Association of Serum Ustekinumab Levels With Clinical Response in Psoriasis

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IMPORTANCE High-cost biologic therapies have transformed the management of immune-mediated inflammatory diseases. To optimize outcomes and reduce costs, dose adjustment informed by measurement of circulating drug levels has been shown to be effective in various settings. However, limited evidence exists for this approach with the interleukin 12 and interleukin 23 inhibitor ustekinumab.

OBJECTIVE To evaluate clinical utility of therapeutic drug monitoring for ustekinumab in patients with psoriasis.

DESIGN, SETTING, AND PARTICIPANTS A prospective observational cohort of 491 adults with psoriasis was recruited to the multicenter Biomarkers of Systemic Treatment Outcomes in Psoriasis study within the British Association of Dermatologists Biologic and Immunomodulators Register from June 2009 to December 2017; samples from some patients were taken between 2009 and 2011 as part of a pilot study with the same inclusion criteria.

EXPOSURE Serum ustekinumab level measured at any point during the dosing cycle using an enzyme-linked immunosorbent assay.

MAIN OUTCOMES AND MEASURES Disease activity measured using the Psoriasis Area and Severity Index (PASI) score. Treatment response outcomes were PASI75 (75% reduction in PASI score from baseline [primary outcome]), PASI90 (90% reduction of PASI score from baseline), and absolute PASI score of 1.5 or less.

RESULTS A total of 491 patients (171 women and 320 men; mean [SD] age, 45.7 [12.8] years) had 1 or more serum samples (total, 853 samples obtained 0-56 weeks from start of treatment) and 1 or more PASI scores within the first year of treatment. Antidrug antibodies were detected in only 17 of 490 patients (3.5%). Early measured drug levels (1-12 weeks after starting treatment) were associated with PASI75 response 6 months after starting treatment (odds ratio, 1.38; 95% CI, 1.11-1.71) when adjusted for baseline PASI score, age, and ustekinumab dose. However, this finding was not consistent across the other PASI outcomes (PASI90 and PASI score of ≤1.5).

CONCLUSIONS AND RELEVANCE This real-world study provides evidence that measurement of early serum ustekinumab levels could be useful to direct the treatment strategy for psoriasis. Adequate drug exposure early in the treatment cycle may be particularly important in determining clinical outcome.

Published online September 18, 2019.

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Supplemental content
Psoriasis is a chronic immune-mediated skin disease affecting at least 2% of the population. Management of psoriasis has been transformed by therapeutic monoclonal antibody biologics, of which the first-line choices are either adalimumab (a tumor necrosis factor inhibitor) or ustekinumab (an interleukin 12 [IL-12] and IL-23 inhibitor). There is wide variation in response to these drugs, with many patients not responding (primary treatment failure) or losing response over time (secondary treatment failure). Some of this heterogeneity may be explained by differences in the bioavailability and quantity of drug available at the target tissue, which in turn is influenced by adherence, drug dose, and pharmacokinetic covariates such as weight and drug immunogenicity (development of antidrug antibodies [ADAs]).

Unlike most other biologics used for inflammatory disease, ustekinumab is dosed according to body weight; patients who weigh less than 100 kg are given 45 mg subcutaneously every 12 weeks, whereas those weighing at least 100 kg are given 90 mg subcutaneously every 12 weeks. Despite this dosing schedule, evidence suggests that ustekinumab dosing is suboptimal in some patients: clinical trial data previously showed that dose escalation increased rates of achieving 75% reduction from baseline in the Psoriasis Area and Severity Index (PASI) score (PASI75) in partial responders (those achieving ≥50% but <75% improvement from baseline PASI score), while patients with a higher baseline body mass index have been reported to receive in excess of the recommended cumulative dose during the first year of treatment. Similarly, response rates to ustekinumab in patients weighing 90 to 100 kg have been reported to be significantly lower than in other weight groups, suggesting that the standard 45-mg dose is inadequate in patients who are approaching the 100-kg threshold. On the other hand, ustekinumab dosing is likely to be excessive in some patients; a recent phase 3b study reported that lengthening intervals between ustekinumab doses did not affect maintenance of response. Taken together, these findings suggest that individualized dose optimization and therapeutic drug monitoring (TDM) of ustekinumab may have clinical utility.

Although several ustekinumab assays are commercially available in both the United States and Europe, monitoring of serum ustekinumab levels is not yet widely used in clinical practice. This is partly owing to limited evidence for TDM of this drug, in contrast to the strong correlation described between tumor necrosis factor inhibitor serum levels, ADAs, and treatment response across multiple immune-mediated inflammatory diseases. Reports on the association between ustekinumab level and response to treatment have been inconclusive, with basic parameter requirements for TDM (eg, therapeutic range and target drug level) yet to be established in the context of psoriasis.

Because the first step toward defining such parameters is to determine the association between drug levels and outcome, we investigated this using a real-world bioresource from the large multicenter cohort study BSTOP (Biomarkers of Systemic Treatment Outcomes in Psoriasis) within the UK pharmacovigilance registry BADBIR (British Association of Dermatologists Biologic and Immunomodulators Register). This study provides evidence that measurement of early ustekinumab levels could be useful to direct treatment strategy in patients with psoriasis; adequate drug exposure early in the treatment cycle may be particularly important in determining clinical outcome.

### Key Points

**Question** Can therapeutic drug monitoring for the interleukin-12 and interleukin-23 inhibitor ustekinumab optimize treatment pathways and outcomes in patients with psoriasis?

**Findings** This cohort study of 491 patients with psoriasis found that early serum ustekinumab levels were associated with a subsequent 75% reduction from baseline in Psoriasis Area and Severity Index score, although this association did not hold across other Psoriasis Area and Severity Index outcomes. Drug immunogenicity appeared to be low, with antidrug antibodies detected in only 17 of 490 patients (3.5%).

**Meaning** This study provides evidence that measurement of early ustekinumab levels could be useful to direct treatment strategy in patients with psoriasis; adequate drug exposure early in the treatment cycle may be particularly important in determining clinical outcome.

### Methods

**Patients and Setting** As described previously, BSTOP is a prospective multicenter (n = 60) observational study, established in 2011 to identify markers of outcomes to systemic therapies for psoriasis. All UK adults fulfilling BSTOP inclusion criteria and enrolled in BADBIR were invited to participate. Venous blood samples were collected between June 2009 and December 2016 during routine clinic reviews; samples from some BSTOP patients were taken between 2009 and 2011 as part of a pilot study with the same inclusion criteria. Clinical response was assessed longitudinally using the PASI score. The current analysis includes patients receiving ustekinumab monotherapy, with 1 or more serum sample and 1 or more recorded PASI scores within the first year of treatment (Figure I). This study was conducted in accordance with the 2008 Declaration of Helsinki.

### Drug Level and ADA Measurements

Venous blood was collected during clinic reviews and centrifuged for 10 minutes (2000g) and serum aliquots were stored frozen.
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Original Investigation Research

Outcome Measures
Primary treatment response was defined as achieving PASI75, with baseline PASI score defined as the most recent PASI score recorded prior to the date of the first drug dose within the preceding 6 months. Secondary outcomes were 90% reduction in PASI score from baseline (PASI90) and PASI score of 1.5 or less (absolute PASI score of 4.5, which approximates to PASI90; written communication, Nina Wilson, PhD, January 2019).

Statistical Analysis
Based on previous work using adalimumab drug levels, we explored the association between ustekinumab level and response in 2 ways. First, we investigated the association between drug levels and response on the same day of the sample; second, we investigated whether drug levels sampled early after treatment start are associated with response at 6 months. Two data sets were therefore derived: a data set comprising samples obtained at steady state (≥16 weeks after treatment start), with a corresponding PASI score on the same day as the sample date, hereafter referred to as the same-day response data set; and a data set comprising samples obtained early in the treatment course (1-12 weeks after treatment start), with a corresponding PASI score at 6 months (122-243 days after treatment start), hereafter referred to as the 6-month response data set. Analyses for PASI75 and PASI90 responses were restricted to patients with a baseline PASI score higher than 10 as an accepted criterion for severe disease, and to minimize confounding due to prebiologic treatments. The latter is particularly relevant in this real-world data set.

Descriptive Analysis
A descriptive concentration effect curve was generated to assess whether clinical response plateaus beyond a certain drug level. Box plots were used to visually compare drug levels by responder group in both the same-day response and 6-month response data sets.

Logistic Regression Analysis
We used univariate logistic regression models with the 6-month response data set to explore the association between early drug levels and treatment response in the presence of other covariates, including those previously identified as factors associated with response in the BADBIR cohort (eg, weight, race/ethnicity, disease and treatment duration, ustekinumab dose, and biologic-naïve status). Given that most samples were not trough levels, we also included time of sample from last ustekinumab dose as a covariate. For continuous covariates, the best-fitting simple nonlinear transformation was chosen based on reduction in the Akaike Information Criterion. Co-variates associated with response at significance level of $P < .10$ were taken forward to a multivariable logistic regression model. Forward selection techniques were then used, with covariate inclusion based on a significance level of $P < .05$. Multivariable models were derived for all 3 PASI outcomes (PASI75, PASI90, and PASI score of 1.5). For PASI90 and PASI score of 1.5 or less, drug level was included as the first covariate and retained at each stage, despite not being significant on univariate analysis. Pseudo $R^2$ and Akaike Information Criterion were calculated to assess model fit. All analyses were undertaken using Stata, version 14, on a complete case basis.

Figure 1. Flow Diagram of Patients Included in the Study

| 726 Patients receiving ustekinumab monotherapy and providing serum samples |
| 235 Excluded because missing a serum sample and/or recorded PASI score ≤12 mo from treatment start |
| 491 Patients with both a serum sample and recorded PASI score ≤12 mo from treatment start |
| 252 Patients with samples obtained at steady state (≥16 wk after treatment start) |
| 237 Patients with PASI score on same date as sample obtained |
| 148 Patients with baseline PASI score >10 (same-day response data set) |
| 144 Patients with PASI score at 6 mo (122-243 d after treatment start) |
| 144 Patients with PASI score at 6 mo (122-243 d after treatment start) |
| 85 Patients with baseline PASI score >10 (6-mo response data set) |

PASI indicates Psoriasis Area and Severity Index.
Results

Patient Cohort and Baseline Characteristics
A total of 491 patients receiving ustekinumab monotherapy had both serum samples and PASI scores available within the first year of treatment (Figure 1, Table 1). The cohort was predominantly male (320 [65.2%]), with a mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) of 32.0 (7.3) and mean (SD) baseline PASI score of 13.3 (6.8). A total of 201 patients (40.9%) were biologic-naive, and 282 (57.4%) were receiving 45 mg of ustekinumab vs 209 (42.6%) receiving 90 mg (Table 1). Patients not providing serum samples were excluded, but their baseline characteristics were similar (eTable 1 in the Supplement).

Response to Treatment
A total of 348 patients (70.9%) achieved PASI75 at some point within a year of starting treatment. PASI75 remains a standard measure of adequate treatment response in UK guidelines.38

Drug Levels and ADAs
Drug levels were sampled according to standard clinical care. Excluding samples obtained on the day the first dose was given, the median time from last dose was 28 days (interquartile range [IQR], 16-57 days; range, 0-98 days; data available for 515 samples), median drug level was 1.19 μg/mL (IQR, 0.37-2.86 μg/mL; range 0-13.1 μg/mL; 800 samples), and ADAs were detected in 17 of 490 patients (3.5%) in 20 samples obtained 29 to 350 days after starting treatment.

Relationship Between Drug Level and Response
All analyses considered all eligible samples. There was a maximum of 4 samples per patient.

Descriptive Analysis
A concentration effect curve showed no clear evidence of an association between steadystate drug levels and same-day absolute PASI (eFigure 1 in the Supplement). Median drug level and spread of drug levels were similar between patients recorded to have responded and those who did not respond on the same day as the serum sample was obtained (same-day response data set; eFigure 2 in the Supplement). However, patients achieving PASI75 at 6 months (6-month response data set) on average had higher early ustekinumab levels (median, 2.78 μg/mL; IQR, 1.78-4.02 μg/mL; range, 0.02-9.78 μg/mL) compared with patients not achieving PASI75 (median, 1.83 μg/mL; IQR, 0.96-2.86 μg/mL; range, 0.02-9.00 μg/mL) (Figure 2A), with overlapping ranges between the 2 groups. A similar pattern was observed for the other 2 response outcomes, PASI90 and PASI score of 1.5 or less (eFigure 3 in the Supplement).

To explore the association between drug level, response, and dose, we split box plot data by ustekinumab doses of 45 mg and 90 mg (Figure 2B). As expected, patients who achieved PASI75 had higher median drug levels than did nonresponders within each dose group. This pattern was also evi-

Table 1. Summary Statistics for the Full Cohort, Same-Day Response Data Set, and 6-Month Response Data Set

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Full Cohort (491 Patients; 853 Samples)</th>
<th>Response Data Set</th>
<th>At 6 mo (85 Patients; 119 Samples)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Complete Data, No. (%)</td>
<td>Mean (SD) Complete Data, No. (%)</td>
<td>Mean (SD) Complete Data, No. (%)</td>
</tr>
<tr>
<td>Baseline PASI score</td>
<td>13.3 (6.8) 452 (92.1)</td>
<td>16.6 (5.2) 148 (100)</td>
<td>16.3 (5.5) 85 (100)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172.2 (10.3) 463 (94.3)</td>
<td>172.4 (10.5) 140 (94.6)</td>
<td>172.1 (10.5) 81 (95.3)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>94.7 (22.7) 435 (88.6)</td>
<td>96.1 (23.7) 140 (94.6)</td>
<td>94.2 (22.9) 80 (94.1)</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>105.8 (16.8) 420 (85.5)</td>
<td>106.5 (17.4) 131 (88.5)</td>
<td>105.2 (15.7) 77 (90.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>32.0 (7.3) 427 (87.0)</td>
<td>32.3 (7.7) 136 (91.9)</td>
<td>31.7 (7.6) 78 (91.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.7 (12.8) 491 (100)</td>
<td>45.2 (13.1) 148 (100)</td>
<td>48.7 (13.3) 85 (100)</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>23.3 (13.1) 464 (94.5)</td>
<td>23.1 (13.1) 142 (95.9)</td>
<td>23.4 (13.0) 82 (96.5)</td>
</tr>
<tr>
<td>White race/ethnicity</td>
<td>421 (85.7) 491 (100)</td>
<td>123 (83.1) 148 (100)</td>
<td>70 (82.4) 85 (100)</td>
</tr>
<tr>
<td>Male sex</td>
<td>320 (65.2) 491 (100)</td>
<td>99 (66.9) 148 (100)</td>
<td>59 (69.4) 85 (100)</td>
</tr>
<tr>
<td>Inflammatory arthritis</td>
<td>289 (61.2) 430 (87.6)</td>
<td>26 (18.8) 138 (93.2)</td>
<td>24 (30.4) 79 (92.9)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>93 (21.1) 441 (89.8)</td>
<td>30 (21.6) 139 (93.9)</td>
<td>19 (24.1) 79 (92.9)</td>
</tr>
<tr>
<td>Palm psoriasis</td>
<td>201 (40.9) 491 (100)</td>
<td>64 (43.2) 148 (100)</td>
<td>37 (43.5) 85 (100)</td>
</tr>
<tr>
<td>Biologic naive</td>
<td>491 (100) NA</td>
<td>148 (100) NA</td>
<td>85 (100) NA</td>
</tr>
<tr>
<td>Dose 45 mg</td>
<td>282 (57.4) NA</td>
<td>82 (55.4) NA</td>
<td>48 (56.5) NA</td>
</tr>
<tr>
<td>Dose 90 mg</td>
<td>209 (42.6) NA</td>
<td>66 (44.6) NA</td>
<td>37 (43.5) NA</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; PASI, Psoriasis Area and Severity Index.

a Summaries for the same-day response and 6-month response data sets are restricted to patients with a baseline PASI score higher than 10.
dent for the outcomes of PASI90 and PASI score of 1.5 or less (eFigure 4 in the Supplement). However, patients who did not achieve PASI75 while taking 90 mg of ustekinumab had slightly higher median drug levels than did nonresponders taking 45 mg of ustekinumab, albeit with overlapping ranges and large variability (Figure 2B).

**Logistic Regression Analysis**

Univariate logistic regression indicated that early drug level was associated with 6-month PASI75 (6-month response data set: odds ratio, 1.27; 95% CI, 1.04-1.56), but there was no evidence of this association for the other 2 PASI outcomes (eTable 2 in the Supplement). Next, multivariable models were derived to explore the association between early drug level and 6-month response in the presence of other relevant covariates. The final model for PASI75 included drug dose, baseline PASI score, and age as well as drug level (odds ratio, 1.38; 95% CI, 1.11-1.71) (Table 2), and shows increasing probability of response with increasing drug level (Figure 3). The model also suggests that patients taking the higher ustekinumab dose (90 mg) have a lower probability of response for a given drug level (Figure 3). To explore this finding further, we inspected box plots of drug levels split by weight and dose (eFigure 5 in the Supplement). Despite overlapping ranges, these box plots

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient (SE)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Pseudo-$R^2$</th>
<th>Samples, No.</th>
<th>Responders, No. (% of Samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PASI75</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug level</td>
<td>0.32 (0.11)</td>
<td>1.38 (1.11-1.71)</td>
<td>.004</td>
<td></td>
<td>0.18</td>
<td>119</td>
</tr>
<tr>
<td>Baseline PASI score</td>
<td>0.10 (0.04)</td>
<td>1.10 (1.01-1.20)</td>
<td>.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.04 (0.02)</td>
<td>1.04 (1.00-1.07)</td>
<td>.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-mg Dose</td>
<td>−1.43 (0.44)</td>
<td>0.24 (0.10-0.56)</td>
<td>.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PASI90</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug level</td>
<td>0.14 (0.09)</td>
<td>1.15 (0.97-1.38)</td>
<td>.11</td>
<td></td>
<td>0.10</td>
<td>115</td>
</tr>
<tr>
<td>Baseline PASI score</td>
<td>0.10 (0.04)</td>
<td>1.11 (1.02-1.20)</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.04 (0.02)</td>
<td>1.04 (1.01-1.08)</td>
<td>.009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PASI score ≤1.5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug level</td>
<td>0.11 (0.08)</td>
<td>1.12 (0.96-1.30)</td>
<td>.15</td>
<td></td>
<td>0.06</td>
<td>186</td>
</tr>
<tr>
<td>Naive to biologics</td>
<td>0.92 (0.33)</td>
<td>2.51 (1.31-4.81)</td>
<td>.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoked</td>
<td>−0.70 (0.34)</td>
<td>0.50 (0.26-0.96)</td>
<td>.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; PASI75, 75% reduction from baseline in Psoriasis Area and Severity Index score; PASI90, 90% reduction from baseline in Psoriasis Area and Severity Index score.

Figure 2. Box Plots Comparing Early Measured Drug Levels by Achievement of 75% Reduction From Baseline in Psoriasis Area and Severity Index at 6 Months

A, Split by response only. The nonresponse group contains 46 samples and the response group contains 73 samples. B, Split by response and by ustekinumab dose. The nonresponse group receiving 45 mg of ustekinumab contains 18 samples, the response group receiving 45 mg of ustekinumab contains 50 samples, the nonresponse group receiving 90 mg of ustekinumab contains 28 samples, and the response group receiving 90 mg of ustekinumab contains 23 samples. In both panels, the middle line is the median, white circles are the means, ends of boxes are the lower and upper quartiles, dark blue circles are outliers (values ≥1.5 times the interquartile range from the lower and upper quartiles), and whiskers show the minimum and maximum values (unless there are outliers, in which case they are 1.5 times the interquartile range from the lower and upper quartiles).
dose characteristics associated with poor response is perhaps surprising. One possible explanation is that patients taking the higher dose exhibit characteristics associated with poor response that have not been accounted for in our model. An alternative explanation may be that a double dose of ustekinumab (90 mg vs 45 mg) fails to adequately compensate for the increased volume of distribution in some people with a higher body weight; we noted that median drug levels were slightly lower in patients taking the higher ustekinumab dose and in patients weighing more than 100 kg.

Our data set should allow for stable estimation of comparable numbers (4-5) of covariates in each of the analyses for early drug level vs the 3 different PASI outcomes. However, we were unable to demonstrate a link between early drug level and the other PASI outcomes, nor between steady state drug levels and same-day response. It is therefore possible that the association between early drug level and PASI75 is owing to a spurious $P$ value or statistical artifact. This contrasts with findings for adalimumab,24 where the same statistical approach showed that both early and steady state drug levels were associated with all PASI outcomes. A fundamental explanation for this may lie in differing mechanisms of biologic action: adalimumab directly inhibits the inflammatory effector cytokine tumor necrosis factor, whereas ustekinumab inhibits IL-12 and IL-23, with the latter being a master regulator of pathogenic T helper 17 cell development.40 Just as the underlying biological effect is more complex for ustekinumab, it may be that the association between drug level and response is correspondingly convoluted.

### Existing Literature

To our knowledge, there are few other analyses in this area, generally limited to descriptive or empirical analyses investigating the association between ustekinumab level and response, which report mixed results. The most recent study in psoriasis included prospective follow-up of only 27 patients, but reported similar findings to ours in that very early drug levels (week 6) were inversely correlated with subsequent response (week 12).25 However, in line with our data, no association was detected between drug levels measured later (in this case, at week 12) and same-day response.

The largest study in patients with psoriasis reported significantly lower drug levels and PASI50 response rates in patients with detectable ADAs compared with those without detectable ADAs.23 Finally, in a Dutch cohort of 41 patients with psoriasis, there was no correlation between ustekinumab level and response; 3 of 41 patients (7.3%) developed ADAs.24

Larger-scale studies have been conducted in the context of inflammatory bowel disease. It is possible that variability in the amount of drug lost via the inflamed gut means that some patients are less able to achieve adequate serum concentrations, meaning that TDM may have greater utility in this setting. An analysis of phase 3 trial data ($n = 1154$) reported a positive association of drug levels with clinical and endoscopic improvement, and an inverse correlation with C-reactive protein level.25 Only 2% of patients developed ADAs.

### Strengths and Limitations

A strength of this study is high external validity, as more than 50% of all UK patients with psoriasis taking biologics are registered in BADBIR, and 95% of UK dermatology centers pre-

### Discussion

#### Key Findings

To our knowledge, this is the largest study to date of ustekinumab drug level monitoring in patients with psoriasis. We report evidence that early ustekinumab levels were significantly associated with 6-month PASI75 response. This finding has particular clinical and practical relevance because assays to measure serum ustekinumab levels are already commercially available in both the United States and Europe.10-15

We also report a low rate (3.5%) of detectable ADAs to ustekinumab within the first year of treatment, compared with the previously reported rate of 37.5% in a cohort of patients taking adalimumab that was derived from the same UK study.20 It is possible that this differential drug immunogenicity accounts, at least partially, for significantly higher rates of drug survival (length of time from initiation to discontinuation of treatment) in patients taking ustekinumab compared with those taking adalimumab.3

The finding that the higher ustekinumab dose is associated with a lower probability of response is perhaps surprising. One possible explanation is that patients taking the higher dose exhibit characteristics associated with poor response that...
scribing biologics for psoriasis contribute data to BADBIR. Our findings highlight the potential clinical utility of this easily measurable early biomarker in optimizing subsequent response. They also serve as a call to action for both industry and academia to develop cost-effective and widely available assays, and to further validate the role of TDM in clinical practice.

One limitation of our study is that, of 491 patients with both a serum sample and PASI score within 1 year of treatment, the same-day response data set included 148 patients and the 6-month response data set included 85 patients. Figure 1 shows the dropoff in patient numbers at each stage of filtering.

A second limitation relates to the difficulty in accounting for the complex association between drug level and response using standard logistic regression modeling. This approach has been successfully used in other settings, notably to define a therapeutic range and target drug level for adalimumab. However, it is possible that ustekinumab's extended dosing interval compared with adalimumab may pose a particular hindrance in this context, as a single or small number of drug levels may represent a relatively poor measure of total drug exposure. This issue may have been exacerbated by pragmatic serum sampling and PASI assessment at routine clinical visits, as opposed to having samples measured and PASI assessments performed only during trough periods. To partially address this issue, we accounted for the timing of samples by including time from last ustekinumab dose as a covariate in modeling, but this did not remain in the final multivariable models after the forward selection process. Finally, the validity of our findings is limited to within 1 year of the start of treatment, as this was the selected cohort duration.

**Conclusions**

Despite the complexities outlined above, we did find a statistically significant association between early drug levels (≤12 weeks) and 6-month PASI75 response in patients with psoriasis taking ustekinumab. This finding suggests that adequate drug exposure early in the treatment cycle may be particularly important in determining clinical outcome with ustekinumab. However, our statistical approach did not take into account patient-level pharmacokinetic parameters such as volume of distribution and clearance, nor potential differences in evolution of PASI score over time vs changing drug levels. Therefore, future work should focus on pharmacokinetic-pharmacodynamic modeling of the whole time course of response to ustekinumab. This modeling may be of particular relevance for biologics with more upstream targets, such as differentiation pathway cytokines as opposed to effector cytokines. Further investigation to confirm the clinical utility of TDM of ustekinumab and other biologics is a key step toward personalization of treatment regimens across multiple immune-mediated inflammatory diseases.
from Genmab. Dr Stocken reported receiving departmental research funding from AstraZeneca. Dr Smith reported receiving departmental research funding from AbbVie, GSK, Pfizer, Novartis, Regeneron, and Roche.

Funding/Support: This work was funded by the Medical Research Council (MRC) Stratified Medicine award (MR/L011808/1), the Psoriasis Association (RG210), the National Institute for Health Research Biomedical Research Centre at King's College London with St Thomas' NHS Foundation Trust, the National Institute for Health Research Manchester Biomedical Research Centre, and the National Institute for Health Research Newcastle Biomedical Research Centre. Ms Tsakok is supported by an MRC Clinical Research Training Fellowship (MR/R001839/1). Dr Dand is supported by Health Data Research UK (MR/S033126/1). Dr Standing is supported by an MRC Clinician Scientist Fellowship (MR/M008665/1). Dr Reynolds is supported by the Newcastle MRC/ESPSC Molecular Pathology Node and the Newcastle National Institute for Health Research Medtech and In Vitro Diagnostics Co-operative.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Group Information: Members of the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) Study Group include Jonathan Barker, MD, FRCP, Marilyn Benham, David Burden, MD, FRCP, Ian Evans, MSc, Christopher Griffiths, MD, FMedSci, Sagar Hussain, PhD, Brian Kirby, MD, Linda Lawson, MSc, Kayleigh Mason, PhD, Kathleen McElhone, PhD, and Ruth Murphy, PhD, FRCP, Anthony Ormerod, MD, FRCP, Caroline Owen, FRCP, Nick Reynolds, MD, FRCP, Catherine Smith, MD, FRCP, and Richard Warren, PhD, FRCP.

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Additional Contributions: Gertjan Wolbink, PhD, Amsterdam Rheumatology and Immunology Center, provided invaluable advice on study design. He was not compensated for his contribution. We also thank the Psoriasis Stratification to Optimise Relevant Therapy (PSORT), British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR), and Biomarkers of Systemic Treatment Outcomes in Psoriasis (BSTOP) study teams for the delivery of the project, our collaborators within the PSORT consortium (Michael R Barnes, Paola di Meglio, Richard Emley, Andrea Evans, and Katherine Payne) and BADBIR study group (Marilyn Benham, Ian Evans, Sagar Hussain, Brian Kirby, Linda Lawson, Kathleen McElhone, Anthony Ormerod, and Caroline Owen). 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. We 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 thank all the patient participants, and acknowledge the enthusiastic collaboration of all of the dermatologists and specialist nurses in the UK and the Republic of Ireland who recruited for this study.

Additional Information: The Psoriasis Stratification to Optimise Relevant Therapy (PSORT) Consortium has a number of industry partners; see http://www.psort.org.uk.

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