Extracorporeal Immunoadsorption Treatment for Rheumatoid Arthritis

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Summary

✓ Immunoadsorption treatment is a non-drug therapy for rheumatoid arthritis. The treatment is based on filtering the patient’s plasma through a column containing staphylococcal protein A.

✓ The treatment is effective in alleviating the symptoms of severe rheumatoid arthritis in some patients. Data on long-term outcomes are not available.

✓ The mechanism of action of this treatment is unclear.

✓ Most adverse effects are associated with the apheresis procedure.

✓ The cost per 12 week course of treatment is likely to be more than C $20,000. The cost-effectiveness of the technology is not yet established.

The mechanism of action is unclear. Sasso et al found that the immunoglobulin-binding capacity of the Prosorba Column corresponds to only 1.5% of the total IgG in the circulation. At the end of treatment, levels of CICs remain essentially unchanged.² Radioimmunoassay studies indicate that the Prosorba Column releases small quantities of SPA into the circulation and that the protein may have an immunomodulatory effect.³

Regulatory Status

The Prosorba Column is indicated for the reduction of the signs and symptoms of moderate to severe RA in adults with long-standing disease, who have failed or are intolerant of disease-modifying anti-rheumatic drugs (DMARDs). Licensing approval for this indication was granted by Health Canada in February 2000 (Dr. Kathleen Savage, Health Canada: personal communication, 2001 Oct 3). The U.S. Food and Drug Administration (FDA) approved the product for use in this application in March 1999, and the CE Mark approval in Europe was granted in March 2000.

Initial approval for the device as a treatment for idiopathic thrombocytopenia purpura (ITP), an immune disorder, was granted by the FDA and by Health Canada in 1987.

Patient Group

Rheumatoid arthritis is a chronic, autoimmune disease characterized by inflammation in the lining of the joints and, in some cases, in other organs. Some patients experience attacks of the disease followed by periods of remission. In others, RA follows a more continuous progression. The disease can eventually result in destruction of the joints and cause severe pain and disability.⁴
RA affects about 300,000 Canadians, and is twice as common in females than in males. Young et al estimate that in their first five years of treatment 11% of RA patients fail to respond to, or are unable to tolerate treatment with at least two of the standard drug therapies for this condition. About 10% of RA patients do not respond to any of the currently available therapies. Some of these patients may be eligible for the Prosorba Column treatment.

Current Practice

Treatment of RA may use a stepped approach, usually beginning with nonsteroidal antiinflammatory drugs (NSAIDs) and later moving to DMARDs. Recently, more aggressive early treatment with DMARDs, sometimes in combination with NSAIDS or corticosteroids, has been advocated as more effective in preventing joint damage. Immunosuppressant drugs may also be used in severe cases of RA. Most patients cannot tolerate long-term treatment with these drugs, and the effectiveness of drug therapy in RA diminishes over time. Treatment may also include non-drug therapies, such as physiotherapy and surgical procedures, such as arthroscopy (to clean out debris in the joint); synovectomy (removal of the joint lining) and joint replacement.

Administration and Cost

The Prosorba Column with apheresis is used once a week for 12 weeks. Guidelines prepared on behalf of the Canadian Arthritis Network (CAN) note that the rationale for this course of treatment came from protocols for ITP and that no other treatment regimen has been studied in RA. The CAN guidelines state that the price for each single-use Prosorba Column is C $1,450. There are also costs of about $250 for the disposable equipment, set-up and operating costs for each session. Based on this estimate, the cost of each course of treatment in Canada will be over C $20,000. Most patients will require repeat treatments. The Arthritis Society in Canada estimates the annual cost of treatment with new drug therapies, such as etanercept and infliximab, to be between C $15-20,000. Another new rheumatoid arthritis drug, leflunomide, costs about C $3,600 for an annual course of treatment.

Griffith and Slurzberg give an estimate of US $25,000 per patient for the annual, direct medical costs of providing the Prosorba Column therapy in the U.S. They note that the cost-effectiveness of the Prosorba Column therapy will depend on the patient population in which it is used and the other treatment options available to these patients.

Rate of Technology Diffusion

Diffusion of the Prosorba Column will be influenced by the unmet treatment needs of patients with severe RA, and also by issues of eligibility and compliance. Based on clinical trial results, there may be a substantial patient drop out rate for the procedure. Moreover, the contraindications for some patients with additional medical conditions will restrict eligibility for this therapy. Policies regarding public funding of this technology will also influence its diffusion. Diffusion might also be affected by changes to the use of SPA-related immunoadsorption treatments that are suggested as further knowledge emerges on the mechanism of action by which the Prosorba Column provides a therapeutic response.

Concurrent Developments

A number of new agents for rheumatoid arthritis have recently been introduced. Many more are in various stages of development. They include the DMARD leflunomide (Arava®) and biological products such as etanercept (Enbrel®), infliximab (Remicade®), and anakinra (Kineret™).

The Evidence

The strongest evidence supporting the efficacy of the Prosorba Column comes from a double-blind, randomized, placebo controlled study conducted in the U.S. Patients in the trial had been diagnosed with RA for an average of 15.5 years and had failed an average of 4.2 second-line drug treatments prior to entry. Forty-seven patients received treatment with the Prosorba Column and 44 received the sham treatment (apheresis only). Efficacy was evaluated seven to eight weeks after the treatment ended. Patients meeting the response criteria of at least ACR 20 were considered to be responders. (ACR 20 is an American College of Rheumatology measure signifying a 20% improvement in the number of tender and swollen joints, and in three of five outcome measures: patient and physician global disease assessment, pain, disability and an acute-phase reactant value. A FDA industry guidance
document provides a useful guide to the types of outcome measures used, and the corresponding claims applied in the development of therapies for RA.\textsuperscript{14}

After treating 91 patients, the trial was halted due to evidence of efficacy.\textsuperscript{11} Of the patients in the Prosorba Column arm, 15 (31.9\%) experienced ACR - defined improvement compared to five (11.4\%) of those who received the sham treatment.\textsuperscript{10} Follow-up of these patients suggested a median duration of response to treatment of 32 weeks. Three of the first 17 responders were still meeting response criteria 84 weeks post-treatment. It should also be noted that in order to be considered responders, these severe RA patients received no DMARD's during follow up. Therefore, they had a DMARD free period for 32 weeks.

The final results of the trial considered the 68 (of 99) patients who completed all treatments and follow-up.\textsuperscript{11} Of these patients, 15/36 (41.7\%) of the Prosorba Column-treated individuals responded, compared to 5/32 (15.6\%) sham-treated patients (p<0.003). On an intention-to-treat basis, 15/52 (28.9\%) of the Prosorba column-treated patients responded compared to 5/47 (10.6\%) patients who received sham treatments (p=0.005).

Outcomes were available for 37 of the 40 patients who enrolled for a second round of the Prosorba Column treatments. Seven of 10 responders in the first round of treatment also responded in the second round. Six non-responders in Phase 1 also failed to experience response in the second round. Of the 21 patients who had received sham treatment in Phase 1, 10 met ACR 20 and six met ACR 50 (improvement of 50\%) with the Prosorba Column treatment.\textsuperscript{12}

A Canadian controlled, multicentre, clinical trial of the Prosorba Column, in combination with DMARD therapy (methotrexate) is underway (Ken d'Entremont, Medexus Inc.: personal communication, 2001 Nov 8).

In the study by Felson et al, five of nine patients who received central venous access for their apheresis procedure developed potentially life-threatening complications such as thromboses and infection.\textsuperscript{10} Consequently, the manufacturer recommends against the use of central venous access. Felson et al also report temporary joint pain was a common side effect in both treatment and sham apheresis groups.\textsuperscript{10} Furst et al found adverse effects such as nausea, rash, itching and fever occurred in one to six percent of treatments, but there was no significant difference in adverse effects between the Prosorba Column and the sham treatment groups.\textsuperscript{11}

Adverse Effects

Medexus advises that any rash should be reported as it may indicate vasculitis (inflammation of the blood vessels) and require discontinuation of the Prosorba Column treatment.\textsuperscript{15}

There is a possibility of increased risk of bleeding in patients undergoing the Prosorba Column treatment, due to heparin leaching from the column (it is primed with heparin to prevent possible clot formation when the plasma passes through).\textsuperscript{16,17} Apheresis is relatively safe,\textsuperscript{18} but adverse events associated with the use of this invasive procedure would need to be considered. According to the Medexus website, most adverse events are "transient and manageable" - such as anemia, hypotension and fatigue, and are associated with the apheresis procedure.

Implementation Issues

The Prosorba Column may provide an option for patients who have a severely disabling condition that cannot be alleviated by other forms of treatment. However, its place in regard to other new treatments is still unclear. No studies have compared the efficacy of the Prosorba Column and these new therapies.

On the basis of intention-to-treat, the response rate for patients with severe RA treated in the randomized controlled trial was modest (<30\%). RA patients with longer disease duration may not respond as well to treatment as those in the early stages of the disease.\textsuperscript{19}

The cost effectiveness of the Prosorba Column treatment is not yet established.\textsuperscript{10} The course of treatment is expensive and repeated courses may be required to maintain benefit. The number of courses of treatment needed is not yet known. As noted by the CAN guidelines, "this cost is to be balanced
against the potential for significant improvement in a subset of patients with very disabling RA that is refractory to standard therapy, who in addition to suffering great personal losses, do use considerable amounts of health care resources". 

The current place of the technology is suggested in the CAN guidelines. These state that immunoadsorption using protein A columns for the treatment of RA should be considered only in the setting of definite active RA; failure of four previous DMARDs, including methotrexate; availability of a plasmapheresis unit with adequate staffing; adequate peripheral venous access; and documented informed consent.

References


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