VERSION 1 – AUTHOR RESPONSE

Answers to Reviewer(s)' Comments

Reviewer: 1

Reviewer Name

Professor Paul Emery

Institution and Country

Leeds Institute of Rheumatic and Musculoskeletal Medicine,

United Kingdom

This is a paper that looks at an important area i.e. tapering and stopping bDMARDs.

The title is not ideal as a predictive factor would be more relevant than a change after starting to withdraw bDMARD, also it is not clear that the numbers of patients in this study allow this conclusion.

As suggested by Pr Emery, to make available factors able to predict success of biologic free remission

in RA patients in clinical remission would be ideal but most of the studies that were focused on predictive factors, whatever the field of research (prediction of response..), have failed to identify such markers. That is why we think that combination of both predictive and predictable factors might be more relevant. To take into account the outcome of parameters during the dose-reduction phase is not an issue since, in clinical practice, we start biologic agent relief according to clinical, biological (CRP) and sonographic data. In contrast, discontinuation of bDMARDs remains a great challenge after the dose-reduction phase. In this case, to have predictive and/or predictable factors prior to discontinuation becomes particularly important. For those reasons, we propose to maintain the present title.

Furthermore, there is a discussion on whether they actually have deep remission.

We agree with Pr Emery. This terminology is not appropriate. All patients were in clinical remission and 89% reached sonographic remission. Moreover, 4 patients received corticosteroids. We propose to change « deep remission » into « clinical remission » since deep remission is rather related to immunological remission.

It is perhaps premature to report the findings of the study when only 14 patients had completed follow up (as stated in abstract, but not clear if that is correct). In the abstract, the timing of withdrawal and the stopping should be spelt out. The numbers of relapses during the spacing period should be included in the abstract. The standard abbreviation is bDMARD rather than DA. Importantly 41 of 53 patients relapsed - this again needs to be made clear in the abstract.

As suggested by the reviewer, we have added these data in the abstract section

Points to address

• The patients without methotrexate should be considered separately and patients who are taking corticosteroid steroid would not normally be considered as being in remission and should be excluded.

We agree with Pr Emery. Patients who are taking corticosteroids would not normally be considered as being in remission. But only 4 patients received corticosteroids and at very low doses, i.e., 1mg, 2.5 mg, 4 mg and 5 mg per day. Their impact on our findings is weak, notably in the multivariate analysis that consider both factors of prediction and of predictability. Indeed, after exclusion of these 4 patients, the same findings were obtained. This point has been added at the end of the « Risk factors of relapse taking into account both factors of prediction and of predictability » paragraph (page 9)

Concerning patients without methotrexate, these patients have not been considered separately. Our work is a real-life study that included all consecutive patients receiving a bDMARDs and in clinical remission since at least one year. The proportion of patients in monotherapy in the present study is in accordance with that reported in registers and observational studies. To our opinion, it was relevant to consider these patients to highlight that combination of bDMARDs with a cDMARD (such as methotrexate or leflunomide) remains the gold standard in RA that leads to a deeper remission as well as to highest chance to achieve bDMARD discontinuation.

• The finding that a deterioration in clinical signs and symptoms predicts relapse, is a new finding, but perhaps not surprising,

We confirm that this is a new finding. It is not surprising. However, our study shows that it is more important to consider the kinetic of parameters during a certain period (the dose-reduction phase here) that their values at a single time (prior to bDMARDs relief)

• I am unsure whether the distinction between predictive and predictability is valid.

The predictability is a notion that has been developed in several studies and that is related to outcome of different parameters during the weeks following the initiation of a DMARD. For example, see the study conducted by Sarzi-Puttini P et al. Adv Ther 2018,35 :1153-68

• It would be interesting to know how many patients had been in sustained deep remission.

Among the 12 patients having no relapse during the follow-up period, 10 had a DAS28-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. This point has been added in the results section.

• The heterogeneity of therapy is an issue, and individual drugs should be analysed separately.

Since the panel of bDMARDs is increasing in RA, we have considered that it is more relevant to identify candidate predictors of relapse after discontinuation that could be applied to any biologic agent, whatever its mechanism of action (see the « discussion section » in which this point has been discussed ; page 9)

• The fact that 25% patients were double negatives (CCP/RF) and 15% had no erosions suggests these are very mild patients possibly different pathogenesis. The numbers of survivors without relapse who were seronegative and without erosions needs to be included.

Only 2 of the double-negative patients had no erosive disease. The number of survivors without relapse who were seronegative and without erosions was limited to 1 patient. These data have been added in the results section. As stated in the discussion section (page 12), markers reflecting autoimmunity (RF and/or anti-CCP) were not associated to the risk of relapse.

• The SDAI of non-relapse of 2.4 was higher than that of relapsers, needs comment.

In table 1, we confirm that the median SDAI was higher in non-relapsers than in relapsers. But this is the value measured at baseline prior to initiate the dose-reduction phase. Once again, to calculate a disease activity score at a given time has less importance than the kinetic of this score over a follow-up period. Thus, sequential assessment of disease activity (tight monitoring) provides more relevant information to predict relapse than a single evaluation at a given time.

• The authors have split the disease duration to show longer duration was predictive of relapse.

Yet in the table there is no difference in duration, if they are going to do this for disease duration they apply the same principle of above/below median to the other parameters.

As suggested, we have changed the values in Table 1; they are now expressed in median. For the analyses, quantitative variables have been expressed according to the median when consensual thresholds were not available.

• Sonography scores are extremely difficult to interpret as it unknown whether patients had relapsed or not at the time points indicated.

We agree with Pr Emery. However, the objective of the Table 2 was to show the outcome of the different US scores during the 2 phases of the study with a focus on the Boolean definition that is close to that used for clinical remission. It is difficult to illustrate at the individual level the relationship between the clinical relapse and the US scores measured at the different time-points. Nevertheless, table 3 highlights that, in contrast to kinetic of SDAI, that of the 3 US scores was not predictive of relapse. These data mean that US scores measured at the different time points are not related to clinical relapse observed at the same time-points

Reviewer: 2

Reviewer Name

Dr Kenneth Baker

Institution and Country

Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University

Please leave your comments for the authors below

Vittecoq et al present a prospective single-centre study of 53 patients with established rheumatoid arthritis in sustained remission (DAS28<2.6 for ≥12 months and SDAI<3.3 at point of enrolment) attempting biologic spacing to eventual discontinuation. Patients taking a variety of biologic agents (mainly anti-TNF drugs) with or without concomitant conventional synthetic DMARDs are included. They aimed to compare rates of disease relapse (SDAI>11) based on baseline variables versus longitudinal changes in disease activity as measured by SDAI and 28-joint ultrasound assessment. Baseline factors predictive of relapse versus no-relapse were female sex and longer disease duration, baseline factors predictive of time-to-relapse were steroid use and disease duration. Longitudinal analyses demonstrate that an increase in SDAI relative to baseline at visits following commencement of biologic spacing is also predictive of relapse. Ultrasound variables were not predictive of relapse (either at baseline or longitudinally).

Overall the quality of the study is good and should be of interest to a wide clinical audience. I have a few minor comments:

1. I am a little confused as to what the primary outcome measure was for the study analysis – is it relapse vs. no-relapse (i.e. binary outcome) or time-to-relapse? Outcomes for both measures appear to be presented in the manuscript, and it is potentially confusing for the reader. For example – female sex was predictive of relapse vs. no-relapse, but then is not mentioned in the survival analysis section, suggesting it is not predictive of time-to-relapse?

We confirm that 2 types of analyses 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 (Table 1). The second one was focused on time to relapse (Table 3 and Figure 3). The last one is the more relevant. We have added these informations in the “statistical analysis” section.

2. In the abstract: “At month 18, 14 patients had completed follow-up; 2 had relapsed while 12 were still in remission” is a bit confusing and suggests that the remainder had been lost to follow-up (rather than the intended meaning: dropped out of the study due to relapse). It would perhaps be clearer to state: “After 18 months of follow-up, 12/53 (23%) maintained biologic-free remission, 39/53 (74%) had relapsed and 2 (4%) were lost to follow-up” (if I have understood the numbers correctly).

We agree with Dr Baker. We have changed this sentence in the abstract

3. Page 8: “among those who relapsed, there were two patients in remission at their last visit who were lost to follow-up” – I am not sure what is meant by this statement? I would suggest that these two patients are censored at the time of last visit and included in the remission group for the purposes of survival analysis, and excluded from binary outcome analyses of relapse vs. no-relapse – how these drop-out patients were handled in the analysis does need to be stated.

We have considered censored cases such as loss of follow-up and drop-out from the study. We confirm that these 2 patients have been censored at the last visit and excluded from the binary outcome analysis but included in the remission group for the survival analysis. This point has been added in the statistical anlysis section.

4. I like the discussion, which links nicely to the published literature. However, I do feel that the overall conclusion of the study is perhaps overstated in that the authors only examined baseline variables/demographics that are routinely collected in clinical practice. It is thus possible that other experimental laboratory biomarkers (e.g. circulating cytokines/chemokines, immunological cellular phenotype, peripheral blood gene expression etc) may be predictive of successful biologic tapering (publications do exist to suggest this). The authors may wish to consider adding a comment about this to the limitations of the study.

We agree with Dr Baker. We have added a comment in the paragraph focused on the limitations of the study. To identify a panel of molecular and cellular biomarkers, reflecting the immunological remission, able to predict the success of major dose-reduction or discontinuation of bDMARDs is a new challenge. Such investigations have not been conducted in the present study but interesting works like the BioRRA

study have been recently reported, suggesting that a composite score incorporating five variables could help to personalize cDMARDs withdrawal (Baker KF etal J Autoimmun 2019) ; Multi-omics approaches to define molecular remission are also promising (Tasaki S et al, Nat Commun 2018)

VERSION 2 – REVIEW

REVIEWER	Dr Kenneth Baker Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University, United Kingdom I am named as an inventor on a patent filed by Newcastle University relating to biomarkers of drug-free remission in rheumatoid arthritis
REVIEW RETURNED	09-Oct-2019

GENERAL COMMENTS	Thank you to the authors for submitting a revised version of this manuscript. All of my previous comments have been addressed and I have no further issues to raise.