



King's Research Portal

DOI:

[10.1016/j.jid.2018.07.028](https://doi.org/10.1016/j.jid.2018.07.028)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Wilkinson, N., Tsakok, T., Dand, N., Bloem, K., Duckworth, M., Baudry, D., Pushpa-Rajah, A., Griffiths, C. EM., Reynolds, N. J., Barker, J., Warren, R. B., Burden, A. D., Rispens, T., Stocken, D., & Smith, C. (2019). Defining the therapeutic range for adalimumab and predicting response in psoriasis: a multicenter prospective observational cohort study. *Journal of Investigative Dermatology*, 139(1), 115-123.
<https://doi.org/10.1016/j.jid.2018.07.028>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

Defining the therapeutic range for adalimumab and predicting response in psoriasis: a multicenter prospective observational cohort study

Nina Wilkinson, PhD, Teresa Tsakok, MA, MRCP, Nick Dand, PhD, Karien Bloem, PhD, Michael Duckworth, BSc, David Baudry, MSc, Angela Pushpa-Rajah, BSc, Christopher EM. Griffiths, MD, FMedSci, Nick Reynolds, MD, FRCP, Jonathan Barker, MD, FRCP, Richard B. Warren, PhD, FRCP, A David Burden, MD, FRCP, Theo Rispens, PhD, Deborah Stocken, PhD, Catherine Smith, MD, FRCP

PII: S0022-202X(18)32482-5

DOI: [10.1016/j.jid.2018.07.028](https://doi.org/10.1016/j.jid.2018.07.028)

Reference: JID 1552

To appear in: *The Journal of Investigative Dermatology*

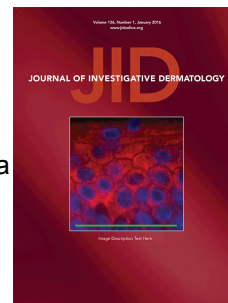
Received Date: 4 April 2018

Revised Date: 28 June 2018

Accepted Date: 15 July 2018

Please cite this article as: Wilkinson N, Tsakok T, Dand N, Bloem K, Duckworth M, Baudry D, Pushpa-Rajah A, Griffiths CE, Reynolds N, Barker J, Warren RB, Burden AD, Rispens T, Stocken D, Smith C, on behalf of the BSTOP study group and PSORT consortium, Defining the therapeutic range for adalimumab and predicting response in psoriasis: a multicenter prospective observational cohort study, *The Journal of Investigative Dermatology* (2018), doi: 10.1016/j.jid.2018.07.028.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Defining the therapeutic range for adalimumab and predicting response in psoriasis: a multicenter prospective observational cohort study

Short title: Therapeutic drug monitoring in psoriasis

Nina Wilkinson, PhD^{1*}; Teresa Tsakok, MA, MRCP^{2*}; Nick Dand, PhD²; Karien Bloem, PhD³; Michael Duckworth, BSc⁴; David Baudry, MSc⁴; Angela Pushpa-Rajah, BSc⁴; Christopher EM Griffiths, MD, FMedSci⁵; Nick Reynolds, MD, FRCP⁶; Jonathan Barker, MD, FRCP²; Richard B Warren, PhD, FRCP⁵; A David Burden, MD, FRCP⁷; Theo Rispens, PhD³; Deborah Stocken, PhD^{8**}; Catherine Smith, MD, FRCP^{2,4***+} on behalf of the BSTOP study group and PSORT consortium

*Joint first authors

**Joint last authors

+ Corresponding author

1. Institute of Health and Society, Faculty of Medical Sciences, Newcastle University, Newcastle-upon-Tyne, UK, NE2 4AX
2. School of Basic & Medical Biosciences, Faculty of Life Sciences & Medicine, King's College London, and St. John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK, SE1 9RT
3. Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam, The Netherlands, 9892 1006 AN
4. St. John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK, SE1 9RT
5. Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester Academic Health Science Centre, NIHR Manchester Biomedical Research Centre, Manchester, UK, M13 9PT
6. Dermatological Sciences, Institute of Cellular Medicine, Medical School, Newcastle University, and Department of Dermatology, Royal Victoria Infirmary, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK, NE2 4HH
7. Institute of Infection, Immunity and Inflammation, University of Glasgow, UK, G12 8TA
8. Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK, LS2 9NL

Corresponding author:

Correspondence to catherine.smith@kcl.ac.uk

Abbreviations

ADA - Anti-drug antibodies; AIC - Akaike Information Criterion; AUC - Area under the curve; BADBIR - British Association of Dermatologists Biologic Interventions Registry; BSTOP - Biomarkers of Systemic Treatment Outcomes in Psoriasis; CI - Confidence interval; ELISA - Enzyme-linked immunosorbent assay; IBD - Inflammatory bowel disease; IMID - Immune-mediated inflammatory disease; OR - Odds ratio; NICE - National Institute for Health and Care Excellence; PASI - Psoriasis Area and Severity Index; RA - Rheumatoid arthritis; RIA - Radioimmunoassay; ROC - Receiver Operating Characteristic; TAXIT - Trough level Adapted infliximab Treatment trial; TNF-alpha - tumor necrosis factor-alpha

ABSTRACT

Biologics have transformed management of inflammatory diseases. To optimize outcomes and reduce costs, dose adjustment informed by circulating drug levels has been proposed. We aimed to determine the real-world clinical utility of therapeutic drug monitoring in psoriasis. Within a multicenter (n=60) prospective observational cohort, 544 psoriasis patients were included who were on adalimumab monotherapy, with at least one serum sample and PASI (Psoriasis Area and Severity Index) score available within the first year. We present models giving individualized probabilities of response for any given drug level: a minimally effective drug level of 3.2 µg/ml discriminates responders (PASI75: 75% improvement in baseline PASI) from non-responders and gives an estimated PASI75 probability of 65% (95% CI 60-71%). At 7ug/ml, PASI75 probability is 81% (95% CI 76-86%); beyond 7ug/ml, the drug level/response curve plateaus. Crucially, drug levels are predictive of response 6 months later, whether sampled early or at steady state. We confirm serum drug level to be the most important factor determining treatment response, highlighting the need to take drug levels into account when searching for biomarkers of response.

This real-world study with pragmatic drug level sampling provides evidence to support the proactive measurement of adalimumab levels in psoriasis to direct treatment strategy, and is relevant to other inflammatory diseases.

INTRODUCTION

Biologic therapies have transformed the treatment paradigm in immune-mediated inflammatory diseases (IMID). Complete disease remission is now achievable in people with psoriasis, rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), where inhibition of the inflammatory cytokine tumour necrosis factor alpha (TNF-alpha) remains the first-line biologic strategy. However, there are wide variations in response, with a significant number of patients not responding (primary treatment failure) or losing response over time (secondary treatment failure) (Garces et al., 2013, Yanai and Hanauer, 2011). Some of this heterogeneity may be explained by differences in the amount of drug available at the target tissue, which in turn is influenced by adherence and pharmacokinetic covariates such as weight and drug immunogenicity (formation of anti-drug antibodies [ADA]). Therapeutic drug monitoring using measurement of serum drug levels (a proxy for tissue levels) and/or ADA thus holds potential to optimize management, and a strong correlation between TNF inhibitor serum trough levels, ADA and treatment response has been described in IBD, RA and psoriasis (Baert et al., 2003, Chen et al., 2015, Lecluse et al., 2010). Indeed, a recent study using adalimumab clinical trial data in 1212 psoriasis patients reported that responders at 16 weeks had higher adalimumab concentrations than non-responders (6.3 vs. 2.2 $\mu\text{g/mL}$). Bodyweight was a significant covariate in the pharmacokinetic model, and the presence of ADA resulted in lower adalimumab exposure and efficacy (Mostafa et al., 2017).

Effective therapeutic drug monitoring requires the definition of a therapeutic range, and although parameters for serum adalimumab levels have been proposed in the context of several IMID (Menting et al., 2015, Pouw et al., 2015, Roblin et al., 2014, Yarur et al., 2016), these have not yet been validated in psoriasis patients. Further, the utility of drug level as a predictor of subsequent response has not been investigated in psoriasis other than in a previous preliminary study by our group (Mahil et al., 2013). Defining clinical outcomes in

IBD and RA is inherently challenging – often relying on composite indices comprising patient-reported criteria and non-specific biochemical markers. Psoriasis provides a disease model less encumbered by such issues, since treatment response can be visually observed and easily quantified. Furthermore, biologics are generally used as monotherapy (whereas patients with IBD and RA are often co-prescribed immunosuppressants such as methotrexate, known to reduce the formation of ADA). Here, we capitalize on a real-world bioresource from a large multicenter cohort study BSTOP (Biomarkers of Systemic Treatment Outcomes in Psoriasis) within the UK pharmacovigilance registry BADBIR (British Association of Dermatologists Biologic Interventions Registry) to investigate the clinical utility of therapeutic drug monitoring as applied to the exemplar TNF inhibitor adalimumab. This work is particularly timely with the imminent release of adalimumab biosimilars to market, as optimizing outcomes may deliver comparable efficacy to newer biologics, but at significantly lower cost. We explore the relationship between drug levels and treatment response, accounting for individual patient characteristics to determine (i) the adalimumab therapeutic range ie. both the minimal effective drug level and the drug level beyond which response plateaus (ii) whether drug level predicts longer-term response. Given the nature of this real-world dataset, findings are generalizable to clinical practice.

RESULTS

Description of the cohort and patient characteristics

At the time of the data cut in April 2017, 2019 patients were currently or previously on adalimumab monotherapy within the BSTOP cohort. 1242 of these consented to give longitudinal serum samples; within this, serum samples were actually collected from 833 patients. Baseline characteristics were similar between those providing and not providing samples (Table 1, eTable 7). Of the 833 patients providing serum samples, 544 patients also

had PASI data within 12 months of starting adalimumab (Figure 1). These 544 patients were included in the analysis (Table 1), and of these, 375 (69%) were biologic-naïve.

The demographics and clinical characteristics of the cohort were consistent with severe disease (predominantly male, with an elevated BMI and mean baseline PASI 13.5 (sd: 6.7) (Table 1). Drug levels were sampled according to standard clinical care (median time from last dose 7 days, IQR 6 to 10 days, range 0 to 14 days, data available on n=349 samples), giving a mean drug level of 5.83 µg/ml (sd: 3.86, range 0.01 to 22 µg/ml).

Figure 1: Flow diagram of patients and samples

Flow diagram showing the rules applied to derive the three datasets.

As Figures 1 and 2 show, three datasets were derived: a therapeutic range dataset to investigate the relationship between drug levels and same-day response; an early dataset to investigate the relationship between drug levels taken before 12 weeks and 6-month response; and a steady state dataset to investigate the relationship between drug levels taken any time after 9 weeks and response 6 months later.

Figure 2: Timeline of drug levels and response in each dataset

Timeline showing when drug level and response was measured in each of the three datasets. In the therapeutic range dataset, response was measured on the same day as drug level. The other two datasets were derived to investigate use of drug levels to predict response 6 months later: in the early dataset, response was measured at 6 months after start of treatment; in the steady state dataset, response was measured 6 months after drug level. Statistical analyses conducted using each dataset are also shown.

Defining the therapeutic range

(i) Drug level discriminates responders from non-responders

Using the therapeutic range dataset (drug levels with PASI recorded on the same day), empirical ROC curves (Menting et al., 2015) were generated for all three outcomes. For

PASI75, drug level discriminated responders from non-responders with an AUC of 0.74 (95% CI 0.68 to 0.79) (Figure 3a, Table 2). A lower limit of 3.2 µg/ml identified patients achieving PASI75 with our pre-set minimum sensitivity of 80% (red dot on Figure 3a; specificity 58%; overall classification accuracy 73%). This drug level showed comparable sensitivity for the secondary outcomes PASI90 (82%) and PASI \leq 1.5 (85%), but specificity and overall classification accuracy were lower (eTable 1).

(ii) Likelihood of response increases with increasing drug level, and then plateaus

Using the therapeutic range dataset (drug levels with PASI recorded on the same day), a descriptive concentration effect curve (Menting et al., 2015) was next generated to confirm that clinical response increases with increasing drug level, then plateaus for groups with median drug level \geq 4.6 µg/ml (red dot on Figure 3b), corresponding to a percentage PASI change of 90.7% (IQR 83.7 to 99.4%, range 16.2% to 100%). However, the interquartile ranges on this curve show variability in response, likely caused by other clinical and confounding factors including ADA, time from last dose, sex, age and disease duration.

Figure 3: (a) Empirical ROC curve (b) Concentration effect curve

(a) Empirical ROC curve for PASI75 response. Cutpoint (red dot) chosen to provide a minimum sensitivity of 80%. (b) Concentration effect curve of median percentage change in PASI against median drug level. These summaries are calculated for approximately equally sized groups of observations (between 23 and 52) having similar drug levels. Vertical bars: interquartile range (IQR); grey horizontal lines: indicators of PASI75 and PASI90 response; red dot: drug level beyond which clinical response plateaus.

(iii) Selecting an upper limit of the therapeutic range taking other covariates into account

To take clinical and confounding covariates into account, multivariable mixed effects logistic regression modelling was carried out using the therapeutic range dataset. The results were consistent with the empirical analysis: for the primary outcome of PASI75, the best-fitting

model included (transformed) drug level and ethnicity as covariates (Table 3, eTable 2) and the probability of PASI75 response plateaued with increasing drug level, supporting the concept of an upper-bounded therapeutic range (Figure 4). We selected 7 $\mu\text{g}/\text{ml}$ as the upper limit of the therapeutic range since this achieves our minimum stipulated 80% probability of response (81%, 95% CI 76% to 86%) (Figure 4), whereas the drug level at which the concentration effect curve appeared to plateau (4.6 $\mu\text{g}/\text{ml}$) has a lower probability of response (73%, 95% CI 68% to 77%).

For the PASI90 and PASI \leq 1.5 outcomes, drug level remained the most important determinant of response. Additional covariates appear significant for PASI90 (baseline PASI, treatment duration and biologic naive status) and PASI \leq 1.5 (gender and biologic naive status).

However, this should be treated with caution given the small number of patients achieving PASI90 and PASI \leq 1.5 (eTable 2, eTable 5, eFigure 1).

Figure 4:

Probability of PASI75 based on same-day drug level (therapeutic range dataset)

Probability of response is split by ethnicity (red is white ethnicity; dark blue is all other ethnicities). The grey vertical line is at a drug level of 7 $\mu\text{g}/\text{ml}$, where there is at least 80% probability of response on average for all patients. This line crosses the red curve for patients of white ethnicity at a probability of response $>80\%$, but the probability is lower for the non-white group (dark blue line). The green dots indicate the proportion of patients per group achieving PASI75. Note that the groups are calculated in the same way as for the concentration effect curve in Figure 2b, and that they are not split by other covariates. The probabilities are marginal predicted means due to the inclusion of a random effect in the model.

Similar curves are seen for probability of PASI75 in the other datasets (early and steady state).

Using drug level to predict subsequent response

i) Early drug levels predict response at 6 months

To determine whether drug levels indicate response status at later time points, multivariable logistic regression modelling was carried out using the early dataset (drug levels taken between 1-12 weeks with PASI recorded at 6 months). For the primary outcome of PASI75,

independent predictors were (transformed) drug level and ethnicity (Table 3, eTable 3). These same covariates were included in the final PASI90 model, and drug level and baseline PASI were included in the PASI \leq 1.5 model (eTable 5). Similar to the analysis using the therapeutic range dataset (exploring the relationship between drug levels and response on the same day), the probability of response at 6 months increases with increasing early drug level (PASI75 Table 3, eFigure 2a; PASI90 and PASI \leq 1.5 eTable 5, eFigures 2b and 2c). The upper limit of 7 μ g/ml (defined in the therapeutic range dataset, Figure 4) corresponds to a 78% (95% CI 71% to 85%) probability of 6-month response using early drug levels (Table 2, eFigure 2a). We also performed a sensitivity analysis by fitting the model to very early samples (4 weeks \pm 1 week after treatment initiation) given our pilot data showing that higher adalimumab levels in responders versus non-responders were detectable at 4 weeks¹¹, and acknowledging the overlap between our early dataset and steady state dataset. We found a similar relationship between drug levels and PASI75 response (eTable 6).

ii) Steady state drug levels predict response 6 months later

Finally, we explored whether steady state drug levels in patients established on therapy could predict treatment outcomes 6 months later. Multivariable mixed effects logistic regression modelling was carried out using the steady state dataset (drug levels taken $>$ 9 weeks after treatment start with PASI recorded 6 months later) (Table 3, eTable 4). Again, for the primary outcome of PASI75, (transformed) drug level was the single most important predictor of response (OR[(sqrt) drug level] 2.78, 95%CI 1.83 to 4.24, $P < .001$) (Table 3), with increasing probability of response with increasing drug level (Figure 4c). This relationship between drug level and response was also seen using the PASI90 and PASI \leq 1.5 outcomes (eFigures 3a and 3b, eTable 5); the covariates palm psoriasis and biologic naive status were also significant for these outcomes respectively.

Clinical utility of the therapeutic range

Table 2 gives the standard estimates of clinical utility for our therapeutic range for PASI75 (3.2 to 7 $\mu\text{g/ml}$). Notably, this has comparable diagnostic accuracy whether used to determine response on the same day as the drug level, or response 6 months later. Bearing our therapeutic range in mind, 72/125 (57.60%) of samples with a corresponding response less than PASI75 had a drug level below 3.2 $\mu\text{g/ml}$, and 69/171 (40.35%) of samples with a corresponding PASI90 response had a drug level greater than or equal to 7 $\mu\text{g/ml}$. This suggests that a significant proportion of the cohort would benefit from treatment modification.

DISCUSSION

Key results

In the largest real-world multicenter cohort across any IMID to date, we have determined the therapeutic range for adalimumab in moderate to severe psoriasis and calculate probabilities of response for any given drug level, for multiple outcomes (PASI75, PASI90 and absolute $\text{PASI} \leq 1.5$). We also show that drug levels can be used to predict response at later time points, whether taken early in the treatment course or at steady state. A minimal effective circulating drug level of 3.2 $\mu\text{g/ml}$ distinguishes PASI75 responders from non-responders, and a target drug level of 7 $\mu\text{g/ml}$ provides an 80% probability of achieving a PASI75 response. As expected, there is a lower probability (51%) of achieving higher disease clearance (PASI90) at the same target drug level. Notably, measurement of ADA provides no additional clinical utility - presumably due to the correlation between drug levels and ADA. These key findings support the practical utility of measuring drug levels at routine clinical visits (irrespective of timing in relation to drug administration, and despite not being trough levels), and provide drug level thresholds at which to consider changes in adalimumab treatment.

Clinical implications

Our findings are consistent with the only other study conducted in psoriasis, which was dual-center and reported a therapeutic range of 3.51 to 7.00 $\mu\text{g/ml}$ (Menting et al., 2015), but did not take into account clinical or other covariates such as ADA, nor comment on clinical utility. This work builds on our previous pilot data, showing that adalimumab levels at 4 weeks were significantly higher in responders than non-responders (Mahil et al., 2013). Very few studies across any IMID have paid attention to early drug levels, and to our knowledge, only one small study in IBD (Baert et al., 2014) has looked at early adalimumab levels as a predictor of subsequent treatment response. This may open up a powerful clinical opportunity to optimize therapy before drug levels have reached steady state, well ahead of clinical relapse. However, it is significant that drug level at steady state (≥ 9 weeks) is also associated with response 6 months later, suggesting that there is potential to optimize therapy even once patients are established on treatment. Our results may be generalizable across other IMID, given comparable therapeutic ranges for adalimumab reported in RA (5-8 $\mu\text{g/ml}$) (Pouw et al., 2015) and IBD (5.0 to 5.9 $\mu\text{g/mL}$ or 4.9 to 7.5 $\mu\text{g/mL}$) (Roblin et al., 2014, Yarur et al., 2016); and comparable mean levels in ankylosing spondylitis (Kobayashi et al., 2012).

A minimal effective drug level indicates the threshold below which treatment should be modified (dose escalation or treatment switch). Such an approach has been tested in IBD, with the TAXIT trial demonstrating similar remission rates in IBD patients on adjusted infliximab dosing based on drug-level, but with fewer flares than the conventional approach (Vande Casteele et al., 2015). An upper limit of the therapeutic range identifies a patient population that might benefit from dose minimization. This has been simulated in an RA cohort and whilst cost-effective, led to a reduction in quality-adjusted life years for at least a quarter of patients (Krieckaert et al., 2015). By comparison, our modelling approach may have an advantage in allowing for individualized prediction of response. Indeed, our data indicate that both the stringency of the outcome (for example PASI75 or PASI90), and the

threshold set for the probability of response, need to be considered when defining the upper limit of the therapeutic range (and therefore the drug level chosen to implement dose minimization). This will help optimize cost-effectiveness and minimize the proportion of patients subjected to inappropriate dose reduction.

From a biological perspective, the finding that clinical response rate plateaus beyond a certain drug level likely reflects the point at which most of the TNF in psoriatic skin is neutralized by adalimumab. In turn, this may indicate that in patients for whom clinical response plateaus at a lower drug level, alternative non-TNF pathways possibly play a greater role in driving their psoriasis.

The finding that biologic naïve status and ethnicity may predict longer-term response requires further validation, as these covariates were not consistent across outcomes. Our data suggest that although biologic naïve status does not appear to be important for achieving PASI75, it does appear to be influential for achieving clearance (PASI90 or PASI \leq 1.5). This is consistent with existing evidence that biologic naïve status may influence outcome (nice.org.uk/guidance/cg153).

Our findings related to ethnicity should be treated with particular caution, because very few patients within the study cohort were of non-white ethnicity. Intriguingly, across the BADBIR cohort as a whole, we found non-white ethnicity to be associated with a reduced likelihood of response to biologics up to one year (Warren R.B. et al., in press).

Finally, we have confirmed serum drug level to be the single most important factor determining treatment response - whether sampled a few weeks after treatment initiation, or at steady state. This underpins the importance of taking drug levels into account when searching for biomarkers and mechanisms of treatment response such as genetic factors.

Indeed, the need to incorporate a richer set of clinical information, such as seropositivity and disease duration, was recently highlighted in an innovative crowdsourced assessment of the

common genetic contribution to predicting TNF-antagonist treatment response in RA (Sieberts et al., 2016).

Strengths and limitations

A key strength of this study is high external validity, since more than 50% of all UK psoriasis patients on biologics are registered on BADBIR, and 95% of UK dermatology centers prescribing biologics for psoriasis contribute data to BADBIR. In order to maximize inclusivity, generalizability and sample size, we developed a prespecified research protocol with inclusion criteria designed to capture a truly representative patient sample. This approach, together with the real-world nature of the cohort necessitating pragmatic sampling, introduces heterogeneity into our dataset. This heterogeneity reflects our strategy to maximize inclusivity and minimize selection bias.

In terms of potential limitations, the validity of the therapeutic range is limited to within one year of start of treatment, since this was the selected cohort duration. Most patients in the UK receive the licensed dose for adalimumab (40 mg fortnightly), so whilst dose escalation would be a logical clinical strategy for individuals with subtherapeutic drug levels, this requires confirmation in a clinical trial setting and would have pharmacoeconomic implications. On the other hand, the advent of adalimumab biosimilars at a fraction of the cost of the original drug means that dose optimization strategies remain highly relevant. Another potential limitation is use of pragmatic serum sampling at routine clinic visits; to account for the timing of samples we included time from last dose as a covariate, and although this was not significant at the univariate level, we only had this data available on around a third of samples. Nevertheless, we identified a comparable range to Menting et al (Menting et al., 2015) who reported on trough drug levels, suggesting that limiting sampling to trough levels may not be an absolute requirement. Finally, covariates are not always consistent across outcomes or datasets, due to statistical artefacts when using different

subsets of patients - thus our findings require replication. Indeed, the model fit as measured by pseudo R^2 indicates that although drug level is important, this model could potentially be improved using covariates that have not been considered in this study.

Conclusions

We provide evidence to support the proactive measurement of drug levels in the management of psoriasis with adalimumab therapy. Drug levels taken both early and at steady state during the treatment course could be used to predict and therefore optimize clinical outcome. These findings are of potential relevance to other IMiD.

MATERIALS & METHODS

Ethics approval

The study was conducted in the spirit of the 1996 International Conference on Harmonisation in Good Clinical Practice (ICH-GCP) 1996, and in accordance with the 2008 Declaration of Helsinki. The study protocol was approved by The South East London REC 2 Ethics Committee (11/H0802/7). Written informed consent was obtained from all subjects prior to enrolment.

Patients and Setting

BSTOP is a prospective, multicenter (n=60) observational study to establish clinically relevant markers of outcomes to systemic therapies in people with severe psoriasis. All adults in the UK fulfilling the BSTOP inclusion and exclusion criteria (BSTOP protocol at <https://bit.do/BSTOPDOCS>) and enrolled onto BADBIR (<http://www.badbir.org/>) were invited to participate. BADBIR has recruited >12,000 psoriasis patients since 2007, and is unique worldwide in terms of size and depth of phenotyping. Inclusion criteria include: dermatologist's diagnosis of psoriasis; age >16 years; and started on, or switched to a

conventional systemic therapy or a biological therapy within the previous 6 months. Detailed information is recorded, including demographics, comorbidities, treatments and adverse effects. Clinical response is assessed longitudinally using the gold standard assessment tool PASI.

Pharmacokinetic Measurements

Venous blood samples were collected between June 2009 and December 2016 during routine clinic reviews, without reference to treatment administration (ie. trough/non-trough not specified), immediately centrifuged at 2000 g for 10 minutes and serum aliquots frozen at -80 °C. In this pragmatic study, samples were not collected from every patient at every time point. Samples within the first year of treatment (n=961, maximum 4 samples/patient) were selected and sent in batches to Sanquin for measurement of adalimumab concentration (enzyme-linked immunosorbent assay, ELISA, µg/ml (Menting et al., 2015)) and ADA (radioimmunoassay, RIA, ADA positive cutoff: >12 arbitrary units/ml (Menting et al., 2015)).

Outcome Measures

Primary treatment response was defined as achieving a 75% reduction in PASI from baseline (PASI75); secondary outcomes were (i) 90% reduction in PASI from baseline (PASI90) and (ii) an absolute measure of response, PASI of ≤ 1.5 (results in Supplementary Material).

Baseline PASI was defined as the most recent PASI recorded prior to the date of the first drug dose within the preceding 6 months (Iskandar et al., 2015, Warren et al., 2015).

Statistical Methods

Analyses for PASI75 and PASI90 responses were restricted to patients with baseline PASI >10 as an accepted criterion for severe disease (nice.org.uk/guidance/cg153) and to minimize

confounding due to pre-biologic treatments – of particular relevance in this real-world dataset.

Identification of therapeutic range

The therapeutic range dataset (Figure 1, Figure 2) included samples that were taken at steady state (≥ 9 weeks (Awni et al., 2003)), with PASI scores recorded on the same day. Empirical Receiver Operating Characteristic (ROC) curve analysis (Menting et al., 2015) was used to identify the lower limit of the therapeutic range – specifically, the drug level at which responders are detected with a minimum sensitivity of 80%.

A descriptive concentration effect curve (Menting et al., 2015) was generated to confirm that clinical response plateaus beyond a certain drug level. Multivariable mixed effects logistic regression was then used to identify an upper drug level, and to explore the relationship between drug level and treatment response in the presence of other relevant covariates. A random intercept term was used to account for correlation between repeated samples on the same patient. Univariate mixed effects logistic regression models explored the relationship between treatment response and i) drug level ii) other confounding covariates including ADA, time from last dose, sex, age and disease duration. For continuous covariates, the best-fitting simple non-linear transformation was chosen based on reduction in the Akaike Information Criterion (AIC). Covariates associated with response at significance level $p < 0.1$ were taken forward to the multivariable modelling stage. Forward selection techniques were then used, with covariate inclusion based on significance level $p < 0.05$. Pseudo R^2 (McFadden's for fixed effect models, conditional and marginal for mixed models (Nakagawa and Schielzeth, 2013)) and AIC were calculated to assess model fit. Finally, an upper limit of the therapeutic range was defined based on this multivariable model for PASI75, with the target probability of response set at 80%.

Using drug level to predict subsequent response

To investigate whether drug level predicts subsequent outcome, two further datasets were derived: an early dataset comprising samples taken between 1 and 12 weeks with a corresponding PASI 6 months (122 to 243 days) after start of treatment and a steady state dataset comprising samples taken at steady state (≥ 9 weeks (Awni et al., 2003)) with a corresponding PASI 6 months (122 to 243 days) after the sample date. Multivariable mixed effects logistic regression models were considered to explore the relationship between drug level and other covariates with patient response 6 months later. For the early dataset a random effect was not included, due to the small number of patients with multiple samples. All analyses were carried out using Stata version 14 (StataCorp, 2015) on a complete case basis.

Conflict of interest

CEMG has received honoraria and/or research grant support (University of Manchester) from Abbvie, Almirall, Bristol Meyers Squibb, Celgene, GSK, Janssen, LEO Foundation, Lilly, Novartis, Pfizer, Sandoz, Sun Pharma and UCB Pharma; NJR has received honoraria, travel support, and/or research grants (Newcastle University) from Abbvie, Almirall, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Leo-Pharma Research Foundation, Novartis, Pfizer, and Stiefel GSK; JB has received honoraria, travel support, and/or research grants (King's College) from Abbvie, Pfizer, Novartis, Janssen, Roche, Regeneron, Lilly, UCB, Sun Pharma, Boehringer Ingelheim and GSK; RBW has received honoraria and/or research grants from Abbvie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo, Lilly, Novartis, Pfizer, Sanofi, Xenoport and UCB; ADB has received honoraria from Abbvie, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo, Lilly, Novartis and Pfizer; TR has received honoraria for lectures from Pfizer, Abbvie, and Regeneron, and a research grant from Genmab; DS has received departmental research funding from AstraZeneca; CS has received departmental research funding from Abbvie, GSK, Pfizer, Novartis, Regeneron and Roche; NW acts as statistician on a trial funded by AstraZeneca; the PSORT consortium has a number of industry partners, see www.psort.org.uk; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The authors acknowledge the substantial contribution of Dr Gertjan Wolbink, who provided invaluable advice on study design; Alice Russell, who provided support with data management and coordination; the PSORT, BADBIR and BSTOP study teams for the administration of the project; The Psoriasis Association for their ongoing support since the

inception of BSTOP and PSORT; and the National Institute for Health Research (NIHR) Biomedical Research Centre at King's College London/Guy's and St Thomas' NHS Foundation Trust, which has provided database infrastructure and support staff.

The authors also acknowledge the invaluable support of the NIHR through the clinical research networks and its contribution in facilitating recruitment to both BSTOP and BADBIR. Finally, we acknowledge the enthusiastic collaboration of all of the dermatologists and specialist nurses in the UK and the Republic of Ireland who recruited to this study (<https://bit.do/PIBSTOP>) – in particular the contribution by Dr Gabrielle Becher, Dr Ruth Murphy, Dr Andrew Wright, Dr Ali Al-Sharqi and Dr Shyamal Wahie.

Funding

This work was supported by PSORT, which is in turn funded by a Medical Research Council (MRC) Stratified Medicine award (MR/L011808/1). The Psoriasis Association (RG2/10), the NIHR Biomedical Research Centre at King's College London/Guy's and St Thomas' NHS Foundation Trust, the NIHR Manchester Biomedical Research Centre and the NIHR Newcastle Biomedical Research Centre. TT is supported by a MRC Clinical Research Training Fellowship (MR/R001839/1). NJR is supported by the Newcastle MRC/EPSRC Molecular Pathology Node and the Newcastle NIHR Medtech and In vitro diagnostics Co-operative. CEMG is a NIHR Senior Investigator.

References

- nice.org.uk/guidance/cg153. Psoriasis: assessment and management, Clinical Guideline [CG153] [accessed 6th February 2018].
- Awni WM, Cascella P, Oleka NA, Velagapudi RB, Kupper H, Chartash E, et al. Steady-state pharmacokinetics (PK) of adalimumab (HUMIRA (TM), Abbott) following 40 mg subcutaneous (sc) injection every other week (eow) in rheumatoid arthritis (RA) patients with and without methotrexate (MTX) background therapy. *Arthritis and Rheumatism* 2003;48(9):S140-S. (abstr.)
- Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *New England Journal of Medicine* 2003;348(7):601-8.
- Baert F, Vande Casteele N, Tups S, Noman M, Van Assche G, Rutgeerts P, et al. Prior response to infliximab and early serum drug concentrations predict effects of adalimumab in ulcerative colitis. *Alimentary Pharmacology & Therapeutics* 2014;40(11-12):1324-32.
- Chen DY, Chen YM, Tsai WC, Tseng JC, Chen YH, Hsieh CW, et al. Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2015;74(3).
- Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. *Annals of the Rheumatic Diseases* 2013;72(12):1947-55.
- Iskandar I, Ashcroft DM, Warren RB, Yiu ZZN, McElhone K, Lunt M, et al. Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. *British Journal of Dermatology* 2015;173(2):510-8.
- Kobayashi S, Harigai M, Mozaffarian N, Pangan AL, Sharma S, Brown LS, et al. A multicenter, open-label, efficacy, pharmacokinetic, and safety study of adalimumab in Japanese patients with ankylosing spondylitis. *Modern Rheumatology* 2012;22(4):589-97.
- Krieckaert CLM, Nair SC, Nurmohamed MT, van Dongen CJJ, Lems WF, Lafeber F, et al. Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects. *Annals of the Rheumatic Diseases* 2015;74(2):361-8.
- Lecluse LLA, Driessen RJB, Spuls PI, de Jong E, Stapel SO, van Doorn MBA, et al. Extent and Clinical Consequences of Antibody Formation Against Adalimumab in Patients With Plaque Psoriasis. *Archives of Dermatology* 2010;146(2):127-32.
- Mahil SK, Arkir Z, Richards G, Lewis CM, Barker JN, Smith CH. Predicting treatment response in psoriasis using serum levels of adalimumab and etanercept: a single-centre, cohort study. *British Journal of Dermatology* 2013;169(2):306-13.
- Menting SP, Coussens E, Pouw MF, van den Reek J, Temmerman L, Boonen H, et al. Developing a Therapeutic Range of Adalimumab Serum Concentrations in Management of Psoriasis A Step Toward Personalized Treatment. *Jama Dermatology* 2015;151(6):616-22.
- Mostafa NM, Nader AM, Noertersheuser P, Okun M, Awni WM. Impact of immunogenicity on pharmacokinetics, efficacy and safety of adalimumab in adult patients with moderate to severe chronic plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology* 2017;31(3):490-7.
- Nakagawa S, Schielzeth H. A general and simple method for obtaining R² from generalized linear mixed-effects models. *Methods in Ecology and Evolution* 2013;4(2):133-42.
- Pouw MF, Krieckaert CL, Nurmohamed MT, van der Kleij D, Aarden L, Rispen T, et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Annals of the Rheumatic Diseases* 2015;74(3):513-8.
- Roblin X, Marotte H, Rinaudo M, Del Tedesco E, Moreau A, Phelip JM, et al. Association Between Pharmacokinetics of Adalimumab and Mucosal Healing in Patients With Inflammatory Bowel Diseases. *Clinical Gastroenterology and Hepatology* 2014;12(1):80-+.

- Sieberts SK, Zhu F, Garcia-Garcia J, Stahl E, Pratap A, Pandey G, et al. Crowdsourced assessment of common genetic contribution to predicting anti-TNF treatment response in rheumatoid arthritis (vol 7, 12460, 2016). *Nature Communications* 2016;7.
- StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP2015.
- Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernelle G, Van Steen K, et al. Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease. *Gastroenterology* 2015;148(7):1320-+.
- Warren R.B. MA, Tomenson B., Mason K.J., Soliman M.M., Burden A.D., Reynolds N.J., Stocken D., Emsley R., Griffiths C.E.M., Smith C. and on behalf of the PSORT Consortium and on behalf of the BADBIR Study Group. Identifying demographic, social and clinical predictors of biologic therapy effectiveness in psoriasis: a multi-centre longitudinal cohort study. *British Journal of Dermatology*. (in press)
- Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker J, Burden AD, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Journal of Investigative Dermatology* 2015;135(11):2632-40.
- Yanai H, Hanauer SB. Assessing Response and Loss of Response to Biological Therapies in IBD. *American Journal of Gastroenterology* 2011;106(4):685-98.
- Yarur AJ, Jain A, Hauenstein SI, Quintero MA, Barkin JS, Deshpande AR, et al. Higher Adalimumab Levels Are Associated with Histologic and Endoscopic Remission in Patients with Crohn's Disease and Ulcerative Colitis. *Inflammatory Bowel Diseases* 2016;22(2):409-15.

Table 1: Summary statistics for the full cohort, therapeutic range dataset, early dataset and steady state dataset

Covariate	Full cohort (n=544 patients with 961 samples)		Therapeutic range dataset (n= 303 patients with 409 samples)		Early dataset (n=120 patients with 159 samples)		Steady state dataset (n=244 patients with 322 samples)	
	Mean (sd)	Complete data n (%)	Mean (sd)	Complete data n (%)	Mean (sd)	Complete data n (%)	Mean (sd)	Complete data n (%)
Baseline PASI	13.5 (6.7)	495 (91.0)	15.9 (5.6)	303 (100.0)	16.2 (6.4)	120 (100.0)	15.9 (5.6)	244 (100.0)
Height (cm)	172.3 (10.3)	520 (95.6)	172.0 (10.1)	295 (97.4)	172.4 (9.3)	114 (95.0)	172.3 (10.3)	239 (98.0)
Weight (kg)	90.9 (20.4)	471 (86.6)	92.3 (20.7)	277 (91.4)	92.3 (22.2)	106 (88.3)	92.9 (21.1)	223 (91.4)
Waist (cm)	102.1 (15.6)	443 (81.4)	103.0 (16.0)	266 (87.8)	103.2 (16.9)	103 (85.8)	103.8 (15.7)	214 (87.7)
BMI (kg/m ²)	30.8 (6.7)	465 (85.5)	31.3 (7.2)	274 (90.4)	31.2 (7.3)	106 (88.3)	31.3 (7.0)	221 (90.6)
Age (years)	44.3 (12.2)	544 (100.0)	44.0 (12.3)	303 (100.0)	43.8 (12.4)	120 (100.0)	44.1 (12.2)	244 (100.0)
Disease duration (years)	22.0 (12.0)	498 (91.5)	21.5 (12.4)	282 (93.1)	20.8 (11.5)	104 (86.7)	21.1 (11.8)	233 (95.5)
	n (%)		n (%)		n (%)		n (%)	
Ethnicity – white	484 (89.0%)	544 (100.0)	272 (89.8)	303 (100.0)	103 (85.8)	120 (100.0)	216 (88.5)	244 (100.0)
Gender – male	338 (62.1)	544 (100.0)	191 (63.0)	303 (100.0)	80 (66.7)	120 (100.0)	161 (66.0)	244 (100.0)
Inflammatory arthritis	109 (23.5)	464 (85.3)	62 (22.6)	274 (90.4)	27 (26.2)	103 (85.8)	54 (24.1)	224 (91.8)
Ever smoked	298 (56.7)	526 (96.7)	172 (57.9)	297 (98.0)	66 (57.9)	114 (95.0)	141 (58.5)	241 (98.8)
Palm psoriasis	87 (16.9)	515 (94.7)	46 (16.0)	288 (95.0)	21 (19.4)	108 (90.0)	38 (16.4)	232 (95.1)
Biologic naive	375 (68.9)	544 (100.0)	237 (78.2)	303 (100.0)	97 (80.8)	120 (100.0)	189 (77.5)	244 (100.0)

Summaries for the therapeutic range, early sample and steady state datasets are restricted to patients with baseline PASI > 10. Height, waist and BMI measurements provided for information only; weight used in modelling.

Table 2: Diagnostic accuracy of the therapeutic range for PASI75 response

	Drug levels and response (same-day)		Drug levels as a predictor of subsequent response (6 months)			
			early		steady state	
Cutpoint ⁺ (µg/ml)	3.2	7	3.2	7	3.2	7
Sensitivity	80.28%	38.38%	86.61%	40.18%	77.46%	39.44%
Specificity	57.60%	84.80%	44.68%	74.47%	55.96%	84.40%
Overall classification accuracy	73.35%	52.57%	74.21%	50.31%	70.19%	54.66%
Positive Predictive Value	81.14%	85.16%	78.86%	78.95%	77.46%	83.17%
Negative Predictive Value	56.25%	37.72%	58.33%	34.31%	55.96%	41.63%
AUC (95% CI)	0.74 (0.68,0.79)		0.70 (0.59,0.80)		0.72 (0.66,0.78)	
Response rate: all samples	69.44%		70.44%		66.15%	
Response rate: samples with drug level < cutpoint *	43.75%	62.28%	41.67%	65.69%	44.04%	58.37%
Response rate: samples with drug level ≥ cutpoint *	81.14%	85.16%	78.86%	78.95%	77.46%	83.17%
Probability of response ** (95% CI)	65% (60,71%)	81% (76,86%)	61% (51,70%)	78% (71,85%)	77% (71,83%)	64% (58,70%)

Note: analyses are based on 409 samples from 303 patients for the therapeutic range, on 159 samples from 120 patients for the early samples and 322 samples on 244 patients for the steady state dataset.

⁺ A cutpoint of 3.2 indicates that samples with a drug level ≥ 3.2 are predicted to correspond with response.

* Response rates for samples above and below cutpoints are equivalent to positive predictive value and (1 – negative predictive value) respectively.

** Derived from the final multivariable models given in Table 3.

Table 3: Final multivariable models for PASI75 response based on drug level and additional covariates (therapeutic range dataset) and predicting PASI75 response 6 months later (early dataset, steady state dataset)

Therapeutic range (Mixed effects logistic regression model)								
	Covariate	Coefficient (s.e)	P value	95% CI	OR (95% CI)	Marginal/ Conditional Pseudo R²	Number of samples	Number of responders (% of samples)
PASI75	Sqrt(drug level)	1.10 (0.20)	<.001	(0.69,1.50)	2.99 (2.00,4.46)	0.25/0.38	409 samples on 303 patients	284 (69.44)
	Ethnicity – white	1.15 (0.46)	.013	(0.24,2.06)	3.17 (1.28,7.85)			
Early samples (Logistic regression model)								
	Covariate	Coefficient (s.e)	P value	95% CI	OR (95% CI)	Pseudo R²	Number of samples	Number of responders (% of samples)
PASI75	Sqrt(drug level)	1.00 (0.26)	<.001	(0.49,1.52)	2.73 (1.63,4.57)	0.10	159 samples on 120 patients	112 (70.44)
	Ethnicity – white	1.05 (0.51)	.039	(0.06,2.04)	2.86 (1.06,7.72)			
Steady state (Mixed effects logistic regression model)								
	Covariate	Coefficient (s.e)	P value	95% CI	OR (95% CI)	Marginal/ Conditional Pseudo R²	Number of samples	Number of responders (% of samples)
PASI75	Sqrt(drug level)	1.02 (0.21)	<.001	(0.60,1.44)	2.78 (1.83,4.24)	0.16/0.50	322 samples on 244 patients	213 (66.15)

Figure Legends

Figure 1: Flow diagram of patients and samples

Flow diagram showing the rules applied to derive the three datasets.

Figure 2: Timeline of drug levels and response in each dataset

Timeline showing when drug level and response was measured in each of the three datasets. In the therapeutic range dataset, response was measured on the same day as drug level. The other two datasets were derived to investigate use of drug levels to predict response 6 months later: in the early dataset, response was measured at 6 months after start of treatment; in the steady state dataset, response was measured 6 months after drug level. Statistical analyses conducted using each dataset are also shown.

Figure 3: (a) Empirical ROC curve (b) Concentration effect curve

(a) Empirical ROC curve for PASI75 response. Cutpoint (red dot) chosen to provide a minimum sensitivity of 80%.

(b) Concentration effect curve of median percentage change in PASI against median drug level. These summaries are calculated for approximately equally sized groups of observations (between 23 and 52) having similar drug levels. Vertical bars: interquartile range (IQR); grey horizontal lines: indicators of PASI75 and PASI90 response; red dot: drug level beyond which clinical response plateaus.

Figure 4:

Probability of PASI75 based on same-day drug level (therapeutic range dataset)

Probability of response is split by ethnicity (red is white ethnicity; dark blue is all other ethnicities). The grey vertical line is at a drug level of 7 $\mu\text{g}/\text{ml}$, where there is at least 80% probability of response on average for all patients. This line crosses the red curve for patients of white ethnicity at a probability of response >80%, but the probability is lower for the non-white group (dark blue line). The green dots indicate the proportion of patients per group achieving PASI75. Note that the groups are calculated in the same way as for the concentration effect curve in Figure 2b, and that they are not split by other covariates. The probabilities are marginal predicted means due to the inclusion of a random effect in the model. Similar curves are seen for probability of PASI75 in the other datasets (early and steady state).

Figure 1

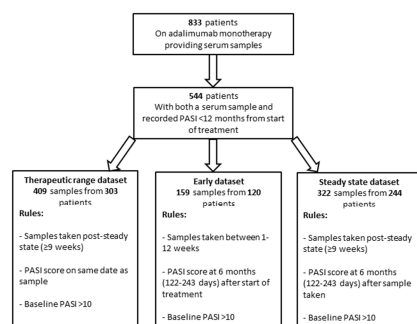


Figure 2

