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Clinical science

Non-trough adalimumab and certolizumab drug levels associated with a therapeutic EULAR response in adherent patients with rheumatoid arthritis

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Abstract

Objectives: Interventions aimed at increasing TNF-α inhibitor serum drug levels (SDLs) may improve treatment response; however, previous studies suggesting SDL cut-offs have not accounted for treatment adherence. The aim of this study was to establish the relationship between adalimumab/certolizumab SDLs and EULAR good *vs* non-/moderate response and to define SDL cut-offs associated with good response in fully adherent patients.

Methods: In a prospective observational study, 475 patients with RA were treated with certolizumab ($n=192$) or adalimumab ($n=283$). At baseline and 3, 6 and 12 months, patients had 28-joint DAS, self-reported treatment adherence and SDLs measured. Fully adherent patients were analysed as a subgroup. Follow-up data at 3, 6 and 12 months were analysed separately. Median SDLs were compared in good *vs* non-/moderate response patients and receiver operating characteristics (ROC) curves were used to establish cut-off SDLs.

Results: Fully adherent good responders had significantly higher median adalimumab/certolizumab SDLs compared with non-/moderate responders ($P=0.04$ and $P=0.0005$, respectively). ROC analysis reported 3 month non-trough adalimumab SDLs discriminated good *vs* non-/moderate response with an area under the curve (AUC) of 0.63 (95% CI 0.52, 0.75), with a cut-off of 7.5 mg/l being 39.1% specific and 80.9% sensitive. Similarly, 3 month non-trough certolizumab SDLs discriminated good *vs* non-/moderate response with an AUC of 0.65 (95% CI 0.51, 0.78), with a cut-off of 26.0 mg/l being 43.9% specific and 77.8% sensitive.

Conclusion: In fully adherent patients, higher SDLs are detected in good responders, suggesting that interventions to improve SDLs, such as encouraging adherence, could improve treatment response. The 3 month non-trough SDL cut-offs of 7.5 mg/l for adalimumab and 26.0 mg/l for certolizumab may be useful in clinical practice.

Keywords: RA, serum drug levels, therapeutic response, certolizumab, adalimumab, TNF-α inhibitors, adherence

Rheumatology key messages

- Adherence is an important confounder when studying serum drug levels in rheumatoid arthritis.
- Non-trough serum drug levels at 3 months are informative of treatment response in adherent patients.
- Interventions aimed at improving serum drug levels, like addressing adherence, may improve treatment response.

Introduction

RA is a systemic inflammatory disease that is often treated with biologic DMARDs (bDMARDs), including TNF-α inhibitors (TNFis) such as certolizumab and adalimumab [1]. These medications are effective in a large proportion of

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patients; however, a significant minority (~30%) experience poor treatment response, as defined by the EULAR response criteria, based on changes in the 28-joint DAS (DAS28) [2–4]. Poor response may subsequently lead to drug cycling, where bDMARDs targeting different biological pathways are trialled serially, with drug selection based on cost and local policies rather than a mechanistic understanding of why treatments are ineffective [5, 6].

Several studies of Adalimumab and certolizumab have shown that low serum drug levels (SDLs) are associated with a reduction in the proportion of patients achieving a 'good' EULAR response, including our previous work [7–10]. Factors previously reported to be associated with decreased SDLs include poor adherence to bDMARDs, increased BMI, increased anti-drug antibody formation and lack of co-administration of MTX [7, 9–12]. Many of these factors are modifiable, providing opportunities for intervention to potentially increase SDLs and improve therapeutic response. For example, BMI could be reduced through lifestyle modifications; MTX co-administration and dose could be increased with patient education and clinician training; and adherence could be improved with motivational interviewing, patient education and clinician training [9–11, 13, 14]. Furthermore, bDMARD dose adjustment, which is an ongoing area of research interest, may be possible in the future to titrate dosing according to SDLs [15].

Improving treatment adherence appears to be an especially important aim in clinical practice, as non-adherence has been consistently reported to correlate with poorer patient outcomes and low TNFi SDLs [9]. Several studies have reported that a significant proportion (9–28%) of RA patients are non-adherent to DMARDs, depending on the measures of adherence used [3, 16–20].

Defining SDL cut-offs for TNFi treatments on a population level could be useful in clinical practice, by providing an indication to clinicians that patients with non-/moderate EULAR response and with subtherapeutic SDLs may benefit from interventions aimed at increasing SDLs (see Fig. 1). However, while cut-offs have been suggested by previous studies, their use in clinical practice has not been formally defined [7–10, 21]. Furthermore, previous studies have found that reduced adherence was associated with low SDLs [9]. Therefore, adherence represents a key confounder when studying SDLs, given that poor adherence will lead to erratic changes in SDLs

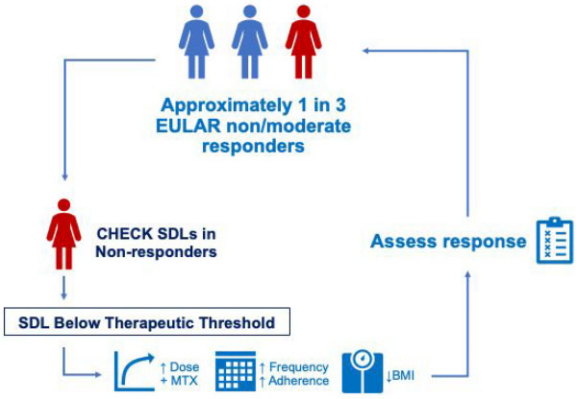

Figure 1. Schematic illustrating a potential clinical paradigm involving the use of SDLs and therapeutic thresholds based on fully adherent patients achieving a good treatment response

that lead to variable effects on treatment response [9, 12, 15]. However, previous studies that have suggested SDL cut-offs have not accounted for adherence by excluding or adjusting based on poor self-reported adherence.

The aims of this study were to establish the relationship between adalimumab and certolizumab non-trough SDLs and EULAR response and to establish therapeutic adalimumab and certolizumab SDL thresholds associated with 'good' EULAR response in a large cohort of fully adherent patients with RA.

Methods

Study population

Patients were recruited to participate in a prospective observational cohort study called Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) prior to initiation of a bDMARD. Patients from 60 centres across the UK were recruited starting in November 2008, with recruitment ongoing.

Patients are recruited to BRAGGSS according to the following inclusion criteria: RA according to the revised 1987 ACR criteria [22], active disease indicated by a DAS28 $\geq$5.1 despite previous treatment with two or more DMARDs including MTX and self-identified ethnicity as being of white European descent. For this analysis, patients from BRAGGSS who were about to commence adalimumab (40 mg every 2 weeks) or certolizumab (400 mg monthly) and who had a baseline visit recorded with one or more follow-up visit where serum samples, clinical data and self-reported adherence data were available at each corresponding time point were included, representing an unselected, representative subgroup of the whole cohort.

At baseline and following initiation of therapy, patients were assessed at ~3, 6 and 12 months. Clinical and patient questionnaires including patient self-reported adherence were collected at each visit. Serum samples were collected and sent to the Centre for Musculoskeletal Research at the University of Manchester for central processing, storage and analysis. Contributing patients provided written informed consent and the study received ethics approval (COREC04/Q1403/37).

Measurement of adalimumab and certolizumab SDLs

A total of 1144 serum samples from 475 patients taken at baseline and 3, 6 and 12 months were tested for non-trough SDLs (see Supplementary Table S1, available at *Rheumatology* online). Adalimumab SDLs were measured in serial samples using sandwich ELISAs (Progenika Biopharma, Derio, Spain), which had an upper limit of 12 mg/l, in 716 samples from 283 patients [23]. Certolizumab SDLs were measured using sandwich ELISAs with no upper limit (Sanquin, Amsterdam, The Netherlands) in 428 samples from 192 patients [24].

Measurement of adherence

Self-reported adherence questionnaires containing five questions about bDMARD compliance were completed by patients at follow-up visits (see Supplementary Table S2, available at *Rheumatology* online). Five possible answers from never to always were available for each question. At

each follow-up visit, patients were considered fully adherent if they answered 'never' in relation to all five questions.

Measurement of clinical response

Treatment response was measured using EULAR response criteria, which is derived from the change in DAS28 with CRP (DAS28-CRP) from baseline at each visit (ΔDAS28, defined as baseline DAS28-CRP – DAS28-CRP at follow-up visits at 3, 6 or 12 months) [25, 26].

Study power

For adalimumab, a sample size of 80 was calculated as having 80% power to detect a difference of 3 g/ml between non-/moderate and good responders (NMRs and GRs, respectively). For certolizumab, a sample size of 60 was calculated as having 80% power to detect a difference of 5 g/ml between NMRs and GRs.

Assessing the relationship between adalimumab and certolizumab non-trough SDLs and EULAR response

Median SDLs were compared between GR *vs* NMRs. Comparisons of SDLs measured at 3, 6 and 12 months were analysed separately. Comparisons of SDLs in patients who were fully adherent were analysed separately as a subgroup.

Statistical analysis

Between-group comparisons were assessed using descriptive statistics, as appropriate, with a threshold for significance set at $P < 0.05$. Statistical analyses were performed in R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 1.4.1106 (RStudio, Boston, MA, USA) (see Supplementary Table S3, available at *Rheumatology* online).

ROC analysis

ROC analysis was used to determine a cut-off value for SDLs between GRs *vs* NMRs as described previously [21]. ROC curves using SDLs measured at 3, 6 and 12 months were created for all patients and separately in fully adherent patients only.

A trade-off between sensitivity and specificity is needed to determine an optimal SDL threshold. A lower SDL threshold would have high sensitivity but low specificity, meaning many patients would be misclassified as likely to respond, but with an SDL below the therapeutic level. Conversely, a higher SDL threshold would have high specificity but low sensitivity and would risk overestimating non-responders even though SDL is at the therapeutic level. Depending on the clinical question, a higher sensitivity or specificity will be favoured. If sensitivity is favoured when defining an SDL threshold, there will be fewer false negatives, meaning that we can be confident that patients with SDLs above the threshold should have a good response if fully adherent. For this reason, sensitivity is preferred over specificity, with an AUC >0.6 considered adequate performance, as described previously [21].

Results

Baseline characteristics

The baseline characteristics of the 475 patients who met the inclusion criteria are shown in Table 1. Baseline characteristics between the patients receiving adalimumab and certolizumab were comparable, with patients being predominantly female, ages in the 50s, with severe, established disease despite treatment with DMARDs (such as MTX). The only statistically significant difference between cohorts was the DAS28 score at baseline, which was slightly higher in the certolizumab cohort {DAS28 median 5.81 [interquartile range (IQR) 5.28–6.36]} compared with the adalimumab cohort [DAS28 median 5.61 (IQR 5.18–6.14)] ($P = 0.042$).

Table 1. Patient characteristics at baseline

Characteristics	Adalimumab ($n = 283$)	Certolizumab ($n = 192$)	*P*-value[a]
Age, mean (S.D.), years	57 (12)	58 (12)	0.5
Female, *n* (%)	206 (73)	139 (72)	>0.9
BMI, mean (S.D.)	28.8 (11.8)	28.6 (6.5)	0.6
Smoking status, *n* (%)			0.8
Current smoker	57 (38)	48 (41)	
Ex-smoker	32 (21)	22 (19)	
Non-smoker	62 (41)	46 (40)	
Unknown smoking status	132	76	
Disease duration, median (IQR), years	7 (3–16)	6 (3–15)	0.7
On concurrent DMARD(s), *n* (%)			0.8
No	34 (12)	22 (11)	
Yes	248 (88)	170 (89)	
Unknown	1	0	
Baseline DAS28-ESR score, mean (S.D.)	5.65 (0.85)	5.77 (0.84)	0.042
Baseline tender joint count, mean (S.D.)	15 (7)	15 (7)	0.2
Baseline swollen joint count, mean (S.D.)	9 (5)	9 (5)	0.2
Baseline CRP, median (IQR)	10 (3–24)	8 (3–22)	0.8
Baseline Patient Global Score, mean (S.D.)	71 (19)	73 (18)	0.4
On MTX, *n* (%)			0.6
No	44 (18)	27 (16)	
Yes	201 (82)	141 (84)	
Unknown	38	24	

[a] Unpaired *t*-test, Wilcoxon rank sum test or Pearson's chi-squared test.

Relationship between SDLs and EULAR response irrespective of adherence

The number of patients with adalimumab or certolizumab SDLs and EULAR response available at each time point is shown in Supplementary Table S4, available at *Rheumatology* online. Box and whisker plots showing SDLs in GRs *vs* NMRs at each time point are shown in Supplementary Fig. S1, available at *Rheumatology* online.

The median SDLs were significantly higher in GRs *vs* NMRs taking adalimumab at 3 and 6 months ($n = 257$, $P < 0.0001$ and $n = 203$, $P < 0.001$, respectively) and in GRs *vs* NMRs taking certolizumab at 12 months ($n = 75$, $P = 0.02$). There was no significant difference between the median SDLs in GRs *vs* NMRs taking adalimumab at 12 months nor in those taking certolizumab at 3 or 6 months (see Supplementary Fig. S1, available at *Rheumatology* online).

Relationship between SDLs and EULAR response in fully adherent patients

The number of patients with adalimumab or certolizumab SDLs, EULAR response, self-reported adherence data and

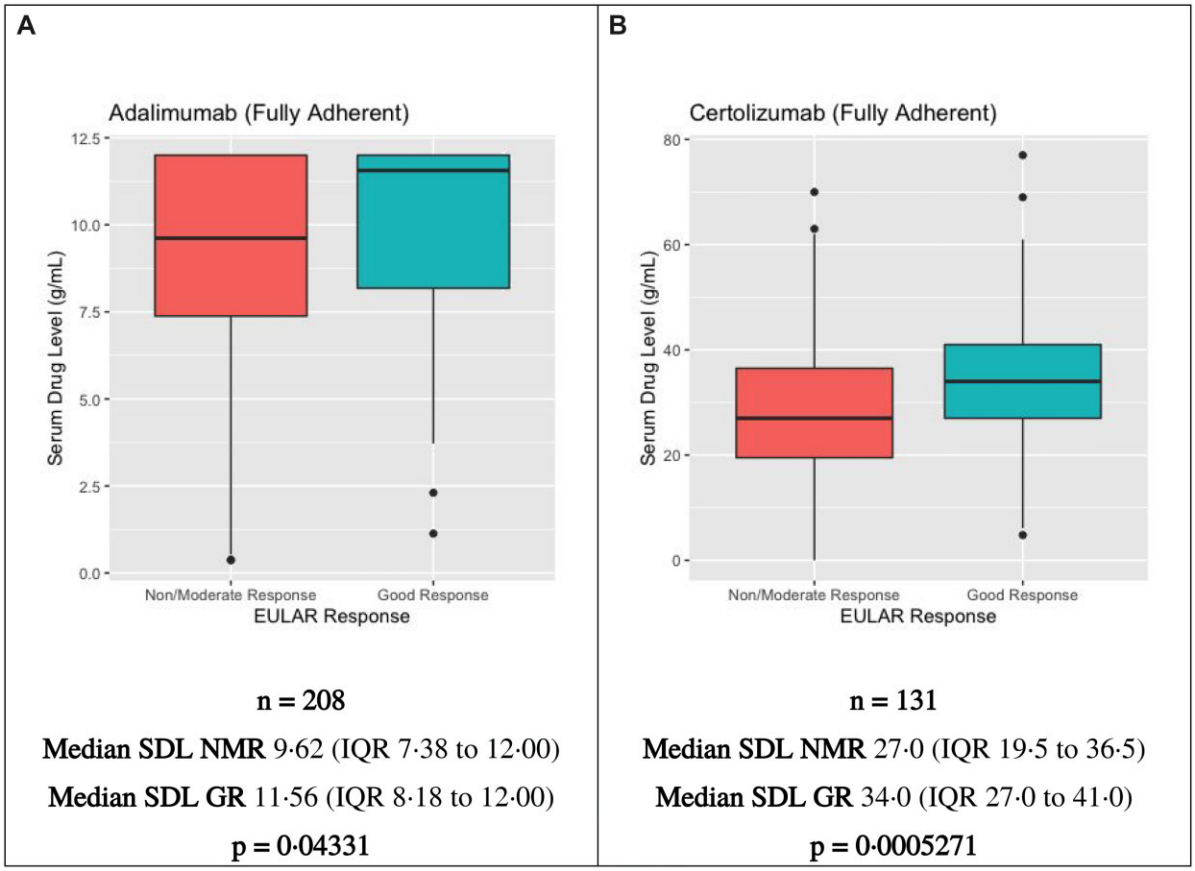

Figure 2. Box and whisker plots comparing SDLs of fully adherent RA patients with EULAR non-/moderate response (red) *vs* good response (blue) after treatment with **(A)** adalimumab or **(B)** certolizumab. Colour version can be viewed online

classified as being fully adherent at each time point is shown in Supplementary Table S5, available at *Rheumatology* online. The median SDLs were significantly higher in fully adherent GRs *vs* NMRs taking adalimumab and in those taking certolizumab (see Fig. 2). When SDLs at 3, 6 and 12 months were analysed separately, the median SDLs were significantly higher in fully adherent GRs *vs* NMRs taking adalimumab at 3 months and in those taking certolizumab at 3, 6 and 12 months (see Supplementary Fig. S2, available at *Rheumatology* online). There was no significant difference between median SDLs in fully adherent GRs *vs* NMRs taking adalimumab at 6 and 12 months (see Supplementary Fig. S2, available at *Rheumatology* online).

ROC curve analysis irrespective of adherence

ROC curves modelling adalimumab or certolizumab SDLs with GRs *vs* NMRs in all patients irrespective of adherence are shown in Supplementary Fig. S3, available at *Rheumatology* online. Certolizumab SDLs at 12 months were able to discriminate GRs *vs* NMRs with an AUC of 0.696 (95% CI 0.573, 0.820), with a lower threshold cut-off of 26.0 mg/l identified as being 58.6% specific and 76.1% sensitive ($n = 27$). However, adalimumab SDLs at 3, 6 and 12 months and certolizumab SDLs at 3 and 6 months were not able to reasonably discriminate GRs *vs* NMRs (AUCs 0.50–0.61).

ROC curve analysis in fully adherent patients

ROC curves modelling adalimumab or certolizumab SDLs with fully adherent GRs *vs* NMRs are shown in Fig. 3. Adalimumab SDLs at 3 months in fully adherent patients were able to discriminate GRs *vs* NMRs with an AUC of 0.634 (95% CI 0.522, 0.746), with a lower threshold SDL cut-off of 7.5 mg/l identified as being 39.1% specific and 80.9% sensitive ($n = 93$) (see Fig. 3A). Certolizumab SDLs at 3 months in fully adherent patients were able to discriminate GRs *vs* NMRs with an AUC of 0.647 (95% CI 0.513, 0.781), with a lower threshold SDL cut-off of 26.0 identified as being 43.9% specific and 77.8% sensitive (see Fig. 3B).

ROC curves based on SDLs at 6 and 12 months are shown in Supplementary Figure S4, available at *Rheumatology* online. Sensitivity and specificity for all potential lower threshold SDL cut-offs for each ROC curve are shown in Supplementary Table S6, available at *Rheumatology* online.

Discussion

This is the first study to assess the relationship between non-trough SDLs incorporating self-reported adherence to their bDMARD to inform potential therapeutic lower SDL cut-offs based on analysis in fully adherent patients. Our results are consistent with those of our previous work and other studies of TNFis in RA, which have found that trough and non-trough

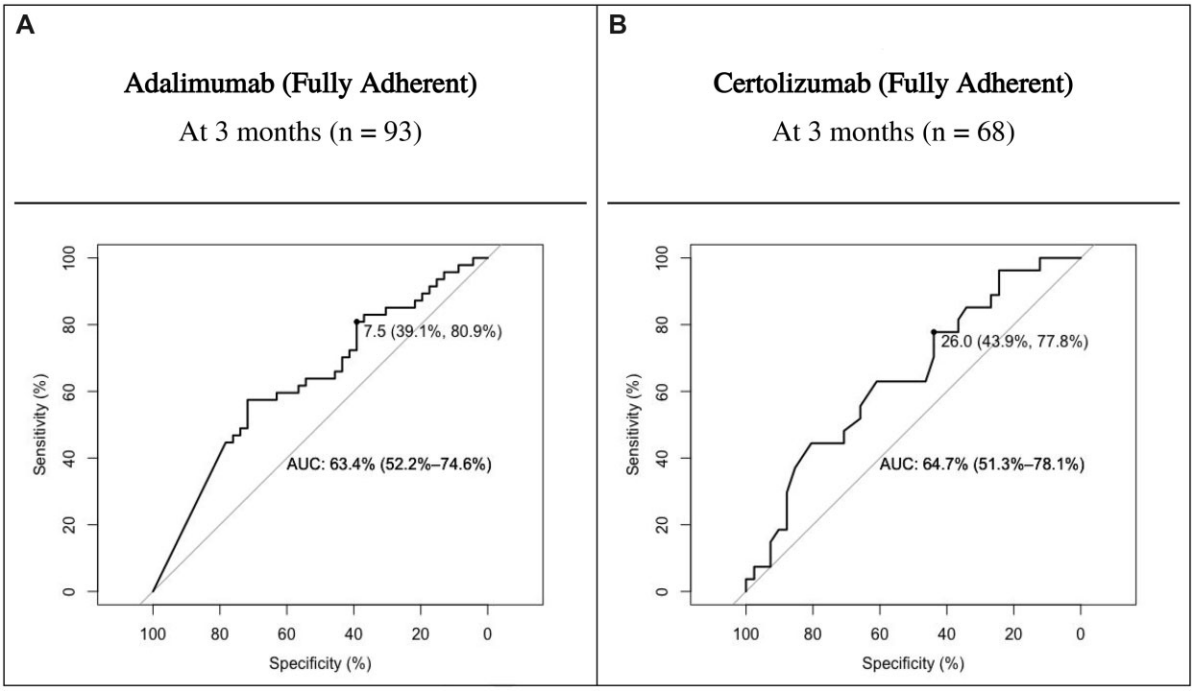

Figure 3. ROC curve analysis. Fully adherent RA patients with EULAR good response *vs* non-/moderate response with SDLs at 3 months after treatment with **(A)** adalimumab or **(B)** certolizumab

SDLs are higher in treatment responders compared with non-responders [7–10]. However, we found that when patient adherence was not taken into account, the association between SDLs and response was not significant at certain follow-up time points (see Supplementary Fig. S1, available at *Rheumatology* online). When analysing only fully adherent patients, the association between SDL and EULAR response was more consistent across time points (see Fig. 2 and Supplementary Fig. S2, available at *Rheumatology* online). This reinforces the impact that adherence has on variations in SDLs, since non-trough SDLs in patients with poor adherence are less informative of future treatment response. Our study therefore supports previous studies that have determined that encouraging adherence can improve SDLs and subsequent treatment response. A previous study showed that SDLs at 3 and 6 months were predictive of response by 12 months; however, our study is the first to suggest SDL cut-offs that can discriminate GRs from NMRs [11].

Our study found that a non-trough adalimumab SDL cut-off of 7.5 mg/l at 3 months was 39.1% specific and 80.9% sensitive at discriminating GRs *vs* NMRs in fully adherent patients with RA when sensitivity of the test was prioritized. A similar study by Pouw *et al.* [21] using trough adalimumab SDLs was able to discriminate GRs with an AUC of 0.70, with a threshold of 5 mg/l identified as being 43% specific and 91% sensitive at classifying GRs at 7 months [9]. A previous study using non-trough SDLs in PsA patients showed that adalimumab concentrations of 4–8 μg/ml were associated with an optimal treatment response at 6 months using concentration–effect curves [27]. In clinical practice, where trough levels are not always available, it is valuable to assess treatment response early (typically within 3–6 months) in order to rapidly control disease and to minimize long-term complications [1]. Our study suggests 3 month SDL cut-offs are particularly informative in patients who are adherent for optimizing the likelihood of a good treatment response.

Our proposed cut-off of 7.5 mg/l is higher than the cut-off of 5 mg/l proposed by Pouw *et al.* [21], but with comparable classification performance, with our cut-off being slightly less sensitive. This is expected given that our threshold was identified in fully adherent patients whose SDLs would be expected to be higher, whereas the analysis performed by Pouw *et al.* [21] included patients irrespective of adherence. The differences between the two studies suggest that by not excluding non-adherent patients, we may underestimate therapeutic thresholds.

The current study is the first to our knowledge to suggest a certolizumab SDL threshold for patients with RA. Our study found that a 3 month non-trough certolizumab SDL threshold of 26.0 mg/l is 43.9% specific and 77.8% sensitive at discriminating GRs *vs* NMRs in fully adherent patients with RA (see Fig. 3). Our previous work demonstrated a drug threshold of 24–29 μg/ml in certolizumab patients was associated with optimal response in RA; however, an exact cut-off was not determined [7]. A study by Gehin *et al.* [8] found that higher non-trough certolizumab levels at 3 months were associated with improved outcomes across a cohort of 91 patients with RA, 61 with PsA and 116 with axial SpA assessed using the Ankylosing Spondylitis Disease Activity Score, clinically important improvement in SpA, EULAR response in RA and improvement in the DAS28 <0.6 in PsA. The authors proposed a non-trough certolizumab cut-off of 20 mg/l at 3 months based on concentration–effect curves but did not perform ROC analysis or assess the sensitivity or specificity of this cut-off. Another study of certolizumab in Crohn's disease reported that a cut-off 6 week non-trough certolizumab SDL of 31.8 mg/l was associated with a Clinical Disease Activity Index response with an AUC of 0.58, a sensitivity of 53.7% and a specificity of 57.6% [28].

Fig. 1 illustrates a possible clinical paradigm in which our findings could be implemented. In the clinic, if a patient at

follow-up has a suboptimal treatment response to a TNFi, SDLs could be measured. If the SDLs are below a therapeutic threshold that would be expected to be effective in a fully adherent patient, then instead of attributing treatment failure to primary inefficacy, a clinician could intervene to improve the SDLs prior to subsequent follow-up. This could be done by addressing adherence. Interestingly, previous work has illustrated that adherence behaviour can be improved in clinical practice through interventions aimed at addressing concerns about medications, focusing on the benefits as well as potential side effects and consistent messages about treatment [14]. In patients with good adherence but who do not achieve a good response at 3 months, subtherapeutic thresholds could prompt addressing immunogenicity, through the introduction of other DMARDs such as MTX, or in the future by increasing the dosage or frequency of administration of the drug. While the majority of patients in the current analysis were on concomitant conventional synthetic DMARD therapy, approximately one-fifth were not (see Table 1) [15]. In theory, this approach could improve drug survival and reduce long-term complications and comorbidity associated with uncontrolled disease activity. Conversely, if the SDLs are above the therapeutic threshold, this implies that there is 'true' inefficacy to the treatment, which could be to an unidentified pathophysiological mechanism by which the patient's disease is not responsive to that treatment modality.

The main strengths of the current study include a large sample size, prospective serial sampling at multiple time points, a well-characterized cohort of RA patients with similar phenotypes and the availability of self-reported adherence. Although serum samples were obtained during routine follow-up appointments as opposed to trough serum samples, which would make levels between samples more comparable, assessing the value of non-trough SDLs is helpful, as non-trough levels are more easily applicable in clinical practice, where it can be challenging to obtain trough samples in outpatient settings [15]. In the future, point-of-care testing to measure SDLs may be implemented, eliminating these issues and making it easier to obtain trough levels in the clinical setting [29, 30]. Furthermore, by analysing fully adherent patients separately, we improve the reliability that the SDLs measured reflect the levels throughout treatment by excluding patients with poor adherence who may have significant fluctuations in SDLs due to suboptimal adherence to the treatment regime.

Several study limitations need to be recognized. First, we only used one measure, self-reported adherence, to assess adherence. Previous studies of adherence to bDMARDs in RA have used various measures to report adherence, including use of the medication possession ratio (MPR), which is a percentage of days during follow-up that a patient has had a supply of medication, with a cut-off MPR of 80% often being used to classify full adherence [16–21]. The method of measuring adherence represents an important variable that can influence analyses such as ours. Self-reported adherence has limitations, given that it is possible patients may erroneously report their adherence either unintentionally due to forgetfulness or purposefully for complex psychological reasons. Previous work has shown that SDLs are not fully explained by adherence, therefore further investigation into other factors affecting SDLs is required [9]. This includes understanding the characteristics of non-adherent patients, in whom treatment response may be influenced by factors other than SDLs alone. For example, a study exploring the characteristics of patients with non-adherence found that patient beliefs and multimorbidity associate with non-adherence [13]. It is therefore possible that adherence is a predictor of multimorbidity or patient scepticism towards pharmacological therapy, which are the mediators/proxies for reduced treatment response. However, SDLs may be modifiable and have been shown to correlate with future response, so it is important to define thresholds to identify suboptimal SDLs.

A second limitation is that there was limited power to address SDLs at 12 months. Indeed, while adalimumab SDLs were statistically different in GRs compared with NMRs at 3 and 6 months, no difference was detected at 12 months. Possible explanations might be that patients who experience poor treatment response despite 12 months of treatment are less likely to be adherent to their medications, therefore their SDLs are less likely to be inaccurate and thus not able to discriminate response. Alternatively, patients who have non-/moderate responses due to low SDLs may be more likely to discontinue their medication before 12 months and therefore 12 month follow-up data are not available. A final limitation is that routine drug level monitoring is not yet recommended for clinical practice due to insufficient evidence of cost-effectiveness, as few prospective studies to address this question have been published to date [31]. However, such studies are under way and the work presented in this article will inform future threshold recommendations if the use of SDL measurements are found to be cost effective.

Conclusions

In conclusion, we found that self-reported adherence associates with higher SDLs and subsequent treatment response, supporting previous studies; however, this is the first study to define a cohort of fully adherent patients when assessing the association between non-trough adalimumab and certolizumab SDLs and treatment response to TNFis in RA. We have confirmed previously reported associations between non-trough SDLs and treatment response to TNFis and further report that this association is more consistent and significant across follow-up time points in fully adherent patients. Based on ROC analysis of SDLs in fully adherent patients, we suggest target 3 month lower threshold SDLs of 26.0 mg/l for certolizumab and 7.5 mg/l for adalimumab may be useful in clinical practice to optimize the likelihood of a good response to treatment. However, replication using other commercially available assays and using other validated measures of adherence is necessary. Additional evaluation of the benefits and cost-effectiveness of therapeutic drug monitoring and the application of such thresholds is now warranted to inform the potential for implementation in clinical practice.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

Data will be shared upon reasonable requests to the corresponding author.

Contribution statement

R.H. was responsible for conception/design of the study, writing the R scripts, analysis and interpretation of data and

drafting the manuscript. M.J. was responsible for the acquisition and interpretation of data. N.N. was responsible for the acquisition and interpretation of data and drafting the manuscript. P.H., D.P. and A.B. were responsible for conception/design of the study, analysis and interpretation of the data and drafting the manuscript. M.J., K.L.H., A.M., J.I. and A.G.W. were BRAGGSS co-investigators and contributed to drafts of the manuscript. All authors read and approved the final manuscript.

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