## Emerging Drug List

### INFLIXIMAB

<table>
<thead>
<tr>
<th>Generic (Trade Name):</th>
<th>Infliximab (Remicade®)</th>
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<tr>
<td>Manufacturer:</td>
<td>Schering Canada Inc.</td>
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<tr>
<td>Indication:</td>
<td>For the treatment of patients with ankylosing spondylitis (AS) who have severe axial skeleton symptoms and elevated serological markers of inflammatory activity; and who have responded inadequately to conventional therapy.</td>
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<td>Current Regulatory Status:</td>
<td>In Canada, infliximab is marketed by Schering Canada Inc., under the brand name Remicade®, for use in rheumatoid arthritis and active Crohn’s disease. Schering-Plough has announced that the European Commission of the European Union has approved centralized marketing of infliximab for the treatment of AS, as described in the Indication section above. The status of a Canadian marketing licence is unknown at the time of this review.</td>
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<tr>
<td>Description:</td>
<td>Infliximab is a chimeric monoclonal antibody that targets and binds tumour necrosis factor (TNF) alpha, inhibiting its activity. TNF alpha is implicated in the early-disease stage of AS. After parenteral administration, infliximab has a terminal half-life of approximately eight to 9.5 days. Infliximab’s route of clearance is still unknown. In Canada, Remicade® is supplied as a preservative-free vial of lyophilized powder containing 100 mg of infliximab.</td>
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<td>Current Treatment:</td>
<td>AS, which is the most common form of spondyloarthopathy, presents more often in men. Patients tend to exhibit stiffness and back pain that typically start in their late teens and early 20s. Sacroiliitis can be noted radiographically; and in some cases, acute anterior uveitis may be documented. Symptom management generally consists of tailored regular exercise and specific therapies (i.e., hydrotherapy, physical therapy), with the use of non-steroidal anti-inflammatory drugs (NSAIDs). Sulfasalazine may be used as a second-line agent. Disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine or gold, have been investigated, with unimpressive results. Steroids that are injected into affected areas have shown some success in refractory disease. Immunosuppressive or immunoregulatory drugs such as chlorambucil, cyclosporine and azathioprine are used rarely. Other adjunctive therapies that include analgesics or muscle relaxants have been used. Recently investigated drugs include etanercept, thalidomide and pamidronate.</td>
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<td>Cost:</td>
<td>The Canadian price for Remicade® is $940 per 100 mg vial.</td>
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Evidence: In a three-month, placebo-controlled trial designed to assess the utility of infliximab in AS, patients (n=70) were randomized to receive either placebo or infliximab 5 mg/kg intravenous infusions administered in a series of three cycles (weeks 0, 2 and 6). The primary endpoint was a 50% or greater improvement in the Bath AS disease activity index (BASDAI). Patients in the active group met this endpoint [53%; 95% confidence interval (CI): 37 to 69] more often than those who received placebo (9%, 95% CI: 3 to 22) at the end of the study. Also, the use of NSAIDs was diminished with active treatment (p=0.004). During an observational extension to this trial, patients (n=65) were followed in an open-label fashion for up to 54 weeks. Infliximab was administered at the same dosage as previously investigated, at six-week intervals, with the exception of patients in the placebo group who received an extra infusion at week 14. On intention-to-treat analysis, at the end of the study, 47% of the infliximab patients and 51% of the placebo and infliximab patients met the primary endpoint, which was described in the previous paragraph. Reduction in NSAID use was still apparent. A similar three-month, placebo-controlled trial (n=40) found positive results with the same infliximab dosage. This study included patients with spondylarthropathies, although 25% of patients had AS with or without peripheral arthritis. At the October 2003 annual meeting of the American College of Rheumatology, the results of a two-year follow-up study were released. Overall, investigators concluded that efficacy was maintained over a prolonged period, with no tolerability penalty evident. An economic evaluation suggested that infliximab offered an improved quality of life for patients with AS, leading to a 31% reduction in disease-associated costs (excluding medication costs). Infliximab’s efficacy or safety was examined in several uncontrolled trials and in two case reports. In two trials, a response was observed in some patients at a lower dosage of 3 mg/kg. A published review of some of the available evidence discussed one controlled study, four open-label trials, a few case reports and some histological data.

Adverse Effects: In the largest controlled trial, infections of the upper respiratory tract were the most frequently encountered complaint (51% infliximab versus 35% placebo; p=0.227). Serious adverse effects were documented in the infliximab group. These occurred as one case of systemic tuberculosis; one case of fever, enlarged lymph nodes and pulmonary lesions; and one case of transient leukopenia. During the extension study, serious adverse
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Events requiring withdrawal included increased transaminase levels; a lupus-like rash; and possible antinuclear antibody associated symptoms (peripheral arthritis) in three cases. Antinuclear antibodies were evident in 25% of patients at the end of the study, when the results of both arms were combined.9

Commentary:

A growing amount of literature explores new technologies aimed at altering TNF alpha activity in patients with AS. The Canadian Rheumatology Association has published a consensus on the use of these agents in the treatment of spondyloarthopathies, recommending their use in some patients refractory to traditional therapy (i.e., NSAID, sulfasalazine in peripheral arthritis).23 The international assessments in AS consensus document, published subsequent to the Canadian guidelines, offers different guidance, but it also suggests that a specialist should implement the use of anti-TNF alpha agents in refractory disease.

Several issues may be of concern to drug-plan managers and decision makers. These include the price of the drug, its potential for long-term use and the possibility of “prescription creep,” if higher than recommended dosage or increased dosage frequency are used.

Unanswered questions remain regarding the optimal dose, long-term safety and impact on disease progression.23,24 Although no trials have compared infliximab with other TNF alpha inhibitors such as etanercept, the choice of drug may be influenced by the route of administration (etanercept is administered subcutaneously) and the perception of potential for harm.24

References:


