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Psoriatic arthritis: the role of self-reported non-adherence, non-trough drug levels, immunogenicity and conventional synthetic DMARD co-therapy in adalimumab and etanercept response

Philippa D. K. Curry [1], Andrew P. Morris [1,2], Meghna Jani [2,3,4], Hector Chinoy [2,4,5], Anne Barton [1,2], James Bluett [1,2,*]; and for OUTPASS Collaborators[‡]

[1]Versus Arthritis Centre for Genetics and Genomics, Centre for Musculoskeletal Research, The University of Manchester, Manchester, UK
[2]NIHR Manchester BRC, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[3]Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, The University of Manchester, Manchester, UK
[4]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK
[5]Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

*Correspondence to: James Bluett, Centre for Musculoskeletal Research, Division of Musculoskeletal & Dermatological Sciences, School of Biological Sciences, The University of Manchester, 1.204 AV Hill, Oxford Road, Manchester M13 9PT, UK. E-mail: james.bluett@manchester.ac.uk

[‡]See supplementary material available at *Rheumatology Advances in Practice* online for a list of the OUTPASS collaborating sites and authors.

Abstract

Objective: The aim of this study was to assess the relationship between self-reported non-adherence, non-trough drug levels, immunogenicity and conventional synthetic DMARD (csDMARD) co-therapy in TNF inhibitor (TNF-i) drug response in PsA.

Methods: Serum samples and adherence questionnaires were collected at baseline, 3, 6 and 12 months for PsA patients prescribed TNF-i. Non-trough adalimumab (ADL) and etanercept (ETN) drug levels were measured at 3 and 6 months using commercially available ELISAs. Clinical response was assessed using PsA response criteria (PsARC) and change in 28-joint DAS (ΔDAS28) between baseline and 3, 6 and 12 months.

Results: In 244 PsA patients (52.5% ADL and 47.5% ETN), self-reported non-adherence was associated with PsARC non-response over 12 months using generalized estimating equation (GEE) modelling ($P=0.037$). However, there was no significant difference between non-trough ADL or ETN drug levels based on self-reported non-adherence. Higher ETN levels at 3 months were associated with PsARC response at 3 ($P=0.015$), 6 ($P=0.037$) and 12 months ($P=0.015$) and over 12 months using GEE modelling ($P=0.026$). Increased ADL drug levels at 3 months were associated with greater ΔDAS28 at 3 months ($P=0.019$). ADL anti-drug antibody-positive status was significantly associated with lower 3- and 6-month ADL levels ($P<0.001$) and ΔDAS28 and PsARC response at 3, 6 and 12 months. Meanwhile, MTX co-therapy was associated with a reduction in immunogenicity at 3 and 6 months ($P=0.008$ and $P=0.024$).

Conclusion: Although both were associated with reduced response, the objectively measured non-trough drug levels showed more significant associations with drug response than self-reported non-adherence measures.

Lay Summary

What does this mean for patients?

Psoriatic arthritis (PsA) is a long-term condition that affects a person's skin and joints, owing to inflammation. Despite a wide range of drugs being available, treatment fails to improve the control of the condition in up to 40% of people with PsA, and this includes advanced biologic therapies that target the immune system. This might be attributable to a person not taking their therapy as prescribed, low levels of the drug in their blood or the presence of anti-drug antibodies. Here, we measured drug levels of two commonly prescribed biologic therapies (adalimumab and etanercept). We asked patients to tell us whether they took their drugs as prescribed and explored the relationship with treatment response. We found that 36% of people reported not taking their drugs as they were advised (non-adherence), and this group were less likely to respond to therapy over 12 months. Meanwhile, people with lower adalimumab and etanercept drug levels were less likely to respond to therapy at multiple time points. There was no clear relationship between drug levels and whether a person said they took their drug or not in this study. Lifestyle factors, including a person's body mass index and presence of antibodies that deactivate the biologics (anti-drug antibodies), were also seen to impact treatment response. Taking a commonly prescribed drug, methotrexate, in addition to advanced biologic therapy was seen to reduce the presence of anti-drug antibodies. Overall, drug levels were more significantly associated with drug response compared with whether a person reported taking their therapy.

Keywords: psoriatic arthritis, TNF inhibitors, non-adherence, immunogenicity, drug levels, drug response.

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Key messages

- Up to 40% of patients with PsA experience suboptimal response to TNF inhibitors.
- Decreased drug levels were more strongly associated with decreased TNF-inhibitor response than self-reported non-adherence.
- Modifiable factors, including BMI, smoking and conventional synthetic DMARD co-therapy, should be considered in drug response optimization.

Introduction

PsA affects 15–30% of patients with psoriasis. A heterogeneous and debilitating disease, it can result in joint erosion, physical disability and psychological morbidity, subsequently increasing work instability and cardiovascular mortality risk [1, 2]. With no cure, drug treatment aims to control joint inflammation and prevent irreversible erosive joint disease.

As the knowledge of psoriatic immunopathogenesis has improved over the last 20 years, the therapeutic development of biologic drugs has expanded dramatically. To date, there are five United States Food and Drug Administration approved TNF inhibitors (TNF-i), with adalimumab (ADL) being the most commonly prescribed in the UK, accounting for ∼55% of prescriptions, followed by etanercept (ETN) [3]. TNF-i are reported to be more cost-effective than conventional synthetic DMARD (csDMARD) alternatives, including MTX and SSZ, with increased costs being offset by significantly improved efficacy [4]. However, suboptimal drug adherence and indirect disease costs can add to the economic burden of PsA [4, 5]. Up to 40% of patients experience a failure of first-line TNF-i therapy, increasing the risk of disease progression and health-care costs [6, 7]. It is not currently possible to predict TNF-i response in PsA accurately, but it is thought to be multifactorial [8]. The identification and validation of robust biomarkers of response would be a major scientific breakthrough, paving the way to precision medicine approaches.

In PsA, lifestyle modifications, including weight loss, smoking cessation, increased exercise, medication adherence and joint stress protection influence disease management, potentially confounding the search for valid biomarkers of treatment response [9]. In RA, suboptimal TNF-i adherence and reduced drug levels have been associated with poorer response [10–12]. However, little is known about the true impact of non-adherence on TNF-i response in PsA, despite treatment non-adherence of ≤78% being reported [13]. Self-reported non-adherence might be subject to bias, but direct drug measurements offer a potentially objective evaluation of non-adherence. Drug levels can be measured using ELISAs and have previously been associated with PsA TNF-i response and anti-drug antibody (ADAb) levels [14]. Despite this, the full relationship between non-trough drug levels and self-reported non-adherence remains unknown [14].

Immunogenicity, the presence of neutralizing ADAb, has been observed across many musculoskeletal conditions, including RA, but differences in the frequency of ADAb have been reported [14]. In PsA, ADAb to the monoclonal antibody ADL have been reported in between 6 and 45% of patients, with ≤97.7% of ADL ADAb being neutralizing [14–17]. Increased ADAb levels are not only associated with decreased treatment response, but also with increased risk of adverse reactions, such as hypersensitivity [15]. In RA, csDMARD co-therapy is associated with a significant reduction in the prevalence of ADAb [18]. The concomitant prescription of TNF-i and csDMARD therapies is common practice in PsA; however, the effect of co-prescription has not been explored fully [14, 15]. Understanding factors affecting the development of ADAb in PsA could optimize TNF-i drug levels and improve drug response. The aims of this study were to assess the relationship between self-reported non-adherence, objectively measured non-trough drug levels, ADAb status, csDMARD co-therapy and drug response to ADL/ETN in PsA.

Methods

Study design

Patients were recruited from the UK multicentre prospective observational study, Outcomes of Treatment in Psoriatic Arthritis Study Syndicate (OUTPASS).

Study participants

Participants were eligible if they fulfilled the following criteria: (i) be willing and able to give full written consent; (ii) have PsA according to The Classification Criteria for Psoriatic Arthritis (CASPAR) as diagnosed by a clinician [19]; (iii) be about to commence treatment with a biologic or small molecule inhibitor therapy; (iv) be ≥18 years of age; and (v) have baseline PsA response criteria (PsARC) or the four-component 28-joint disease activity score (DAS28) available. Written consent from all participants was obtained in accordance with the Declaration of Helsinki. OUTPASS is approved by the National Research Ethics Service Committee North West—Greater Manchester Central ethics committee (reference 13/NW/0068). Patients were eligible for this study if they were prescribed the TNF-i ETN or ADL, had available 3- or 6-month blood samples and had baseline and 3-, 6- or 12-month follow-up PsARC or DAS28 disease activity scores.

Clinical, demographic and blood sample data collection

Serum samples, clinical and demographic data, including disease activity, age, sex, NSAID usage, CS and csDMARD co-therapy information, and lifestyle questionnaires, including self-reported adherence data, were collected. Data were collected at baseline (before biologic commencement) and routinely at 3, 6 and 12 months.

Measures

Self-reported non-adherence

Self-reported non-adherence was measured at 3, 6 and 12 months using two questionnaires previously used in adherence studies of inflammatory arthritis [treatment questionnaire and medication adherence report scale 5 (MARS5); Supplementary Table S1, available at *Rheumatology Advances in Practice* online) [10, 20]. Adherence was classified as self-report of never missing or delaying a dose, unless

medically advised. Non-adherence was dichotomized in both questionnaires as previously described [10, 20]. Ever non-adherence was recorded if patients had self-reported being non-adherent at 3, 6 or 12 months.

Disease activity

Disease activity was assessed at baseline and all follow-up time points using two assessments, DAS28, with CRP preferentially used over ESR, if available, and/or the PsA specific PsARC composite score [21–23]. DAS28 response was assessed as the difference in DAS28 score between baseline and follow-up (ΔDAS28).

Measurement of pharmacological biomarkers

Drug and ADAb measurements

ADL and ETN random non-trough drug levels were measured using previously validated and commercially available ELISA Promonitor Progenika Biopharma assays at 3 and 6 months [14].

ADL ADAb levels were measured using a validated radioimmunoassay at 3 and 6 months (Sanquin Diagnostic Services). Patients with ADAb levels >12 a.u./ml were classified as being antibody-positive as previously described [14].

Statistical analysis

Summary statistics for baseline clinical characteristics are described. Continuous variables are presented as the mean (S.D.) and median [interquartile range (IQR)], as appropriate. Mann–Whitney *U* tests were used to assess differences in non-trough drug levels for different non-adherence levels. Univariate logistic and linear regression analysis was used to test the association between non-adherence and change in disease activity at a given time point. Generalized estimating equation (GEE) analysis with an identity link was used to test the association with continuous outcomes across time points, and with a logit link for binary outcomes across time points, as described previously [24]. Statistical significance was predefined as $P \leq 0.05$. All analyses were undertaken in Stata for Windows v.14 (April 2015) [25].

Results

Patient characteristics

A total of 244 patients in OUTPASS prescribed ETN ($n = 116$) or ADL ($n = 128$) were eligible for analysis. Characteristics for the cohort are presented in Table 1, with more than half of patients being female and the median BMI classified as overweight (28.2 kg/m^2). Baseline DAS28 for the cohort was moderate (mean baseline DAS28 = 4.9), and >60% of patients had at least one co-morbidity in the overall cohort. In both drug groups, >56% of patients were co-administered NSAIDs and >71% received concomitant csDMARDs. The most commonly prescribed csDMARD was MTX, with almost half of patients (49.2%) prescribed the drug alongside their TNF-i therapy.

Characteristics and response to therapy

Table 2 presents the clinical characteristics significantly associated with drug response as measured by ΔDAS28 at 3 months. Patients with increased disease severity at baseline (baseline DAS28, disease duration and patient global score) had significantly improved ΔDAS28. In comparison, having an increasing number of co-morbidities or higher BMI was associated with

Table 1. Table of clinical characteristics of OUTPASS patients

Characteristic	TNF inhibitors ($n = 244$)	Missingness (%)	Adalimumab ($n = 128$)	Missingness (%)	Etanercept ($n = 116$)	Missingness (%)
Demographics						
Age, mean (S.D.), years	49 (12)	3.3	49 (12)	3.9	50 (13)	2.6
Sex, female, *n* (%)	145 (60.4)	1.6	72 (57.1)	1.6	73 (64.0)	1.7
BMI, median (IQR), kg/m^2	28.2 (25.1–33.6)	12.3	29.0 (25.6–34.0)	13.3	28.0 (25.0–33.3)	11.2
Current smoking status, *n* (%)	24 (11.3)	12.7	15 (13.6)	14.1	9 (8.7)	11.2
Co-morbidities, *n* (%)						
0	87 (39.4)	9.4	45 (39.1)	10.2	42 (39.6)	8.6
1	65 (29.4)		36 (31.3)		29 (27.4)	
2	42 (19.0)		21 (18.3)		21 (19.8)	
>3	27 (12.2)		13 (11.3)		14 (13.2)	
Disease status						
Disease duration, median (IQR), years	4.0 (2.0–9.0)	3.3	4.0 (2.0–9.0)	3.9	4.0 (2.0–9.0)	2.6
Baseline DAS28, mean (S.D.)	4.9 (1.0)	9.0	4.8 (0.9)	10.9	5.0 (1.0)	6.9
Baseline ESR, median (IQR), mm/h	15.0 (6.0–30.0)	44.7	15.5 (7.0–30.0)	50.0	15.0 (6.0–30.0)	38.8
Baseline CRP, median (IQR), mg/l	5.0 (4.0–15.0)	14.8	5.0 (3.0–14.0)	15.6	6.0 (4.0–15.0)	13.8
PsARC swollen joint count, mean (S.D.)	9.5 (7.7)	6.2	9.0 (7.0)	3.1	10.1 (8.5)	9.5
PsARC tender joint count, mean (S.D.)	20.0 (16.3)	6.6	19.5 (17.0)	4.7	20.6 (15.6)	8.6
PsARC physician global score, mean (S.D.)	3.6 (0.8)	2.5	3.5 (0.8)	1.6	3.7 (0.9)	3.5
PsARC patient global score, mean (S.D.)	3.6 (0.9)	1.6	3.5 (0.8)	1.6	3.7 (0.9)	1.7
Medication						
NSAID use, *n* (%)	143 (58.8)	0.4	72 (56.6)	0.8	71 (61.2)	0.0
Reported csDMARD use, *n* (%)		0.0		0.0		0.0
MTX	120 (49.2)		65 (50.8)		55 (47.4)	
CSA	3 (1.2)		1 (0.8)		2 (1.7)	
LEF	27 (11.1)		12 (9.4)		15 (12.9)	
SSZ	74 (30.3)		33 (25.8)		41 (35.3)	
HCQ	18 (7.4)		10 (7.8)		8 (6.9)	
None reported	68 (27.9)		36 (28.1)		32 (27.6)	

csDMARD: conventional synthetic DMARD; DAS28: 28-joint DAS; IQR: interquartile range; OUTPASS: Outcomes of Treatment in Psoriatic Arthritis Study Syndicate; PsARC: PsA response criteria.

Table 2. Associations between clinical characteristics and TNF inhibitor response, measured by change in 28-joint DAS at 3 months

Baseline characteristic	*P*-value	Effect estimate (95% CI)
BMI	**0.031**	$\beta = -0.04$ (−0.07, 0.00)
Co-morbidity count	**0.015**	$\beta = -0.20$ (−0.37, −0.04)
Baseline DAS28	**<0.001**	$\beta = 0.38$ (0.19, 0.57)
Disease duration	**0.026**	$\beta = 0.03$ (0.00, 0.06)
Patient global score	**0.047**	$\beta = 0.25$ (0.00, 0.50)

Significant *P*-values are shown in bold.
DAS28: 28-joint DAS.

Table 3. Ever non-adherence over 6 and 12 months in the OUTPASS cohort

Adherence questionnaire	Time point (months)	TNF-i non-adherence (%)	ADL non-adherence (%)	ETN non-adherence (%)
MARS5	6	36.1	27.7	45.2
	12	43.5	36.7	51.0
Treatment	6	20.4	18.6	22.3
	12	26.1	24.8	27.6

ADL: adalimumab; ETN: etanercept; MARS5: medication adherence report scale 5; OUTPASS: Outcomes of Treatment in Psoriatic Arthritis Study Syndicate; TNF-i: TNF inhibitor.

decreased response to therapy as measured by ΔDAS28. No clinical characteristics were significantly associated with PsARC response at 3 months. Data for clinical characteristics associated with PsARC response and ΔDAS28 at 6 and 12 months and GEE modelling was reflective of ΔDAS28 3-month results, with increased baseline severity (ESR, CRP, baseline DAS28 and disease duration) being associated with increased response and the presence of multiple co-morbidities associated with decreased response (Supplementary Table S2, available at *Rheumatology Advances in Practice* online).

Non-adherence

Table 3 describes self-reported ever non-adherence at 6 and 12 months for the cohort. In this cohort (52.5% ADL and 47.5% ETN), 36.1% of patients self-reported ever-non-adherence within the first 6 months of treatment, rising to 43.5% by 12 months of therapy. Breakdowns of 3-, 6- and 12-month non-adherence levels are reported in Supplementary Table S3, available at *Rheumatology Advances in Practice* online. Self-reported non-adherence was described at higher levels using the dichotomized MARS5 questionnaire (20.5–51%) compared with the treatment questionnaire (11–27.6%). Self-reported non-adherence was higher in patients prescribed ETN (14.6–51%) compared with ADL (11–36.7%) at all questionnaire time points, except at 12 months using the treatment questionnaire.

Impact of clinical characteristics on self-reported non-adherence

Table 4 presents clinical characteristics associated with self-reported non-adherence measured by the treatment and MARS5 questionnaires during GEE modelling over 12 months. Univariate linear and logistic regression for 3, 6 and 12 months is presented in Supplementary Table S4, available at *Rheumatology Advances in Practice* online. Patients who were female, younger, asthmatic, had longer disease duration and lower baseline disease severity (ESR) were significantly more likely to be non-adherent via the MARS5 questionnaire at multiple time points and under GEE modelling. Patients with longer disease duration and lower baseline disease severity (tender joint count) were more likely to be non-adherent using the treatment questionnaire at multiple time points, and patients on CS co-therapy had increased ever non-adherence at 6 months and over 12 months under GEE modelling.

Table 4. Clinical characteristics associated with self-reported non-adherence over 12 months using generalized estimating equation modelling

Measure of non-adherence	Baseline characteristic	*P*-value	Effect estimate (95% CI)
MARS5	Sex (female)	**0.047**	OR = 0.58 (0.34, 0.99)
	ESR	**0.014**	OR = 0.98 (0.96, 0.99)
	Age	**<0.001**	OR = 0.96 (0.94, 0.98)
	Asthma	**0.037**	OR = 2.17 (1.05, 4.50)
Treatment	CS co-therapy	**0.048**	OR = 2.11 (1.01, 4.43)

Significant *P*-values are shown in bold.
MARS5: medication adherence report scale 5; OR: odds ratio.

Self-reported non-adherence and response to therapy

Non-adherence, reported using the treatment questionnaire, was associated with PsARC non-response over 12 months using GEE modelling {$P = 0.037$ [odds ratio (OR) = 0.50, 95% CI 0.26, 0.96]}. There was no significant association between non-adherence reported via the MARS5 questionnaire and response. Importantly, there was no association of whether a patient returned a self-reported adherence questionnaire and response under univariate or GEE modelling.

Drug levels

Mean ± S.E.M. non-trough drug levels at 3 and 6 months, respectively, were 7.6±0.63 and 8.8±0.61 μg/ml for patients prescribed ADL and 3.1±0.31 and 3.5±0.27 μg/ml for patients prescribed ETN. There was a significant association between 3- and 6-month non-trough drug levels for paired samples for ADL ($P < 0.001$) and ETN ($P = 0.005$).

Ever non-adherence levels, using the MARS5 and treatment questionnaires for patients with undetectable ETN or ADL 3- or 6-month non-trough drug levels are reported in Supplementary Table S5, available at *Rheumatology Advances in Practice* online. Non-adherence levels range between 0 and 30% for ADL and between 22.7 and 47.8% for ETN. There was no significant difference in non-trough drug levels for either drug between patients who self-reported that they were non-adherent and those who self-reported adherence at any time point using either questionnaire (Supplementary Figs S1 and S2, available at *Rheumatology Advances in Practice* online).

Clinical characteristics and drug levels

In univariate analysis (Supplementary Table S6, available at *Rheumatology Advances in Practice* online), patients with higher BMI had decreased 3-month ADL levels. Older ETN-treated patients or current smokers had decreased 6-month levels. Patients with increased tender joint count at baseline had decreased drug levels for either drug at 3 months. Concerning GEE analysis, patients with a history of co-morbidities, such as strokes, had decreased non-trough ADL

Table 5. Association between adalimumab and etanercept drug levels and response over 12 months

Measure of response	Response time point (months)	TNF-i	Drug level time point	*P*-value	Effect estimate (95% CI)
PsARC	3	ETN	3	**0.015**	OR = 1.37 (1.07, 1.77)
	6	ETN	3	**0.037**	OR = 1.29 (1.02, 1.63)
	12	ETN	3	**0.015**	OR = 1.45 (1.07, 1.94)
	12 (GEE modelling)	ETN	GEE	**0.026**	OR = 1.19 (1.02, 1.38)
ΔDAS28	3	ADL	3	**0.019**	β = 0.05 (0.01, 0.09)

Significant *P*-values are shown in bold.
ADL: adalimumab; ΔDAS28: change in 28-joint DAS; ETN: etanercept; GEE: generalized estimating equation; OR: odds ratio; PsARC: PsA response criteria.

Table 6. Clinical characteristics associated with being anti-drug antibody-positive over 6 months

ADAb time point	Baseline characteristic	*P*-value	Effect estimate (95% CI)
3 months	Liver disease	**0.020**	OR = 16.00 (1.56, 164.35)
Over 6 months (GEE modelling)	Ever smoked	**0.030**	OR = 3.10 (1.12, 8.64)
	Liver disease	**0.036**	OR = 12.01 (1.18, 122.39)

Significant *P*-values are shown in in bold.
ADAb: anti-drug antibody; GEE: generalized estimating equation; OR: odds ratio.

and ETN levels, and those who were smokers and females had decreased ETN drug levels across 6 months.

Drug levels and response to therapy

Higher ETN non-trough drug levels at 3 months were associated with PsARC response at 3 [$P = 0.015$ (OR = 1.37, 95% CI 1.07, 1.77)], 6 [$P = 0.037$ (OR = 1.29, 95% CI 1.02, 1.63)] and 12 months [$P = 0.015$ (OR = 1.45, 95% CI 1.07, 1.94)] (Table 5). Increased ETN levels at 3 and 6 months were associated with PsARC response over 12 months under GEE modelling [$P = 0.026$ (OR = 1.19, 95% CI 1.02, 1.38)]. Increased ADL non-trough drug levels at 3 months were associated with greater ΔDAS28 at 3 months [$P = 0.019$ ($\beta = 0.05$, 95% CI 0.01, 0.09)]. Additionally, neither ETN nor ADL levels were significantly associated with whether a patient had returned an adherence questionnaire under univariate or GEE modelling, suggesting no evidence of responder bias.

ADAb development

Overall, 17.1% of ADL patients were ADAb-positive at 3 months, rising to 18.9% at 6 months. Of patients with undetectable non-trough drug levels at 3 months, 71.4% were ADAb-positive. At 6 months, 63.6% of patients with undetectable non-trough drug levels were ADAb-positive. Patients with higher ADAb levels at 3 months were more likely to have higher ADAb levels at 6 months [$P < 0.001$ ($\beta = 1.12$, 95% CI 0.99, 1.22] with 4.8% of the cohort testing positive at both time points.

Impact of clinical characteristics on ADAb development

Patients with liver disease were more likely to be ADAb-positive at 3 months [$P = 0.020$ (OR = 16.00, 95% CI 1.56, 164.35)] and over 6 months using GEE modelling [$P = 0.036$ (OR = 12.01, 95% CI 1.18, 122.39)] (Table 6). Patients who had ever smoked were more likely to be ADAb-positive over 6 months using GEE modelling [$P = 0.030$ (OR = 3.10, 95% CI 1.12, 8.64)].

ADAb and drug levels

Being ADAb-positive at 3 and 6 months was associated with lower ADL levels at 3 [$P < 0.001$ ($\beta = -6.50$, 95% CI −9.65, −3.35)] and 6 months [$P < 0.001$ ($\beta = -6.94$, 95% CI −9.67, −4.21)], respectively, and in GEE modelling across 6 months [$P < 0.001$ ($\beta = -6.58$, 95% CI −8.43, −4.72)].

ADAb and response to therapy

Patients who were ADAb-positive at 3 months had a decreased change in DAS28 at 6 months [$P = 0.038$ ($\beta = -0.93$, 95% CI −1.81, −0.05)] and change in DAS28 over 12 months under GEE modelling [$P = 0.042$ ($\beta = -0.52$, 95% CI −1.03, −0.02)]. Patients who were ADAb-positive at 3 months were less likely to be a PsARC responder at 3 months [$P = 0.045$ (OR = 0.30, 95% CI 0.09, 0.98)] and less likely to be a PsARC responder over 12 months under GEE modelling [$P = 0.012$ (OR = 0.34, 95% CI 0.14, 0.79)].

In a joint model of drug response, ADAb classification and ADL non-trough drug levels were significantly associated with ΔDAS28 at 3 months ($P = 0.035$). To understand which was most significantly associated, both ADAb and ADL levels were fitted separately using backward elimination, with ADL levels being most significantly associated with ΔDAS28 at 3 months, as previously reported. ADL levels were not significantly associated with PsARC at any time point or ΔDAS28 over 12 months, regardless of inclusion of ADAb classification in the model.

ADAb and self-reported non-adherence

ADAb classification was not significantly associated with self-reported non-adherence at any time point in univariate or GEE analysis. Self-reported non-adherence was not significantly associated with response at any time points in models accounting for ADAb.

Prescription of csDMARDs in ADL patients

ADAb were tested in 125 ADL-treated patients, of whom 73.6% received csDMARD co-therapy pre-biologic (Supplementary Table S7, available at *Rheumatology Advances in Practice* online). MTX was the most prescribed csDMARD (52%), with a median dose of 20 mg (IQR: 15–25 mg), followed by SSZ (26.4%) and LEF (9.6%).

Prescriptions of HCQ (8%) and CSA (0.8%) were also reported. In addition to their ADL prescription, 22.4% of patients were prescribed at least two csDMARDs.

Prescription of csDMARDs and ADL ADAb status

No significant association was seen between whether a patient was on ADL monotherapy or csDMARD co-therapy and ADAb status at either 3 [$P = 0.245$ (OR = 0.53, 95% CI 0.18, 1.54)] or 6 months [$P = 0.163$ (OR = 0.40, 95% CI 0.11, 1.44)] via logistic regression or under GEE modelling [$P = 0.206$ (OR = 0.55, 95% CI 0.22, 1.39)].

In separate logistic regression analysis for the use of individual csDMARDs, MTX co-therapy was significantly associated with being ADAb-negative at 3 [$P = 0.008$ (OR = 0.20, 95% CI 0.06, 0.66)] and 6 months [$P = 0.024$ (OR = 0.32, 95% CI 0.07, 0.83)]. This result was supported under GEE modelling [$P = 0.003$ (OR = 0.23, 95% CI 0.87, 0.60)]. No other csDMARDs were significantly associated with ADAb status at any time point via logistic regression or under GEE analysis. Neither the number of csDMARDs nor MTX dose was associated with ADAb status at either 3 or 6 months via logistic regression or under GEE analysis.

csDMARDs and response to therapy

There was no statistically significant association between csDMARD co-therapy and PsARC response at either 3 [$P = 0.748$ (OR = 1.20, 95% CI 0.40, 3.56)] or 6 months [$P = 0.823$ (OR = 1.13, 95% CI 0.38, 3.43)] or using GEE modelling [$P = 0.845$ (OR = 1.10, 95% CI 0.43, 2.77)]. There was also no significant association with ΔDAS28 at 3 [$P = 0.481$ ($\beta = 0.18$, 95% CI −0.33, 0.70)] or 6 months [$P = 0.425$ ($\beta = 0.27$, 95% CI −0.41, 0.95)] or using GEE modelling [$P = 0.361$ ($\beta = 0.22$, 95% CI −0.25, 0.70)].

Discussion

In this large UK multicentre study exploring different measures of non-adherence and response to TNF-i treatment in patients with PsA, we report that non-adherence is common; self-reported non-adherence is poorly correlated with direct measurements of drug level, but non-trough drug levels are correlated better with clinical response measures.

The results support findings from previous publications, reporting a high frequency of non-adherence for patients on both ADL (36.7%) and ETN (51%) therapies by 12 months [13, 26]. Interestingly, non-adherence levels were higher in patients prescribed ETN than ADL. One explanation is that the increased injection frequency for patients prescribed ETN compared with ADL might lead to a reluctance to administer therapy, but this requires confirmation in studies designed to explore reasons for non-adherence. Younger age, female sex, longer disease duration and decreased baseline severity (ESR) were associated with increased self-reported non-adherence in this cohort. Increased TNF-i non-adherence rates in younger and female musculoskeletal patients have been described previously, with the health belief model potentially explaining increased non-adherence in younger patients [27–31]. Here, the perceived risk on health might be decreased in younger, often healthier, patients, hence the importance of taking preventative action (adherence) diminished. Meanwhile, patients with chronic conditions might be less likely to adhere to therapies over an extended period, and patients with lower disease severity at baseline might feel a reduced necessity for the medication and be less likely to adhere with drug management.

In contrast to studies in RA, the present study did not find a consistent association of self-reported non-adherence with clinical response; self-reported non-adherence was significantly associated with PsARC non-response only when collected using the treatment questionnaire and over a 12-month period [10]. One explanation is that the sample size tested was less than that investigated in studies of RA, potentially limiting the power to detect associations [10]. Another explanation is that self-reported adherence questionnaires might be influenced by bias, either owing to recall bias or patients under-reporting non-adherence to meet expectations of clinicians. In support of bias as a possible reason for the lack of association, we found poor correlation between self-reported non-adherence and both ADL and ETN drug levels in this study, regardless of ADAb status. These findings contradict those reported in TNF-i-treated RA patients [24, 32]. It could be argued that measurement of drug levels could be less reliable than self-reported measures in assessing non-adherence because only non-trough drug levels were available. This could lead to an increase in randomness, reducing the power to detect potential associations; furthermore, it might reflect the impact of white coat adherence, with patients improving adherence before attending a clinic visit when their blood sample was taken. However, in keeping with previous rheumatic studies, we showed that increased TNF-i levels and ADAb status were significantly associated with better response in this cohort [10–12, 14, 24, 32–35], suggesting that it might be a better measure of non-adherence than self-reported questionnaires. Interestingly, smoking was associated with ADAb status and drug levels. Further work is needed to establish the full impact of smoking, and meanwhile clinicians should use interventions to encourage patients to stop smoking, with the aim of optimizing drug levels and response. In the present analysis, co-morbidities, including increased BMI, asthma and liver disease, in addition to disease duration and severity at baseline, were associated with decreased drug response, decreased drug levels and increased ADAb levels, as supported by previous rheumatic disease studies [8, 14, 30, 36–38]. Of note, patients with liver disease might be more likely to develop ADAb owing to MTX being contraindicated in these individuals. These associations highlight the importance of managing modifiable factors and the identification of target groups for personalized interventions, with the aim of improving patient drug response and quality of life. Future prediction modelling, prospective studies and health economics analysis will be required to determine whether monitoring drug levels and ADAb status is clinically useful and how much of drug response variance they account for.

Concerning the role of csDMARD co-therapy in immunogenicity in ADL patients, we found that csDMARD co-therapy was common (>73%) in this cohort. Despite this, we report that only those on MTX co-therapy showed a significant association with decreased ADAb, with MTX reducing the risk of ADL ADAb development by ≤80%. A lack of further significant associations could be attributable to smaller sample sizes of the other co-therapies leading to a reduction in power; therefore, larger studies with increased power are needed. A lack of association between overall csDMARD use vs. ADL monotherapy and ADAb status could support the findings that only MTX co-therapy decreases the presence of

ADAb in these patients. A trend towards co-therapy with csDMARDs and PsARC and ΔDAS28 response at all time points suggests that further work in larger cohorts is required to explore the impact of csDMARD co-therapy. The frequency of ADAb development in PsA patients treated with ADL is in keeping with previous publications [14–17, 35]. However, previous studies draw conflicting conclusions about the effect of csDMARD co-therapy on ADAb production in such patients [14, 15, 39]. A previous smaller study reported a lack of association, highlighting the strength of the larger cohort size in this study [14]. Conversely, two larger studies, one of which focused on patients with psoriasis, found that concomitant use of immunosuppressors, including MTX, was associated with a reduction in detectable ADAb [15, 39]. However, those studies did not investigate whether different csDMARDs had differing effects. We also found that a considerable number of TNF-i patients are co-prescribed multiple additional csDMARDs, accounting for >21% of ADL patients in this cohort. However, we found no additional advantage of patients being prescribed more than one csDMARD therapy in protecting against the development of ADAb. Future validation of the role of MTX co-therapy in the development and reversal of immunogenicity and response in PsA is needed in larger cohorts, and the cost-effectiveness should be established before routine co-prescription of MTX with ADL in PsA patients is recommended.

A strength of this study is the availability of well-documented adherence information at multiple time points in a large PsA cohort [14, 35]. We were also able to exclude a large responder bias effect, whereby patients who are more adherent might be more likely to return self-adherence questionnaires, because there was no difference in outcome measures identified between those who did and did not return the self-report questionnaires. Given that more than one-third of patients in this UK PsA cohort self-reported non-adherence to their TNF-i therapy, this highlights an unmet need for optimizing drug adherence and, subsequently, drug response in these patients, and interventions to address modifiable factors, such as patients' beliefs of drug necessity, might be useful in this context.

A limitation of this study was that imputation of missing response data was not implemented and, as such, the cohort sizes were modest. Larger collaborative studies, using imputation, are needed to increase the confidence in findings. Importantly, given the increasing accessibility of cheaper biosimilars, future studies might be able to recruit larger numbers of patients on biologic therapies more easily, allowing the validation of results presented here. Furthermore, owing to the heterogeneity reported in the presentation of PsA, larger future cohorts should explore differences between subtypes of PsA when conducting response studies. Although ADL and ETN are the most frequently prescribed biologic therapies for PsA, other biologics are available, and larger PsA studies would also allow an exploration of response to these therapies [6]. Additionally, unlike RA, PsA lacks well-established measures of drug response [23]. Here, PsARC and DAS28 were used, because these are measures commonly used in the clinic. Furthermore, PsARC is currently the only PsA-specific response criterion available, although it still prioritizes joint phenotypes, and DAS28 is commonly used as a measure of response in PsA and RA drug response studies [10, 14]. Although the use of two commonly used measures of response improves the generalizability of these results, it is important to note that multiple PsA phenotypes, including psoriasis and axial disease, are not well captured in these response measures. Future work should prioritize the development and universal adoption of a measure of response that is reflective of all disease domains in PsA. This will aid the identification, validation and implementation of biomarkers of response. There is no gold-standard method of measuring self-reported non-adherence; however, both methods used in this study have been used previously, including in immunosuppressed cohorts [10, 40]. Despite this, significant associations between self-reported non-adherence and response were seen only when using the Treatment questionnaire, and not the MARS5. This suggests discrepancies between questionnaires and the aspect of non-adherence that they are measuring. Although we conducted a separate analysis on the effect of five commonly prescribed csDMARDs on the presence of ADAb, the numbers of patients on other csDMARD co-therapies, and on different MTX doses, were small and limited the power to draw definitive conclusions. Identifying the optimal MTX dose needed to prevent ADAb production in future studies could aid disease management. Hence, larger studies with a wider array of prescription patterns are required to determine whether other csDMARDs co-prescribed with ADL are associated with a reduction in the presence of ADAb.

Conclusion

In conclusion, we show that although both self-reported non-adherence and drug levels are associated with ADL and ETN response in PsA, objectively measured drug levels offer more significant associations with drug response. Objectively measured drug levels could offer an interesting and modifiable opportunity to improve drug response, but cost-effectiveness studies are required to assess their full clinical utility. Furthermore, modifiable factors, such as BMI, smoking, presence of multimorbidity and ADAb, should be taken into consideration when aiming to optimize therapeutic response. MTX might be useful in reducing immunogenicity in ADAb-positive patients in an aim to improve drug response.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data that support the findings of this study are available from the corresponding author (J.B.) on reasonable request. The data are not publicly available owing to privacy/ethical restrictions.

Contribution statement

Philippa D. K. Curry: Conceptualization, Methodology, Formal analysis, Investigation, Writing Original Draft/Review & Editing, Visualization. **Andrew P. Morris:** Conceptualization, Methodology, Writing Original Draft/Review & Editing, Supervision. **Meghna Jani:** Writing Original Draft/Review & Editing, Supervision. **Hector Chinoy:** Writing Original Draft/Review & Editing, Supervision. **Anne Barton:** Conceptualization, Methodology,

Writing Original Draft/Review & Editing, Supervision. **James Bluett:** Conceptualization, Methodology, Writing Original Draft/Review & Editing, Supervision. All authors have read and approved the final manuscript.

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References

1. Gladman DD, Ang M, Su L *et al.* Cardiovascular morbidity in psoriatic arthritis. Ann Rheum Dis 2009;68:1131–5.
2. Kamalaraj N, El-Haddad C, Hay P, Pile K. Systematic review of depression and anxiety in psoriatic arthritis. Int J Rheum Dis 2019;22:967–73.
3. Clunie G, McInnes IB, Barkham N *et al.* Long-term effectiveness of tumour necrosis factor-α inhibitor treatment for psoriatic arthritis in the UK: a multicentre retrospective study. Rheumatol Adv Pract 2018;2:rky042.
4. D'Angiolella LS, Cortesi PA, Lafranconi A *et al.* Cost and cost effectiveness of treatments for psoriatic arthritis: a systematic literature review. Pharmacoeconomics 2018;36:567–89.
5. Schwartzman S, Li Y, Zhou H, Palmer JB. Economic impact of biologic utilization patterns in patients with psoriatic arthritis. Clin Rheumatol 2017;36:1579–88.
6. Aaltonen K, Heinonen A, Joensuu J *et al.* Effectiveness and drug survival of TNF-inhibitors in the treatment of psoriatic arthritis: a prospective cohort study. Semin Arthritis Rheum 2017;46:732–9.
7. Hunter T, Grabner M, Birt J *et al.* Identifying inadequate response among patients with ankylosing spondylitis and psoriatic arthritis prescribed advanced therapy in a real-world, commercially insured adult population in the USA. Clin Rheumatol 2022;41:2863–74.
8. Curry PDK, Morris AP, Barton A, Bluett J. Do genetics contribute to TNF inhibitor response prediction in psoriatic arthritis? Pharmacogenomics J 2022;23:1–7.
9. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:957–70.
10. Bluett J, Morgan C, Thurston L *et al.*; BRAGGSS. Impact of inadequate adherence on response to subcutaneously administered anti-tumour necrosis factor drugs: results from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate cohort. Rheumatology 2015;54:494–9.
11. Pouw MF, Krieckaert CL, Nurmohamed MT *et al.* Key findings towards optimising adalimumab treatment: the concentration–effect curve. Ann Rheum Dis 2015;74:513–8.
12. Hum RM, Ho P, Nair N *et al.*; BRAGGSS Collaborators. Non-trough adalimumab and certolizumab drug levels associated with a therapeutic EULAR response in adherent patients with rheumatoid arthritis. Rheumatology 2023;62:2090–7.
13. Xu C, Teeple A, Wu B, Fitzgerald T, Feldman SR. Treatment adherence and persistence of seven commonly prescribed biologics for moderate to severe psoriasis and psoriatic arthritis in a U.S. commercially insured population. J Dermatolog Treat 2022; 33:2270–7.
14. Jani M, Chinoy H, Barton A, for OUTPASS. Association of pharmacological biomarkers with treatment response and longterm disability in patients with psoriatic arthritis: results from OUTPASS. J Rheumatol 2020;47:1204–8.
15. Valenzuela F, Flores R. Immunogenicity to biological drugs in psoriasis and psoriatic arthritis. Clinics 2021;76:e3015.
16. Ducourau E, Rispens T, Samain M *et al.* Methotrexate effect on immunogenicity and long-term maintenance of adalimumab in axial spondyloarthritis: a multicentric randomised trial. RMD Open 2020;6:e001047.
17. Van Schie KA, Hart MH, De Groot ER *et al.* The antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region. Ann Rheum Dis 2015;74:311–4.
18. Hiltunen J, Parmanne P, Sokka T *et al.*; FinADASpA Study Group. Immunogenicity of subcutaneous TNF inhibitors and its clinical significance in real-life setting in patients with spondyloarthritis. Rheumatol Int 2022;42:1015–25.
19. Taylor W, Gladman D, Helliwell P *et al.*; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006; 54:2665–73.
20. Hai A, Chan Y, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: a measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol 2020;86:1281–8.
21. van Gestel AM, Prevoo ML, van 't Hof MA *et al.* Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism CRI. Arthritis Rheum 1996;39:34–40.
22. Clegg DO, Reda DJ, Mejias E *et al.* Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1996;39:2013–20.
23. Fransen J, Antoni C, Mease PJ *et al.* Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis 2006;65:1373–8.
24. Jani M, Chinoy H, Warren RB *et al.*; Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate Collaborators. Clinical utility of random anti-tumor necrosis factor drug-level testing and measurement of antidrug antibodies on the long-term treatment response in rheumatoid arthritis. Arthritis Rheumatol 2019;67:2011–9.
25. StataCorp. Stata statistical software: Release 14. College Station: StataCorp LP, 2015.
26. Souza AF, Da Silva MR, Dos Santos JB *et al.* Medication adherence and persistence of psoriatic arthritis patients treated with biological therapy in a specialty pharmacy in Brazil: a prospective observational study. Pharm Pract (Granada) 2021;19:2312.
27. Smolen JS, Gladman D, McNeil HP *et al.* Predicting adherence to therapy in rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis: a large cross-sectional study. RMD Open 2019;5:e000585.

28. Vogelzang EH, Hebing RCF, Nurmohamed MT *et al.* Adherence to etanercept therapy in rheumatoid arthritis patients during 3 years of follow-up. PLoS One 2018;13:e0205125.
29. Maranini B, Bortoluzzi A, Silvagni E, Govoni M. Focus on sex and gender: what we need to know in the management of rheumatoid arthritis. J Pers Med 2022;12:499.
30. Hope HF, Hyrich KL, Anderson J *et al.* The predictors of and reasons for non-adherence in an observational cohort of patients with rheumatoid arthritis commencing methotrexate. Rheumatology (Oxford) 2020;59:213–23.
31. Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the health belief model. Health Educ Q 1988;15:175–83.
32. Jani M, Isaacs JD, Morgan AW *et al.*; BRAGGSS. High frequency of antidrug antibodies and association of random drug levels with efficacy in certolizumab pegol-treated patients with rheumatoid arthritis: results from the BRAGGSS cohort. Ann Rheum Dis 2017; 76:208–13.
33. Sanmarti R, Inciarte-Mundo J, Estrada-Alarcon P *et al.* Towards optimal cut-off trough levels of adalimumab and etanercept for a good therapeutic response in rheumatoid arthritis. Results of the INMUNOREMAR study. Ann Rheum Dis 2015;74:e42.
34. Chen DY, Chen YM, Tsai WC *et al.* Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. Ann Rheum Dis 2015;74:e16.
35. Vogelzang EH, Kneepkens EL, Nurmohamed MT *et al.* Anti-adalimumab antibodies and adalimumab concentrations in psoriatic arthritis; an association with disease activity at 28 and 52 weeks of follow-up. Ann Rheum Dis 2014;73:2178–82.
36. Ballegaard C, Skougaard M, Guldberg-Møller J *et al.* Comorbidities, pain and fatigue in psoriatic arthritis, psoriasis and healthy controls: a clinical cohort study. Rheumatology (Oxford) 2021;60:3289–300.
37. Bassi M, Singh S. Impact of obesity on response to biologic therapies in patients with inflammatory bowel diseases. BioDrugs 2022; 36:197–203.
38. Mok CC, Van Der Kleij D, Wolbink GJ. Drug levels, anti-drug antibodies, and clinical efficacy of the anti-TNFα biologics in rheumatic diseases. Clin Rheumatol 2013;32:1429–35.
39. van der Kraaij G, Busard C, van den Reek J *et al.* Adalimumab with methotrexate vs. adalimumab monotherapy in psoriasis: first-year results of a single-blind randomized controlled trial. J Invest Dermatol 2022;142:2375–83.e6.
40. Lia M, Caprioli F, Michielan A *et al.*; SOLE Study Group. Translation and initial validation of the medication adherence report scale (MARS) in Italian patients with Crohn's disease. Dig Liver Dis 2019;51:640–7.