IL-18: A potential inflammation biomarker in Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome (WAS) is a rare primary immunodeficiency disease caused by dysregulation of the actin cytoskeleton in hematopoietic cells. Clinical features include recurrent infections, thrombocytopenia, and predisposition to hematological malignancy, which necessitate definitive treatment in the form of hematopoietic stem cell transplant (HSCT) or gene therapy. A significant inflammatory phenotype occurs in 70–80% of children, including severe eczema, inflammatory bowel disease (IBD), and vasculitis, which can be difficult to manage [1]. Furthermore, about 20% of patients have ongoing or episodic autoinflammation after HSCT, particularly where myeloid chimerism is low [2–5]. We sought to characterize the inflammatory signature in WAS patients, with a view to identifying potential biomarkers and opportunities for targeted therapeutic interventions.

Serum cytokine concentrations of IL-1β, IL-18, IL-18bp, IL-6, TNF-α, IFN-γ, and chemokines IP-10 and MCP-1 were quantified from healthy donors and WAS patients using ELISA (IL-18 and IL-18bp) or multiplex Meso Scale Discovery (MSD) assays. Circulating protein levels were correlated to clinical parameters such as presence of inflammatory symptoms or need for anti-inflammatory medications and laboratory markers including donor chimerism and vector copy number (VCN) for those post-HSCT or gene therapy, respectively (Table 1).

The study cohort consisted of 12 patients with WAS, from whom samples were collected over a 2-year period (2017–2019). Four WAS patients were followed through definitive stem cell therapy allowing for serial measurements, giving a total of 16 patient samples, which were compared with 19 healthy control (HC) samples. Of the WAS samples, five were predefinitive treatment and 11 post-treatment with either HSCT or gene therapy. Note that 55% of those post-HSCT or gene therapy were considered to have partial myeloid correction (<50% donor chimerism or VCN < 0.5 in myeloid cells). All WAS patients prior to definitive therapy were noted to have moderate-severe eczema. Additional inflammatory features such as IBD, vasculitis, and arthritis were seen in 27% of those either pre- or post-definitive therapy with partial myeloid correction. In contrast, none of the patients at least 1-year post-HSCT or gene therapy with good myeloid correction had ongoing inflammatory symptoms (Table 1).

The most striking finding was that serum IL-18 levels in WAS were significantly elevated when compared with HC, particularly in patients with IBD (Fig. 1A). Interestingly, IL-18 remained elevated in patients post-HSCT with partial myeloid correction, but returned to normal in those with good myeloid correction, correlating with the presence or absence of inflammatory symptoms. These observations were further confirmed in a WAS patient in whom multiple sampling was carried out; a decline in circulating IL-18 level after gene therapy correlated with improvement in inflammatory symptoms and weaning of anti-inflammatory medications (Fig. 1B and Patient 8, Table 1). Circulating levels of other candidate pro-inflammatory cytokines and chemokines were otherwise comparable between WAS and healthy donors (Supporting Information Fig. S1).

IL-18 is a member of the IL-1 family of cytokines. Epithelia and myeloid (monocytes, macrophages, and dendritic cells) lineage are the predominant source of IL-18. Although originally described as an important inducer of IFN-γ and Th1 differentiation, increasing evidence supports the expanding role of IL-18 in mediating inflammation, through activation of Th2, IL-17-producing γδ T cells, and macrophages [6]. Release of bioactive IL-1β is dependent on inflammasome activity [7] and the finding of elevated serum IL-18 is consistent with our previous findings of dysregulated inflammasome activity in WAS [8]. Bioactive IL-1β secretion is also inflammasome dependent, and we have previously demonstrated increased IL-1β secretion in murine and human in vitro models of infection and inflammation [8]. Herein, we did not observe elevated levels of IL-1β in WAS serum, most likely due to its short half-life; this labile nature makes it difficult to detect, as reported in patients with other autoinflammatory conditions [9]. Support for a contributing role of IL-1β in WAS-associated inflammation, however, is the improvement in symptoms for both of the patients in our cohort receiving the recombinant IL-1 receptor (IL-1R) antagonist (Table 1).

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Table 1. Characteristics of WAS patients in study cohort

<table>
<thead>
<tr>
<th>Patient</th>
<th>WAS mutation</th>
<th>Pre-/posttreatment (conditioning)</th>
<th>Time post treatment</th>
<th>IL-18 (pg/mL)</th>
<th>Myeloid correction</th>
<th>Lymphoid correction</th>
<th>Inflammatory features</th>
<th>Anti-inflammatory medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c.143C&gt;T (p.Thr48Ile)</td>
<td>Post-HSCT (Flu/Treo/Campath)</td>
<td>8 years</td>
<td>284.3</td>
<td>100%</td>
<td>100%</td>
<td>Resolved eczema</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Deletion of whole gene</td>
<td>Post-HSCT (Bu/Cyclo)</td>
<td>10 years</td>
<td>211.8</td>
<td>100%</td>
<td>100%</td>
<td>Resolved eczema</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>c.374G&gt;A (p.Gly125Glu)</td>
<td>Pre</td>
<td>-</td>
<td>241.2</td>
<td>-</td>
<td>-</td>
<td>Eczema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-HSCT (Flu/Treo/Campath)</td>
<td>1 year</td>
<td>1563.8</td>
<td>44%</td>
<td>98%</td>
<td>Ecema/skin GvHD</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>c.302T&gt;C (p.Leu101Pro)</td>
<td>Pre</td>
<td>-</td>
<td>813.99</td>
<td>-</td>
<td>-</td>
<td>Eczema</td>
<td>Eumovate (sirolimus and prednisolone for hemolytic anemia)</td>
</tr>
<tr>
<td>5</td>
<td>c.374G&gt;A (p.Gly125Glu)</td>
<td>Post-GT (Bu/Flu)</td>
<td>1 year</td>
<td>456.1</td>
<td>VCN 0.18</td>
<td>VCN 0.63</td>
<td>Resolved eczema</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>c.1483DelG (p.Asparagine495Methionine fs164X)</td>
<td>Pre</td>
<td>-</td>
<td>804.6</td>
<td>-</td>
<td>-</td>
<td>Eczema</td>
<td>Eumovate (prednisolone for cytopenias)</td>
</tr>
<tr>
<td>7</td>
<td>c.250T&gt;C (F84L)</td>
<td>Post-HSCT (Flu/Melph)</td>
<td>18 years</td>
<td>299.3</td>
<td>0%</td>
<td>91%</td>
<td>Intermittent arthritis, resolved eczema</td>
<td>Naproxen</td>
</tr>
<tr>
<td>8</td>
<td>c.97C&gt;T (p.Q33X)</td>
<td>Pre</td>
<td>-</td>
<td>3000+</td>
<td>-</td>
<td>-</td>
<td>Eczema, IBD</td>
<td>Prednisolone, anakinra, topical hydrocortisone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-GT (Bu)</td>
<td>1 month</td>
<td>1874.4</td>
<td>VCN 0.92</td>
<td>-</td>
<td>Eczema, IBD</td>
<td>Prednisolone, anakinra, topical hydrocortisone</td>
</tr>
<tr>
<td>9</td>
<td>c.1225G&gt;T (p.Gly409)*</td>
<td>Post-HSCT (Flu/Treo/Campath)</td>
<td>5 years</td>
<td>14429.7</td>
<td>7%</td>
<td>93%</td>
<td>Vasculitis, IBD, eczema</td>
<td>Weaning prednisolone, anakinra, colchicine, sulphasalazine, topical trimovate</td>
</tr>
</tbody>
</table>

(Continued)
Anakinra. This treatment inhibits signaling through the IL-1R complex, the receptor for IL-1β and IL-1α (but not IL-18). IL-18 bioactivity is physiologically regulated via its binding protein, IL-18 binding protein (IL-18bp). We found no significant difference in serum IL-18bp levels between WAS patients and HC (data not shown), and the ratio of IL-18 to IL-18bp was double that of healthy controls in four patients tested (0.14 vs. 0.076, respectively).

IL-18 is an unusually stable cytokine due to the lack of gene-associated RNA destabilizing elements, making it an attractive biomarker of inflammation. The cytokine is increasingly utilized in diagnosis and follow-up of other autoinflammatory conditions, such as macrophage activation syndrome, systemic juvenile idiopathic arthritis (sJIA), and adult onset Still disease (AOSD) [6]. We propose that

![Figure 1](https://example.com/figure1.png)
IL-18 may also be a useful biomarker for inflammation in WAS and speculate that it may also play a direct pathophysiological effector role. Use of recombinant IL-18bp or anti-IL-18 therapies may therefore be useful for treatment of inflammation in WAS, and further studies of larger cohorts evaluating IL-1 family cytokines are warranted.

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References


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