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S100A8/A9 AND S100A12 AS POTENTIAL PREDICTIVE BIOMARKERS OF ABATACEPT RESPONSE IN POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

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on behalf of Pediatric Rheumatology Collaborative Study Group (PRCSG) and Paediatric Rheumatology International Trials Organisation (PRINTO)

Background:

The calcium-binding proteins S100A8/A9 (calprotectin) and S100A12 (extracellular newly identified receptor for advanced glycation end-products binding protein [EN-RAGE]) are involved in multiple signalling pathways to mediate inflammation, can be secreted by activated monocytes/macrophages and exhibit cytokine-like extracellular functions. Circulating levels of these proteins have been associated with disease and clinical responses in systemic juvenile idiopathic arthritis (sJIA), including treatment response.1 Studies suggest that serum S100A8/A9 and S100A12, which are released at inflammation sites, are more specific biomarkers of local inflammation (e.g. in the synovium) than systemic biomarkers such as CRP and ESR.2,3

Objectives:

To investigate if baseline S100A8/A9 and S100A12 predict clinical response to abatacept treatment in polyarticular JIA (pJIA), and to assess whether changes from baseline in S100A8/A9 or S100A12 can be better prognostic markers for response to abatacept treatment than CRP in pJIA.

Methods:
Data are from a phase III trial of SC abatacept for the treatment of pJIA (NCT01844518). This 24-month, single-arm, open-label, international, multicentre, two-part study included male and female patients with pJIA aged 2–17 years. This analysis examined the correlation between biomarkers (S100A8/A9, S100A12 and high-sensitivity CRP [hsCRP]) and disease activity (measured using Juvenile Arthritis Disease Activity Score [JADAS]) at baseline, baseline biomarker values as predictors of future treatment response (ACR and JADAS endpoints), and the correlation between change from baseline in biomarker values and treatment response at Day 113.

**Results:**

Of 219 total patients, 158 (72%) had S100A8/A9 values and 155 (71%) had S100A12 values at baseline. Median S100A8/A9 and S100A12 values were 3295 ng/mL (normal range, 716–3004 ng/mL) and 176 ng/mL (normal range, 32–385 ng/mL), respectively. S100A8/A9, S100A12 and hsCRP (median 0.20 mg/dL; normal <0.6 mg/dL) had a low-to-moderate but significant association with disease activity at baseline; coefficients for associations between JADAS71-CRP low disease activity (LDA) and the biomarkers S100A8/A9, S100A12 and hsCRP were 0.23 (p=0.0038), 0.16 (p=0.0448) and 0.26 (p=0.0001), respectively. Baseline S100A8/A9 level above the median was associated with lower odds of ACR100 at Day 113 (p=0.0052). Figure 1 shows the associations of baseline biomarker values with Day 113 ACR and JADAS scores in the overall population. Baseline S100A8/A9 or S100A12 did not significantly influence ACR50 or ACR70 responses at Day 113, but high baseline values were associated with reduced odds of ACR90 (p=0.01), ACR100 (p=0.005), ACR-inactive disease (ID) (p=0.0001), and JADAS71-CRP (LDA) (p=0.02). By Day 477, elevated baseline S100A12 was still significantly associated with lower odds of ACR100 overall (0.467; p=0.0248) but baseline S100A8/A9 was not; at Day 645, neither was significantly associated with ACR100 response. At Day 113, changes from baseline in S100A8/A9 and S100A12 were correlated with ACR100 (coefficients of 0.22 [p=0.0082] and 0.26 [p=0.0015], respectively) and with ACR-ID (0.22 [p=0.0067] and 0.26 [p=0.0014], respectively); change in hsCRP was not significantly correlated with disease response.

**Conclusion:**

S100A8/A9 and S100A12 may serve as prognostic biomarkers to predict response to abatacept treatment at Day 113. Changes from baseline S100A8/A9 and S100A12 levels were more highly correlated with efficacy outcomes including ACR100 and ACR-ID at Day 113 compared with hsCRP.
References:

Figure 1. Effect of baseline S100A8/A9 or S100A12 level on efficacy response at Day 113 in the overall population

<table>
<thead>
<tr>
<th>Efficacy response</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR50</td>
<td>0.820 (0.402, 1.674)</td>
<td>0.5864</td>
</tr>
<tr>
<td>ACR70</td>
<td>0.698 (0.372, 1.311)</td>
<td>0.2636</td>
</tr>
<tr>
<td>ACR90</td>
<td>0.393 (0.193, 0.800)</td>
<td>0.0100</td>
</tr>
<tr>
<td>ACR100</td>
<td>0.269 (0.107, 0.876)</td>
<td>0.0052</td>
</tr>
<tr>
<td>ACR-ID</td>
<td>0.235 (0.112, 0.494)</td>
<td>0.0001</td>
</tr>
<tr>
<td>JADAS71-CRP (LDA)</td>
<td>0.475 (0.249, 0.907)</td>
<td>0.0242</td>
</tr>
</tbody>
</table>

ACR50/70/90/100/50/70/90/100% improvement in ACR criteria; ID: inactive disease; JADAS71-CRP: Juvenile Arthritis Disease Activity Score in 71 joints using CRP; LDA=low disease activity; OR=odds ratio.

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