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**Running head:** CRP, IL-17A, and IL-17F responsive to ustekinumab in PsA

# Serum CRP, IL-17A, and IL-17F levels are responsive to ustekinumab in psoriatic arthritis: lessons from the PSUMMIT study programme

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**ABSTRACT**

**Objectives**

To evaluate the associations of CRP and circulating Th17-associated cytokines with psoriatic arthritis (PsA) disease activity and therapeutic response to ustekinumab.

**Methods**

Measurement of IL-17A, IL-17F, IL-23 and CRP concentrations was performed on serum samples collected as part of the two PSUMMIT phase 3 studies of ustekinumab in PsA (n=927). In post hoc analyses, relationships of IL-17A, IL-17F, and CRP levels at baseline, weeks 4 and 24 with baseline skin and joint disease activity and response to therapy were evaluated using General Linear Models and Pearson‘s product-moment correlation tests.

**Results**

Baseline serum levels of IL-17A and IL-17F were positively correlated with baseline skin disease scores (r = 0.39 to 0.62). IL-23 correlated to a lesser extent (r= 0.26-0.31). No significant correlations were observed between these cytokines or CRP and baseline joint disease activity. There was no significant association of baseline levels of IL-17A, IL-17F, IL-23 or CRP with therapeutic response to ustekinumab in either skin or joints. Significant reductions from baseline in levels of IL-17A, IL-17F, and CRP were seen with ustekinumab treatment compared to placebo. Ustekinumab treated subjects who achieved PASI75 or ACR20 responses after 24 weeks of treatment had greater reductions in CRP (geometric mean decreases of 51-58% vs. 32-33%; $p<0.05$), but not IL-17A or IL-17F levels than non-responders.

**Conclusion**

Baseline serum IL-23/-17 levels correlated with skin but not joint disease activity, suggesting tissue-specific variations. However, neither baseline Th17-associated cytokine levels nor CRP were predictive of therapeutic response to ustekinumab in the skin or joints, despite rapid reductions following ustekinumab therapy.

**INTRODUCTION:**

Psoriatic arthritis (PsA) comprises part of the spondyloarthritis spectrum, and affects 10-30% of people with psoriasis (1). PsA encompasses enthesitis, synovitis and osteitis, in addition to variable skin involvement, resulting in a highly heterogeneous clinical presentation. Therapeutic options for psoriasis and PsA were limited until the development

of biologic drugs, including TNF inhibitors, antibodies targeting the IL-12/-23/Th17 pathway (including ustekinumab, guselkumab, secukinumab and ixekizumab) and JAK inhibitors), that facilitated specific immune intervention and transformed management and outcomes.

Despite these advances, there remains significant unmet need in the management of PsA, with many patients exhibiting no or only partial response to available therapies, or a dichotomous response in skin and musculoskeletal systems. Moreover, no clear predictive biomarkers of response to therapy exist as yet, though clearly they would confer value in defining those patients most likely to benefit from a given intervention.

Clinical trials using targeted biologic therapies offer an opportunity to identify potential theranostic biomarkers and better understand underlying inflammatory processes that drive disease in humans. Two PSUMMIT phase 3 studies demonstrated the efficacy of ustekinumab, a human IgG1κ monoclonal antibody that binds to the p40 subunit common of both IL-12 and IL-23, for the cutaneous and musculoskeletal components of PsA (2,3), significant inhibition of radiographic progression of joint damage (4) and improvement in patient reported outcomes (5). Serum samples were collected as part of these studies to allow the further characterisation of Th17-associated cytokines in PsA and effects of IL-12/IL-23 inhibition with ustekinumab on these levels.

The objective of the analyses reported here was to evaluate the association of serum levels of Th17-associated cytokines with PsA disease activity, the pharmacodynamic impact of ustekinumab on serum levels of these cytokines and whether this correlated with therapeutic response.

**MATERIALS AND METHODS**:

**Study design and participants**

Detailed descriptions of the phase 3 multicentre, double-blind, placebo-controlled PSUMMIT 1 (NCT01009086) and 2 (NCT01077362) study designs, patient populations and results have been reported elsewhere (2,3). Briefly, in both studies, patients with active PsA were randomly assigned (1:1:1) to receive ustekinumab 45 mg, ustekinumab 90 mg or placebo at baseline, week 4, and every 12 weeks thereafter. PSUMMIT 1 included only patients naïve to TNF biologic therapies (n=615), whereas PSUMMIT 2 included both anti-TNF-naïve (n=132) and anti-TNF-experienced (n=180) patients. The primary endpoint in both studies was the proportion of participants with at least 20% improvement in the American College of Rheumatology (ACR) response criteria (ACR20) at week 24. Clinical changes in skin disease were evaluated using a week 24 endpoint of at least 75% improvement in the psoriasis area severity index (PASI75). For biomarker analyses, subjects who achieved less than a 50% improvement in PASI (PASI50) were considered inadequate responders and acted as the reference group for comparison to PASI75 responders.

**Biomarker assays and analyses**

Serum IL-17A and IL-17F protein levels were assayed at weeks 0, 4, and 24 in PSUMMIT 1 and at weeks 0 and 4 in PSUMMIT 2. Serum CRP levels were measured at weeks 0, 4, and 24 in both studies. Because of limited available sample volumes, IL-23 was assayed in PSUMMIT 2 only. Due to the inability of the assay to distinguish between free IL-23 and IL-23 bound by ustekinumab, only baseline levels of IL-23 were measured. Samples were assayed using:

Single Molecule Counting™ Human Immunoassay Kits (formerly Singulex Inc, currently MilliporeSigma) for IL-17A, IL-17F, and IL-23; and CardioPhase® hsCRP assay (performed centrally at Covance, LLC) for CRP. Samples from PSUMMIT 1 and 2 were assayed independently in separate batches.

**Statistical analyses**

Levels of serum protein biomarkers generally had log-normal distributions and were $log_2$-transformed for statistical analyses and data display. Significance of differences between groups was evaluated by General Linear Model analyses, with significance defined at the $p<0.05$ level. Significance of correlations between variables was evaluated by Pearson's product-moment correlation test, with significance defined as $p<0.05$ and correlation coefficient $r > 0.25$ or $< -0.25$. Data from the two studies were analysed independently.

**RESULTS**

**Correlation of baseline serum cytokine levels and clinical characteristics.** The baseline characteristics of the PSUMMIT 1 and 2 study populations have been reported previously and are shown in **Supplementary Table 1** and clinical outcomes in **Supplemental Table 2**. Serum CRP, IL-17A, IL-17F and IL-23 levels at the baseline week 0 study visit (before first dose of study agent administered) were compared with the skin and joint scores at this visit. Baseline serum levels of IL-17A and IL-17F were positively correlated with clinical skin disease scores, as measured by body surface area (BSA) and PASI, in both PSUMMIT studies, with correlations ranging from r = 0.39 to 0.62 (**Table 1**). Correlations of IL-23 with PASI and BSA were also observed to a lesser degree, with r of 0.26 and 0.31, respectively (**Table 1**).

However, there were no significant correlations observed between these cytokines and baseline joint disease activity as measured by swollen and tender joint counts (r = -0.04 to 0.18) (**Table 1**). Intriguingly, serum CRP levels were not significantly correlated with either baseline joint or skin disease activity (r = 0.04 to 0.19). As expected for short half-life variables, there was no significant correlation of any of these four serum biomarkers with duration of PsA or psoriasis (r = -0.12 to 0.15).

Distributions of the baseline serum biomarker levels did not significantly differ among sub-classifications of PsA, including asymmetric peripheral arthritis, distal interphalangeal joint arthritis, polyarticular arthritis and spondylitis with peripheral arthritis (**Supplementary Figure 1**).

**Correlation of serum cytokine levels and response to therapy.** The associations of baseline serum levels of IL-17A, IL-17F, IL-23, and CRP with clinical response at week 24 were evaluated. Regardless of whether response was measured by skin improvement (PASI75 responders compared to PASI50 non-responders at week 24; **Figure 1**) or joint symptom improvement (ACR20 responders vs non-responders at week 24; **Figure 2**), there were no significant associations with baseline levels of IL-17A, IL-17F, CRP, or IL-23 in either the ustekinumab or placebo arms.

**Pharmacodynamic changes in serum biomarker.** We next evaluated biomarker concentrations over time upon drug exposure. At week 4, there was a statistically significant reduction from baseline in levels of IL-17A, IL-17F, and CRP in the ustekinumab treatment arms compared to placebo arm in both PSUMMIT 1 and 2 ($p<0.05$), with geometric mean decreases ranging from 18 to 35% in CRP, 24 to 44% in IL-17A, and 27 to 38% in IL-17F levels in the ustekinumab treatment arms (**Figure 3; Supplementary Table 3**). Further decreases in

CRP levels were observed at week 24 in both studies, remaining significantly different from changes in the placebo arm ($p<0.05$). Week 24 levels of IL-17A and IL-17F, the latter measured only in PSUMMIT 1, remained decreased in both ustekinumab treatment arms, though remained significant versus changes in the placebo arm only for IL-17F in the ustekinumab 90mg arm ($p=0.038$) (**Figure 3A**). Thus the p40 pathway is functionally linked to the elaboration of cytokine expression and the acute phase response in PsA.

The extent of changes in IL-17A, IL-17F, and CRP after 4 or 24 weeks treatment with ustekinumab did not significantly differ among sub-classifications of PsA (**Supplementary Figure 2**).

**Correlation of pharmacodynamic serum biomarker changes with clinical response.** We next assessed whether pharmacodynamic changes in serum biomarker levels were distinct in clinical responders in the ustekinumab treatment arms. Because of the reduced sample sizes available in this subgroup analysis and the similar pharmacodynamic changes for both ustekinumab arms, the 45mg and 90mg ustekinumab treatment arms were combined to improve statistical power. At week 24 for ustekinumab treated subjects in both PSUMMIT studies, CRP decreased from baseline levels both in those who achieved a PASI75 response and in those who did not achieve a PASI50 response (non-responders), but with a significantly greater reduction in the PASI75 responders versus the PASI50 non-responders (geometric mean decreases of 58% vs. 33% in PSUMMIT 1 and 51% vs. 32% in PSUMMIT 2; $p<0.05$) (**Figure 4**). This difference between clinical response groups was not apparent at week 4. IL-17A levels were decreased significantly more in PASI75 responders compared to PASI50 non-responders only in PSUMMIT 2 at week 4 (geometric mean decreases of 50% vs. 28%; $p=0.0054$), but not in PSUMMIT 1 at either week 4 or week 24 (**Figure 4**). Changes in IL-

17F levels were not significantly different in PASI75 responders compared to PASI50 non-responders in either study.

Similarly, ustekinumab treated subjects who achieved an ACR20 response had significantly greater reductions from baseline in CRP, compared to ACR20 non-responders, at week 24 in both studies (geometric mean decreases of 64% vs. 38% in PSUMMIT 1 and 59% vs. 28% in PSUMMIT 2; $p<0.05$) and at week 4 only in PSUMMIT 1 (40% vs. 24% decrease; $p<0.05$) (**Figure 5**). Changes in serum levels of IL-17A and IL-17F were not associated with ACR20 response to ustekinumab in either study (**Figure 5**).

**DISCUSSION:**

The results presented here have clinical and drug development implications. While serum IL-17A, IL-17F and IL-23 levels correlated with baseline severity of skin disease, they did not correlate with clinical assessments of joint disease in patients with active PsA. Neither baseline IL-17A, IL-17F, nor CRP levels predicted response to ustekinumab therapy in the skin or joints, despite rapid (within four weeks) reductions in IL-17A, IL-17F and CRP following ustekinumab therapy. Responders (those that achieved PASI75 or ACR20) to ustekinumab had significant reduction in CRP at week 24, compared to non-responders (did not achieve PASI50 or ACR20), but not in IL-17A or IL-17F levels.

A stronger correlation of IL-23/-17 levels with skin disease is consistent with the emerging evidence base suggesting tissue-specific variations in the pathologic drivers within PsA. Recent pathogenesis and therapeutic studies indicate a dominant role for IL-17-related pathways in the skin in psoriatic disease (6–12). In contrast, the musculoskeletal component of PsA appears more heterogeneous and less clearly defined. Belasco et al (6) reported that while gene expression in PsA synovium was more closely related to gene expression in psoriasis skin lesions than expression in synovium in other forms of arthritis (including RA and osteoarthritis), PsA synovium and skin gene expression patterns were clearly distinct. Specifically, pathway analysis indicated that the IL-17 gene signature was stronger in the skin than synovium in PsA, while TNF and interferon-$\gamma$ gene signatures were equivalent in both tissues. However, it should be noted that demonstrating clinical relevance and plausible effector function of an inflammatory pathway does not always translate into therapeutic outcomes, as demonstrated by the failure or limited success of anti-IL-17 monotherapy studies in RA (13–15).

Many immune cells, both Th17 and innate, are known to release IL-17A and IL-17F in response to IL-23, so the rapid reduction of IL-17A and IL-17F following inhibition of IL-12/-23 with ustekinumab was not unexpected. However, considering the established pathogenic role of IL-17 in PsA, it was somewhat surprising that response to ustekinumab, in skin and/or joints, did not correlate with either baseline levels or changes in circulating IL-17A/F. The reasons for this are unclear. It may be that the changes in IL-17A/F levels at a target tissue level (skin and joints) in response to ustekinumab are not reflected in the blood, while inhibition of other members of the IL-17 superfamily beyond IL-17A/F may play a role in treatment response. However, these data indicate that baseline levels of circulating IL-23,

IL-17A/F and changes in IL-17A/F are not predictive of clinical response to ustekinumab in PsA and, as such, these cytokines cannot serve as theranostic biomarkers in this setting. One limitation of this study is the lack of data from additional therapeutics, which indicate whether these results are specific to ustekinumab or more generic to IL-23 inhibition. It will be interesting to observe changes in IL-23/-17 pathway cytokines in response to agents targeting this pathway via different routes, such as p19 IL-23, IL-17RA or combined IL-17 A and IL-17F inhibition, and how these correlate with clinical outcomes.

Finally, while the biomarkers studied in the PSUMMIT programme did not translate into therapeutic utility, it is important that relevant biomarker studies associated with phase 3 clinical trial programmes are published in order to increase our understanding of this complex disease and further dissect the role of the IL-23/IL-17 pathway.

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**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Kristen Sweet had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**ROLE OF THE STUDY SPONSOR**

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**FIGURE LEGENDS**

**Figure 1. Associations of week 24 PASI response with baseline serum biomarker levels.** Baseline week 0 serum levels of CRP, IL-17A, IL-17F, and IL-23 (PSUMMIT 2 only) in (A) PSUMMIT 1 and (B) PSUMMIT 2, presented as median, interquartile range, and range in box and whiskers plot of $log_2$-transform of biomarker concentrations for subjects in the indicated treatment group, stratified by PASI response status at week 24 (white, PASI50 non-responder; gray, PASI75 responder). Subjects with intermediate response between PASI50 and PASI75 were not included. Samples sizes reported in **Supplementary Table 2**. Abbreviations: NR, non-responder; PBO, placebo; R, responder; UST, ustekinumab

**Figure 2. Associations of week 24 ACR20 response with baseline serum biomarker levels.** Baseline week 0 visit serum levels of CRP, IL-17A, IL-17F, and IL-23 (PSUMMIT 2 only) in (A) PSUMMIT 1 and (B) PSUMMIT 2, presented as median, interquartile range, and range in box and whiskers plot of log2-transform of biomarker concentrations for subjects in the

indicated treatment group, stratified by ACR20 response status at week 24 (white, ACR20 non-responder; gray, ACR20 responder). Samples sizes reported in **Supplementary Table 2**. Abbreviations: NR, non-responder; PBO, placebo; R, responder; UST, ustekinumab

**Figure 3. Pharmacodynamic changes in serum biomarker levels.** Changes from week 0 baseline visit in serum levels of CRP (top), IL-17A (middle), and IL-17F (bottom) in (A) PSUMMIT 1 and (B) PSUMMIT 2 are presented as the mean ± standard error of within-subject $\log_2$(fold/baseline) values at the indicated visits, stratified by treatment group (- - - Placebo; ·····Ustekinumab (UST) 45mg; ── UST 90mg). * p<0.05 for UST 45mg vs. placebo; † p<0.05 for UST 90mg vs. placebo. Samples sizes and statistics reported in **Supplementary Table 3**.

**Figure 4. Associations of week 24 PASI response with changes in serum biomarker levels in participants treated with ustekinumab.** For subjects in the either ustekinumab 45mg or 90mg treatment groups, changes from week 0 baseline visit in serum levels of CRP (top), IL-17A (middle), and IL-17F (bottom) in (A) PSUMMIT 1 and (B) PSUMMIT 2, are presented as median, interquartile range, and range in box and whiskers plot of within-subject $\log_2$(fold/baseline) values at the indicated visits, stratified by week 24 PASI response status (white, PASI50 non-responder = NR; gray, PASI75 responder = R). Subjects with intermediate response between PASI50 and PASI75 were not included. Samples sizes reported in **Supplementary Table 4**. * p<0.05 vs. 0 (no change) within indicated response group at indicated visit; † p<0.05 week 24 PASI75-R vs. PASI40-NR at indicated visit.

**Figure 5. Associations of week 24 ACR20 response with changes in serum biomarker levels in participants treated with ustekinumab.** For subjects in the either ustekinumab 45mg or 90mg treatment groups, changes from week 0 baseline visit in serum levels of CRP (top), IL-17A (middle), and IL-17F, (bottom) in (A) PSUMMIT 1 and (B) PSUMMIT 2, are presented as median, interquartile range, and range in box and whiskers plot of within-subject $\log_2$(fold/baseline) values at the indicated visits, stratified by week 24 ACR20 response status (white, non-responder = NR; gray, responder = R). Samples sizes reported in **Supplementary Table 4**. * $p<0.05$ vs. 0 (no change) within indicated response group at indicated visit; † $p<0.05$ week 24 ACR20 R vs. NR at indicated visit.

**Table 1. Correlation between baseline clinical characteristics and baseline levels of serum biomarkers**

| Baseline clinical characteristic | Baseline level of serum biomarker | | | |
|---|---|---|---|---|
| | **CRP** | **IL-17A** | **IL-17F** | **IL-23** |
| ***PSUMMIT 1*** | | | | |
| Body Surface Area | 0.06 (0.1301) [614]* | **0.42 (<0.0001) [474]** | **0.57 (<0.0001) [237]** | n.a |
| Psoriasis area severity index | 0.09 (0.0253) [615] | **0.39 (<0.0001) [474]** | **0.56 (<0.0001) [237]** | n.a |
| Swollen Joint Count 66 | 0.09 (0.0241) [615] | 0.02 (0.6025) [474] | 0.07 (0.2803) [237] | n.a |
| Tender Joint Count 68 | 0.05 (0.1750) [615] | 0.11 (0.0143) [474] | 0.18 (0.0044) [237] | n.a |
| Swollen Joint Count 28 | 0.11 (0.0065) [615] | -0.04 (0.3989) [474] | -0.03 (0.6124) [237] | n.a |
| Tender Joint Count 28 | 0.04 (0.2818) [615] | 0.06 (0.2232) [474] | 0.09 (0.1581) [237] | n.a |
| Psoriatic arthritis duration | 0.07 (0.0936) [615] | 0.08 (0.0676) [474] | 0.06 (0.3505) [237] | n.a |
| Psoriasis duration | 0.00 (0.9749) [615] | 0.09 (0.0487) [474] | 0.15 (0.0204) [237] | n.a |
| ***PSUMMIT 2*** | | | | |
| Body Surface Area | 0.17 (0.0025) [311] | **0.56 (<0.0001) [310]** | **0.54 (<0.0001) [298]** | **0.31 (<0.0001) [306]** |
| Psoriasis area severity index | 0.17 (0.0025) [308] | **0.62 (<0.0001) [307]** | **0.56 (<0.0001) [295]** | **0.26 (<0.0001) [303]** |
| Swollen Joint Count 66 | 0.19 (0.0010) [312] | 0.11 (0.0579) [310] | 0.15 (0.0113) [298] | 0.08 (0.1890) [306] |
| Tender Joint Count 68 | 0.13 (0.0219) [312] | 0.09 (0.1110) [310] | 0.12 (0.0410) [298] | -0.01 (0.8261) [306] |
| Swollen Joint Count 28 | 0.14 (0.0134) [312] | 0.00 (0.9405) [310] | 0.03 (0.5560) [298] | 0.03 (0.6298) [306] |
| Tender Joint Count 28 | 0.14 (0.0161) [312] | 0.05 (0.4023) [310] | 0.08 (0.1633) [298] | -0.03 (0.5438) [306] |
| Psoriatic arthritis duration | 0.07 (0.2377) [312] | 0.01 (0.8152) [310] | -0.02 (0.7728) [298] | -0.12 (0.0406) [306] |
| Psoriasis duration | 0.08 (0.1833) [312] | 0.03 (0.5654) [310] | 0.04 (0.4830) [298] | -0.09 (0.1005) [306] |

* From Pearson's product-moment correlation analyses of the indicated baseline clinical characteristic (rows) versus baseline serum levels of indicated biomarker (columns), stratified by study, reported are the correlation coefficient r (p-value) [sample size]. Bolded font for significant correlations with r > 0.25 or < -0.25.

Abbreviations: n.a., not available (data not generated)