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 psooriatic 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.

A panel of international experts in the field of rheumatology recently came together to consider indications beyond rheumatoid arthritis for IL-6 pathway inhibitors.

**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-6R (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.

The FaSScinate study was a small phase II randomised proof of concept study, which randomised 87 patients with systemic sclerosis to either placebo or subcutaneous tocilizumab treatment. Many of the patients had chronic established systemic sclerosis. The primary endpoint was the difference in mean change from baseline in modified Rodnan skin score at week 24. The least squares mean change in modified Rodnan score at 24 weeks was −3.92 in the tocilizumab group and −1.22 in the placebo group (difference −2.70, 95% CI −5.85 to 0.45; P=0.0915). At the end of the study, week 48, there was numerical difference with less progression in skin thickening observed in the tocilizumab group (−6.33) compared with the placebo-treated group (−2.77) [figure 1]. The difference just failed to reach statistical significance (treatment difference −3.55, −7.23 to 0.12; P=0.0579), which may be a result of the small number of patients in each group.

Importantly, patients who were treated with tocilizumab had less reduction in forced vital capacity at 48 weeks than the placebo-treated group (P=0.0373) [figure 2]. Therefore, IL-6 inhibition may be a promising strategy for this orphan disease for which there is currently no effective treatment.

**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. 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. Bechet’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 GIACCTA 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. 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.

Systemic lupus erythematosus
Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by autoantibody formation resulting in diverse symptoms. Patients with SLE have elevated serum concentrations of IL-6, which are higher in active versus inactive disease.13-15 Serum IL-6 was shown to correlate with SLE activity index (SLEDAI), erythrocyte sedimentation rate (ESR), and serum C reactive protein (CRP) concentrations16 and to correlate with clinical manifestations such as anaemia.16 In a murine model of SLE, treatment with an anti-murine IL-6 monoclonal antibody showed beneficial effects on autoimmunity and suppressed the production of anti-double-stranded deoxyribonucleic acid (anti-dsDNA).17 In this context, anti-IL-6 monoclonal antibody inhibited B cell and T cell proliferation and mixed lymphocyte reactions and prevented the development of severe kidney disease.17

In a small open-label study, 16 patients with mild to moderate SLE were treated bi-weekly for 12 weeks with one of three doses of tocilizumab: 2, 4, or 8mg/kg.18 Patients were followed for an additional 8 weeks. Tocilizumab reduced disease activity in patients with SLE, and significant improvements in SLEDAI and Systemic Lupus Activity Measure (SLAM) scores were observed after 14 weeks. Arthritis improved in all seven patients with symptoms at baseline, and four patients saw their symptoms resolved. Illei et al. also showed that tocilizumab therapy reduces autoantibody production in SLE: the frequency of plasma cells decreased significantly over 14 weeks; levels of anti-dsDNA autoantibodies decreased by a median of 47% in patients treated with 4mg/kg and 8mg/kg doses of tocilizumab.

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 200mg over a 24-week double-blind treatment phase.24 While there was no significant difference from placebo among the treatment arms for the primary endpoint (proportion of patients achieving the SLE Responder Index (SRI-4) at week 24), there was improvement measured in the primary and key secondary end points with the 10mg dose. Additionally, in a post-hoc analysis of the subgroup of patients with high disease activity at baseline showed higher response rates with the 10mg dose. To date, there has been no large placebo-controlled trial in this condition.

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 primary site of inflammation or disease activity. 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>
<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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</thead>
<tbody>
<tr>
<td>Wegener’s granulomatosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<td>Giant cell arteritis</td>
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<td>Kawasaki disease</td>
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<td>Henoch–Schönlein purpura</td>
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<td>Behçet’s disease</td>
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<td>Takayasu’s arteritis</td>
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<td>+</td>
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</tbody>
</table>

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.
There is a need to train physicians to be more comfortable in talking to patients. A controlled trial is under way to examine the effect and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy. Sirukumab was shown to have a specific effect of IL-6 cytokine blockade as opposed to the receptor blockade, although it remains as to whether this may be unique to IL-6 blockade, and whether it is a consequence of circumstances, there is real biology underlying depression.

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. The findings above have led to interest in IL-6 inhibition as a possible treatment for depression and associated disorders.

Improvement in mental health and a 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. The findings above have led to interest in IL-6 inhibition as a possible treatment for depression and associated disorders.

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 Behcet’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.

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. The findings above have led to interest in IL-6 inhibition as a possible treatment for depression and associated disorders.

Table 2 Clazakizumab PASI scores in psoriatic arthritis

<table>
<thead>
<tr>
<th>Week 16</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>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 24</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>
</tr>
</thead>
<tbody>
<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.

Elevated levels of endogenous IL-6 in systemic anti-IL-6 receptor antibody treatment. *Biol Blood Marrow Transplant* 2011;17:1862–8.


