ABSTRACT
Interleukin (IL)−6 inhibition has been approved for the treatment of rheumatoid arthritis, systemic juvenile arthritis, polyarticular juvenile idiopathic arthritis, giant cell arteritis, and, in some countries, Castleman’s disease. IL-6 has also been implicated in several non-rheumatoid arthritis inflammatory and immune conditions such as systemic sclerosis, vasculitides, systemic lupus erythematosus, and psoriatic arthritis. In orphan diseases, such as systemic sclerosis, which are associated with significant morbidity and mortality and for which there are no approved treatments, IL-6 inhibition may offer a promising treatment strategy. It is also becoming clear that IL-6 may have an important role not only in inflammatory and immune diseases but also in non-immune mediated diseases such as endogenous depression and depression associated with chronic inflammatory conditions. Several studies have explored the effect of IL-6 pathway inhibition in Crohn’s disease and adult-onset Still’s disease, suggesting that IL-6 may be important in their pathogenesis.


CONSIDERING THE ROLE OF IL-6 IN NON-RHEUMATOID ARTHRITIS INFLAMMATORY AND IMMUNE DISEASE
IL-6 inhibition is effective and approved for the treatment of several inflammatory diseases including rheumatoid arthritis, systemic juvenile arthritis, polyarticular juvenile idiopathic arthritis, and giant cell arteritis. In some countries, it is also approved for the lymphoproliferative disorder Castleman’s disease. However, IL-6 inhibition is ineffective in the treatment of certain other inflammatory diseases such as ankylosing spondylitis. For example, the BUILDER one study, which compared the human anti-IL-6 receptor (IL-6R) monoclonal antibody tocilizumab with placebo in patients with ankylosing spondylitis, tocilizumab was ineffective in treating tumour necrosis factor (TNF) inhibitor-naive patients. In the accompanying sections, we will review the evidence that supports the application of IL-6 blocking interventions in the management of specific diseases.

Systemic sclerosis
Systemic sclerosis is an autoimmune disease causing significant morbidity and mortality. There is no approved treatment for this disease. Evidence shows that polymorphisms in the IL-6 gene are associated with systemic sclerosis. In patients with systemic sclerosis, spontaneous production of IL-6 and soluble IL-6 receptor (sIL-6R) by peripheral blood leukocytes is elevated compared with healthy controls. This increase in IL-6 concentrations is correlated with the modified Rodnan skin score, with patients with high IL-6 concentrations tending to have worse outcomes.

Vasculitis syndromes
Other conditions in which IL-6 has been implicated include vasculitides. The association between cytokines and different vasculitides are listed in table 1. Elevated IL-6 activity is often associated with active disease in many vasculitides (table 1). In patients with Takayasu’s arteritis, a disease affecting the large blood vessels, serum IL-6 concentrations have been shown to be elevated significantly during the active phase of the disease compared with healthy controls. In Behçet’s disease, although increased concentrations of IL-6 are seen during active disease and remission, they are higher during active disease.

A phase II randomised, placebo-controlled trial of tocilizumab in giant cell arteritis recruited patients with giant cell arteritis who were aged 50 and over and had new onset or relapsing disease. Thirty patients were randomised 2:1 to receive either tocilizumab (8 mg/kg) or placebo intravenously. Thirteen infusions were given at 4-week intervals until week 52. Both groups received oral prednisolone, starting at 1 mg/kg per day and tapered down to zero according to a standard reduction scheme defined in the study protocol. The primary outcome was the proportion of patients who achieved complete disease remission at a prednisolone dose of 0.1 mg/kg/day at week 12. The mean time to relapse and the mean time to prednisolone dose were longer in the tocilizumab group than in the placebo treated group (figure 3). These differences were statistically significant, showing that tocilizumab allows for more rapid withdrawal or tapering of steroid treatment. The placebo-treated group had a higher incidence of cardiovascular complications (five patients) than the tocilizumab-treated group (one patient).

The GIACTA study, a 52-week, phase III, global, randomised, double-blind, placebo-controlled trial investigating the efficacy
and safety of tocilizumab in patients with giant cell arteritis, has also shown the efficacy of adding tocilizumab to steroid tapered therapy in patients with giant cell arteritis. Tocilizumab treatment combined with prednisone tapering over 26 weeks was superior to placebo plus prednisone tapering over 26 or 52 weeks in terms of patients achieving sustained glucocorticoid remission.10 Recently, the FDA approved tocilizumab for the treatment of giant cell arteritis in the US.11 There is also evidence for involvement of IL-6 in polymyalgia rheumatica, with patients having increased serum IL-6 concentrations compared with normal controls, and changes in serum IL-6 concentrations correlating with clinical manifestations during prolonged corticosteroid therapy.12 Because polymyalgia rheumatica and giant cell arteritis are clinically related syndromes, by extrapolation there is a strong interest in the potential of using tocilizumab therapy in patients who have long-standing polymyalgia rheumatica requiring high doses of steroids.

**Psoriatic arthritis**

Evidence exists that IL-6 concentration is elevated in patients with psoriatic arthritis, with patients having higher serum and synovial concentrations of IL-6 compared with healthy volunteers and patients with skin psoriasis, though lower levels than rheumatoid arthritis patients.20–23 Elevated IL-6 in patients with psoriatic arthritis has also been shown to correlate with the number of painful and swollen joints, rheumatology attitudes index, physician’s assessment of disease, serum CRP, and ESR.20,22 In a 24-week randomised, double-blind, placebo-controlled, dose-ranging study, patients with active psoriatic arthritis were randomised 1:1:1:1 to receive subcutaneous placebo or subcutaneous clazakizumab, an anti-IL-6 monoclonal antibody, at dosages of 25, 100, or 200 mg every 4 weeks with or without methotrexate.24 The primary endpoint was response rate according to ACR20 at week 16. This study showed that clazakizumab therapy was able to significantly improve arthritis score, with approaching 50% of patients achieving ACR20 response in the clazakizumab-treated group compared with 29% receiving placebo treatment (figure 4).

However, only small improvements in skin disease were reported (table 2). This study shows that clazakizumab could be useful in improving physical function in patients with psoriatic arthritis who have well-controlled skin disease.

**CONSIDERING THE ROLE OF IL-6 IN NON-IMMUNE MEDIATED DISEASE**

**Depression**

A more controversial topic is the role of IL-6 in non-immune mediated conditions such as endogenous depression. The ability of IL-6 to mediate function of different tissues is well known, and IL-6 and the soluble receptor system are well designed to modify systemic effects in tissues and organs away from...
The prediction, therefore, is that if we interfere with IL-6 biology we will likely see consequential changes in metabolic and psychological neuroplasticity systems.

Available data suggest that some degree of balance needs to be maintained between pro-inflammatory and anti-inflammatory cytokines to regulate synaptic plasticity and memory formation in individual neurons and the whole brain. It is well known that depression is common in patients with chronic inflammatory conditions. A major survey in patients with arthritis found that one third of respondents had at least one of anxiety and/or depression. There is also evidence that inflammatory conditions are strongly associated with depression. Figure 5 illustrates that patients with rheumatoid arthritis are more likely to have depression, especially if they have active arthritis, as reflected by increased CRP concentration, with CRP concentration associated with the severity of depression.

It has long been supposed that the reason why chronic inflammatory disease causes depression is that cytokines such as IL-6 and TNFα can reach the brain through the hypothalamic-pituitary-adrenal axis. In addition, it is also proposed that these cytokines act on the blood-brain barrier to relay inflammatory signals from the periphery to the brain. In hepatitis C, an inflammatory condition of the liver, type-1 interferon treatment may yield depressive symptoms by lowering brain serotonin levels, altering IL-6 and IL-8 concentrations and increasing cortisol and adrenocorticotropic hormone concentrations.

### Table 1 Vasculitis syndromes: associated cytokines

<table>
<thead>
<tr>
<th>Vasculitis syndrome</th>
<th>TNF-α</th>
<th>IL-1</th>
<th>IL-2</th>
<th>IL-6</th>
<th>IL-8</th>
<th>IL-10</th>
<th>IL-12</th>
<th>MCP1</th>
<th>IFN-γ</th>
<th>TGF-β</th>
<th>VEGF</th>
<th>PDGF</th>
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<tr>
<td>Wegener’s granulomatosis</td>
<td>+</td>
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<td>Giant cell arteritis</td>
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<td>Henoch–Schonlein purpura</td>
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<tr>
<td>Takayasu’s arteritis</td>
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IFN, interferon; MCP1, monocyte chemoattractant protein 1; PDGF, platelet derived growth factor; TNF, tumour necrosis factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

Figure 3 Clinical efficacy of tocilizumab in giant cell arteritis.
The findings from a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions suggest that cytokines may have a causal role in depression, with the implication that cytokine modulators may be novel drugs for depression in patients with chronic inflammation. The role of cytokines in endogenous depression is controversial. However, a possible role of cytokines, including IL-6, in endogenous depression, as well as depression that occurs in patients with chronic inflammatory disease, is biologically plausible. A meta-analysis has provided strong evidence that concentrations of cytokines, including TNFα and IL-6, are elevated in patients with major depression. However, following a negative review from the FDA, Choy EH, et al.

**Figure 4** Clinical efficacy of clazakizumab in psoriatic arthritis. MTX, methotrexate.

Table 2 Clazakizumab PASI scores in psoriatic arthritis

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=41)</th>
<th>Clazakizumab 25 mg (n=41)</th>
<th>Clazakizumab 100 mg (n=42)</th>
<th>Clazakizumab 200 mg (n=41)</th>
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<tr>
<td><strong>Week 16</strong></td>
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<tr>
<td>PASI 75</td>
<td>6 (14.6)</td>
<td>5 (12.2)</td>
<td>7 (16.7)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>PASI 50</td>
<td>15 (36.6)</td>
<td>14 (34.1)</td>
<td>13 (31.0)</td>
<td>8 (19.5)</td>
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<tr>
<td><strong>Week 24</strong></td>
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</tr>
<tr>
<td>PASI 75</td>
<td>5 (12.2)</td>
<td>8 (19.5)</td>
<td>12 (28.6)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>PASI 50</td>
<td>12 (29.3)</td>
<td>17 (41.5)</td>
<td>16 (38.1)</td>
<td>10 (24.4)</td>
</tr>
</tbody>
</table>

PASI, psoriasis area severity index.

**Figure 5** Increased CRP concentration is associated with depression in rheumatoid arthritis. BDI-II, Beck Depression Inventory II score; CRP, C-reactive protein.

with acknowledging that symptoms exist. Yet, in addition to a reaction to a set of circumstances, there is real biology underlying depression.

**CONSIDERING IL-6 TO IMMUNITY AND BEYOND—THE FUTURE**

Various off-label uses of tocilizumab are being reported in the literature. A pilot randomised trial has been conducted in active Crohn’s disease, suggesting a clinical effect; a case series has been reported in adult-onset Still’s disease and a case report in Takayasu’s arteritis, indicating that IL-6R inhibition with tocilizumab may be a future treatment option for these conditions. A study has also shown that tocilizumab may have activity in the corticosteroid refractory graft versus host disease and in chronic kidney rejection. Individual case reports also exist in amyloidosis, polymyositis, and refractory relapsing polychondritis. There have also been reports of successful treatment of refractory diseases, including Behçet’s disease, uveitis, and TNF receptor-associated periodic syndrome. Heterogeneity in synovial phenotypes may explain heterogeneity in response to drug therapy in rheumatoid arthritis and possibly other autoimmune diseases. Identifying and stratifying patients by synovial phenotype, using serum biomarkers, may assist in future clinical decision making.

IL-6 pathway inhibition may provide hope as a treatment strategy, not only for rheumatic diseases with no currently approved treatment options, but also for other conditions such as giant cell arteritis, with potential as a glucocorticoid sparing approach to treatment. Targeting IL-6 may also represent a possible future treatment or disease modification approach for patients with depression with or without a chronic inflammatory condition.

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