Association of Pharmacological Biomarkers with Treatment Response and Longterm Disability in Patients with Psoriatic Arthritis: Results from OUTPASS

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ABSTRACT. ***Objective.*** To identify (1) whether tumor necrosis factor inhibitor (TNFi) drug levels/anti-drug antibodies (ADAb) are associated with treatment response and disability in patients with psoriatic arthritis (PsA); and (2) the factors associated with TNFi drug levels.

Methods. Patients were recruited from a national multicenter prospective cohort with longitudinal serum samples and 28-joint count Disease Activity Scores (DAS28)/Health Assessment Questionnaire (HAQ) measurement over 12 months.

Results. Adalimumab (ADA) drug levels were significantly associated with ΔDAS28 (β 0.055, 95% CI 0.011–0.099; p = 0.014) and inversely with HAQ over 12 months (β –0.022, 95% CI –0.043 to –0.00063). Factors significantly associated with ADA drug levels were ADAb levels and body mass index.

Conclusion. Drug level testing in ADA-initiated PsA patients may be useful in determining treatment response/disability over 12 months. (First Release December 15 2019; J Rheumatol 1204–8; doi:10.3899/jrheum.190253)

Key Indexing Terms:
IMMUNOGENICITY DRUG LEVELS TREATMENT RESPONSE
TUMOR NECROSIS FACTOR-α INHIBITORS ANTI-DRUG ANTIBODIES

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In up to 40% of inflammatory arthritis patients, disease activity fails to significantly improve with tumor necrosis factor-α inhibitors (TNFi) either because of primary inefficacy or loss of response. One explanation is immunogenicity leading to the development of anti-drug antibodies (ADAb) and subtherapeutic drug levels, as seen in patients with rheumatoid arthritis (RA)[1,2]. ADAb to monoclonal antibodies such as adalimumab (ADA) and infliximab in RA have been associated with effects on response[1] and drug safety[3]. ADAb to ADA have been deemed to be neutralizing in 98% of cases[4]. TNFi immunogenicity differs according to the underlying disease, with some conditions more immunogenic than others[5]. Very few data exist on whether such pharmacological tests associate with TNFi treatment response in psoriatic arthritis (PsA)[6] and there are no data on whether they affect patient-reported outcomes (PRO). Yet there is considerable interest in implementation of such tests across inflammatory conditions (such as RA), with a Medtech Innovation Briefing[7] and Diagnostic Assessment Committee to review therapeutic drug monitoring in the United Kingdom, by the National Institute for Health and Care Excellence (NICE)[8].

Current international guidelines for PsA do not

recommend the routine testing of TNFi drug levels for guiding treatment[9], because the clinical utility and cost-effectiveness have not been established. Establishing optimal TNFi drug level thresholds is likely to have many benefits if such tests are to be used routinely in the future[10]; however, thresholds are likely to vary depending on the underlying condition. Further, determining modifiable factors associated with therapeutic drug levels may optimize future management. The objectives of this study were to identify (1) whether the presence of ADAb/drug levels predicts treatment response and disability in TNFi-treated PsA patients, (2) a drug level threshold for optimal therapeutic response, and (3) the factors associated with drug levels.

MATERIALS AND METHODS

Patients. A multicenter national UK prospective observational study was established in 2013 — the Outcomes of Treatment in PsA Study Syndicate (OUTPASS). Patients are eligible for recruitment if they (1) had PsA defined by ClASsification for Psoriatic ARthritis (CASPAR) criteria, and (2) were about to commence a biologic as per NICE (≥ 3 tender and swollen joints, not responding to adequate trials of at least 2 disease-modifying antirheumatic drugs, administered either individually or in combination). Disease activity (28-joint count Disease Activity Score; DAS28) scores and serum samples were collected at baseline, 3, 6, and 12 months following initiation of TNFi therapy. Patient self-reported adherence to TNFi[2] and Health Assessment Questionnaire (HAQ) were measured at each timepoint. Adherence to biologics has been demonstrated to affect drug levels[2], and in PsA has been reported to be as low as 18–46% in recent studies[11]. HAQ scores were used as a PRO in our study as they are regularly used by NICE in technology appraisals to derive utility gains and to estimate costs of treatments[12]. Contributing patients provided written informed consent, and the study was approved by a multicenter ethics committee (MREC reference: 13/NW/0068).

Clinical response. Change in DAS28 C-reactive protein (ΔDAS28) was calculated as the difference between each timepoint (3/6/12 months) posttreatment and pretreatment DAS28 scores. Concentration–effect curves for ADA and etanercept (ETN) were determined to establish using an optimal drug level cutoff for each TNFi on a population level. To generate such curves, all patients were ordered from high to low drug levels with correlating ΔDAS28, as described previously[13].

Measurement of pharmacological biomarkers. ADAb were measured using radioimmunoassay (RIA) and drug levels using ELISA at 3/6/12 months at Sanquin Diagnostic Services. These assays have been previously validated and used in several previous biologic therapeutic drug monitoring studies[1,2]. Patients were classed as ADAb-positive if the antibody level was > 12 AU/ml[1].

Statistical analyses. To assess differences between groups, we used the independent sample t test, chi-square, or Mann–Whitney U test, as appropriate. Generalized estimating equation (GEE) with an identity link for longitudinal outcomes was used to test the association between ADAb/drug levels, treatment response, and HAQ as well as longitudinal/baseline factors with drug levels. GEE allows the relationships between variables of the model at different timepoints to be analyzed simultaneously. The β (regression coefficient) reflects the relationship between the longitudinal development of the outcome (treatment response) and the longitudinal development of corresponding predictor variable (drug levels/ADAb levels) using all available longitudinal data. Statistical analyses were performed using Stata for Windows version 13.0 and Graph Pad Prism 6.04 for figures.

RESULTS

Patients. One hundred fifty-three samples were suitable for pharmacological testing (n = 97 ADA; n = 56 ETN). Mean (SD) age in the total population was 51 (12) years, with a median (interquartile range) body mass index (BMI) of 28.9 kg/m^2 (26.0–34.9; Table 1). In ADA-treated patients, 20% (n = 10/49) were positive for ADAb. No ADAb were detected in ETN-treated patients with PsA.

Treatment response and HAQ scores over time. Using GEE, ADA drug levels were significantly associated with ΔDAS28 over 12 months (β 0.055, 95% CI 0.011–0.099; p = 0.014) and inversely with HAQ scores over 12 months (β –0.022, 95% CI –0.043 to –0.00063). ΔDAS28 was not independently associated with ADAb level (β –0.0015, 95% CI –0.0031 to 0.000047; p = 0.057). There was no significant association between ETN drug levels and ΔDAS28 over 12 months (β –0.039, 95% CI –0.31 to 0.23; p = 0.77). At 6 months, 3 patients with good European League Against Rheumatism (EULAR) response had low titer ADAb (between 14–23 AU/ml) detected; however, they had therapeutic ADA drug levels (4.5–7.1 μg/ml) that may contribute to their response. At 12 months, 1 patient with good EULAR response had ADAb detected at 13 AU/ml with ADA drug levels of 3.6 μg/ml.

Concentration-effect curves and factors associated with drug levels. ADA concentrations between 4–8 μg/ml (Figure 1) were associated with an optimal treatment response at 6 months using concentration-effect curves[13]. Of samples with ADA levels measured in the study, distribution of levels was as follows: 19.6% (n = 19) < 4 μg/ml; 35.1% (n = 34) 4–8 μg/ml; 16.5% (n = 16) > 8 to < 11 μg/ml; and 28.9% (n = 28) ≥ 11 μg/ml. Factors that were inversely associated with ADA drug levels were ADAb level (β = –0.0073, 95% CI –0.0014 to 0.18; p < 0.0001) and BMI (β –0.15, 95% CI –0.29 to –0.00450; p = 0.043) in the final GEE model (adjusting for age, sex, adherence, BMI).

Of the patients receiving methotrexate (MTX) and taking ADA, 93.7% (15/16) did not have ADAb detected and 6.3% (1/16) did, compared to 27.3% (9/33) ADAb-positive and 72.7% (24/33) ADAb-negative patients who were not taking MTX (p = 0.087).

DISCUSSION

The strengths of our study include the well-characterized cohort of patients, availability of serial HAQ scores, patient-reported adherence, and prospective sampling over 12 months. ADA drug levels have been associated with treatment response in RA[2] and psoriasis[14]; however, minimal data exist on the measurement of such biomarkers in PsA. The study also demonstrates that an ADA concentration between 4–8 μg/ml was associated with an optimal response, with levels higher than 8 μg/ml conferring no additional benefit on efficacy (Figure 1). This threshold is not dissimilar to a previous study that estimated an optimal range between 5–8 μg/ml in PsA[6] and 3.51–7.00 μg/ml in patients with psoriasis[14]. More recently, such concentration-effect curves in RA have been used to determine ADA drug level

Table 1. Demographic and clinical characteristics at baseline stratified by anti-drug antibody (ADAb) status.

Baseline Characteristics	Total Patient Population, n = 75	Patients Taking Adalimumab, n = 49	Patients with ADAb, n = 10**	Patients without ADAb, n = 39**
Age, yrs, mean (SD)	51.0 (12)	51.0 (12)	47.8 (13)	52.7 (12)
Female, n (%)	46 (61.3)	29 (59.5)	9 (90)*	20 (51)*
BMI, kg/m^2	28.9 (26.0–34.9)	28.1 (26.0–32.9)	26.6 (23.1–27.6)	28.7 (26.0–34.2)
Disease status				
Disease duration, yrs	5.0 (3.1–10.0)	5.0 (3.4–8.7)	6.4 (4.9–15.0)	4.4 (2.7–8.7)
DAS28, mean (SD)	4.9 (0.9)	4.8 (1.0)	4.8 (1.3)	4.8 (0.9)
HAQ score, mean (SD)	1.2 (0.6)	1.1 (0.6)	0.9 (0.5)	1.1 (0.6)
Tender joint count (28 joints)	8 (4–16)	6 (4–14)	8 (8–11)	6 (4–14)
Swollen joint count (28 joints)	4 (3–8)	4 (3–7)	5 (3–7)	4 (3–7)
ESR, mm/h	17 (8–35)	17 (8–35)	12 (12–34)	18 (8–35)
CRP, mg/l	7.5 (4–15)	6 (4–15)	5.0 (5–58)	6.5 (4–15)
Patient global score	70 (50–80)	70 (50–80)	70 (50–82)	65 (50–80)
nbDMARD therapy, n (%)				
Methotrexate use	25 (33)	16 (27.1)	1 (10.0)	15 (38.4)
Methotrexate dose, mg/week	22.5 (15–25)	22.5 (17.5–25)	20 (12.5–22.5)	22.5 (17.5–25)
Sulfasalazine	22 (29)	11 (22.4)	1 (10.0)	10 (25.6)
Leflunomide	5 (6.7)	2 (4.1)	1 (10.0)	1 (2.7)
Hydroxychloroquine	4 (6.7)	3 (6.1)	0	3 (7.7)

* There is a statistically significant difference for female sex (p = 0.03). ** Patients taking adalimumab who developed ADAb during 12-month followup. Data for categorical variables are presented as percentage of non-missing data. Values are median (IQR) unless otherwise specified. nbDMARD listed are the most frequently used in the cohort. BMI: body mass index; CRP: C-reactive protein; DAS28: 28-joint count Disease Activity Score; HAQ: Health Assessment Questionnaire; nbDMARD: nonbiologic disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; IQR: interquartile range.

thresholds to assess whether patients with high drug levels may be able to prolong their dosing interval by 50%. RA patients with ADA concentrations of > 8 μg/ml were able to prolong their dosing interval to once every 3 weeks without loss of disease control after 28 weeks[10]. Our study therefore supports testing the feasibility of such a strategy in PsA using a similar threshold.

In contrast, ETN drug levels were less valuable as predictors of treatment response. Our study was limited by a small sample size; however, measuring ETN drug levels to guide treatment consistently appears to be less useful in patients with RA and psoriasis. This may be due to its shorter half-life, the higher frequency of administration leading to wider variation in pharmacokinetics, or immunogenicity playing less of a role in efficacy in ETN-treated patients[2]. While loss of response is recognized in ETN-treated patients with PsA, the mechanism underlying this is not completely clear. One possibility is the development of binding antibodies not detected by RIA or ELISA, leading to changes in the pharmacokinetics of the drug. However, very few studies have detected ADAb to ETN and in those that have, the clinical relevance remains uncertain[2,15].

A limitation of using DAS28 as the primary outcome is that not all affected joints in PsA may be identified within the score; however, it was used because of the familiarity of research teams accurately determining these scores in a UK observational setting. In polyarticular PsA, treatment response measured using DAS28 scores has been demonstrated to discriminate effectively between biologics and placebo treatment response[16]. DAS28 scores have subsequently been used in published observational PsA cohort studies[6,17].

Drug level testing in ADA-initiated PsA patients may be useful in determining treatment response and disability over 12 months. Identification of a drug level threshold for optimal response may help tailor ADA therapy for patients with PsA in the future, with potential opportunities for serum concentration–guided dose tapering. The results of our study extend the utility of such tests to PsA and could be used in subsequent cost-effectiveness analyses of TNFi pharmacological tests to inform evidence-based treatment decisions and future policy recommendations.

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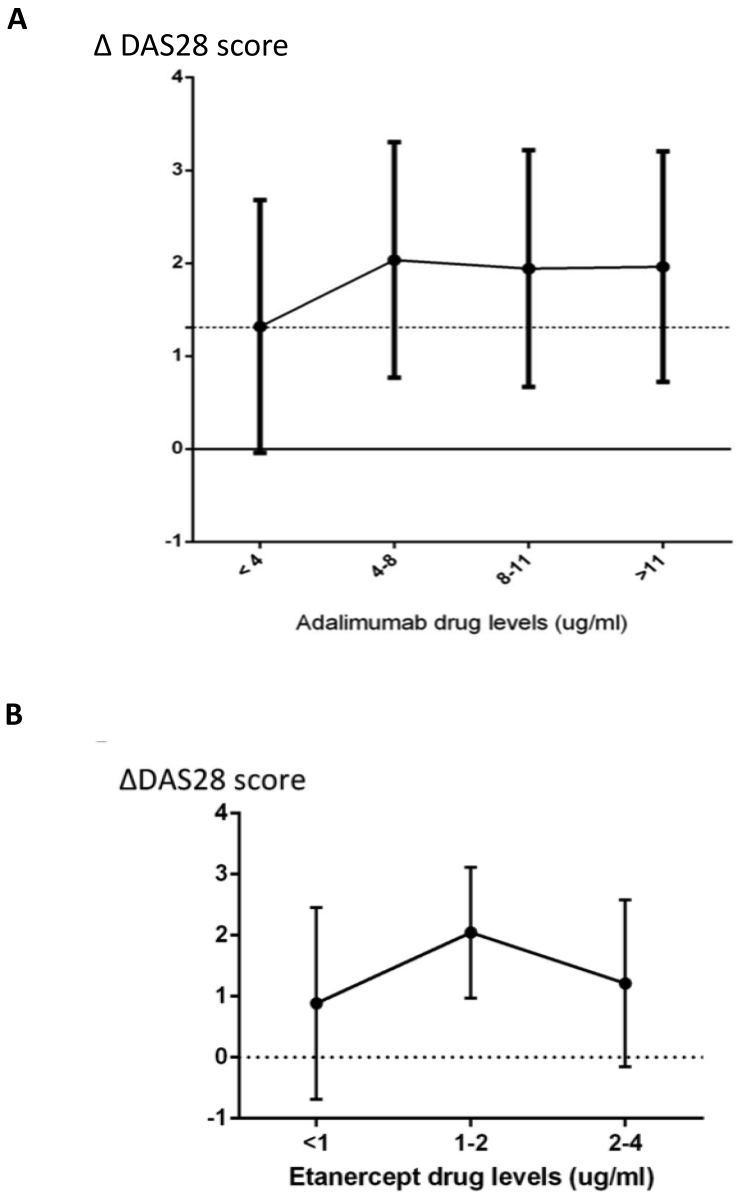

Figure 1. Concentration–effect curve at 6 months for (A) adalimumab, and (B) etanercept-treated patients using drug level thresholds. DAS28: 28-joint count Disease Activity Score.

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APPENDIX 1.

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