

## Extracorporeal Therapy in Rheumatoid Arthritis

a report by

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In two respects, biologicals represent what may be called a revolution in the pharmacotherapy of rheumatoid arthritis (RA). Firstly, they are the most powerful drugs available in controlling both the inflammation and destruction of the affected joints. Secondly, their development and efficacy are thoroughly science-based, as their mode of action is directly derived from the understanding of the role of cytokines in inflammation. Well designed and conducted randomised clinical trials (RCTs) with biologicals have set the standard of investigation-derived evidence in the treatment of RA. Currently, any intervention has to meet this level of both pathophysiological understanding and proof of efficacy.

Despite the success of biologicals, there are still approximately 30% of patients who do not sufficiently respond to these drugs and who have also previously failed to respond to disease-modifying anti-rheumatic drugs (DMARDs). For these patients, and for all those who are unable to benefit from the immunosuppression that inevitably accompanies these compounds, there is an urgent need for alternatives. In sharp contrast to biologicals and like so many traditional DMARDs, extra-corporeal therapy has a long-standing history, yet it has produced only poor evidence and understanding over the decades.

During the 1980s, many conditions were treated with therapeutic plasma exchange, predominantly those that did not respond to the medication available. RA was one of them, although the trials performed did not come close to meeting standards currently required. There was no definite hypothesis, no biometric calculation, no clear-cut definition of inclusion and exclusion criteria, no randomisation with appropriate controls and no statistical significance, as the numbers of patients treated were rather low. No evidence for the efficacy of plasma exchange could therefore be generated.

However, the side effects were considerable – particularly the undesirable depletion of coagulation factors that led to the necessity of restricting plasma exchange to a frequency of every other day. This conflicted with the rationale of removing as much of the circulating pathogenic material as possible.

Depletions of more than 70% could only be reached when replacing the removed plasma with frozen plasma from healthy donors, making the procedure even more complicated, more expensive and increasing the possibility of infection.

To overcome this limitation, a more selective method of treatment was developed. The separated plasma was no longer replaced but was passed through a filter that was designed to selectively adsorb certain molecules, while leaving the rest of the patient's plasma (including coagulation factors) unchanged. For auto-immune and rheumatic diseases those filters were designed to adsorb antibodies and immune complexes by binding to the Fc receptor of immunoglobulins ((Igs) immunoadsorption). Dextran sulphate, phenyl alanine, tryptophan or *Staphylococcus aureus* protein A are examples of materials used in immunoadsorption.

The severity of side effects was dramatically reduced, while the efficacy of Ig depletion rose by up to 95% or more. This was achieved by continuous or frequently repeated treatments. The invasive procedure and high costs continued to prevent widespread use and certainly contributed to the continued lack of good clinical studies in the field.

In the late 1990s, Daniel J Wallace and Craig W Wiesenhutter et al. assembled a small number of promising case studies on yet another method – the prosorba column. This was a protein A immunoadsorber with a remarkably low capacity of only 1,250ml of treated plasma. It seemed possible that this device might be able to remove antibodies in a quantitative way and, promisingly, analyses showed a decrease of not more than 10% to 15% in patient Ig levels. Furthermore, the treatment only needed to be carried out once a week, with antibodies being completely resynthesised during the intervals.

This observation of clinical improvement encouraged the author to propose a multicentre prospective RCT in 1999. This study was the first, and to date remains the only, study focusing on extra-corporeal therapy in any auto-immune or rheumatic disease, to generate class I evidence for the efficacy of this treatment in



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ameliorating both the signs and symptoms of the disease.

Patients taking part in the study all had a proven diagnosis of RA with an average duration of approximately 16 years, high inflammatory activity and a history of more than five failed DMARD therapies. All underwent a washout period of one to three months for DMARDs before randomisation. The individuals randomly assigned to the control group underwent a sham apheresis procedure with the plasma bypassing the adsorber instead of running through it. Both patient and attending physician were unaware that the procedure was a sham. The treatment schedule was one treatment per week with an average of 1,250ml of plasma over 12 weeks and clinical evaluation eight weeks after finalisation.

It had been calculated that approximately 260 patients would be enrolled in the study. However, after 91 patients had been treated, the Data Safety and Monitoring Board stopped the study for ethical reasons, because of the clear superiority of the outcomes among patients in the treated group compared with those in the control group. In an intention-to-treat analysis, 30% of the patients reached the ACR20 criteria – i.e. an improvement of 20% or more over a range of inflammatory symptoms – while there was only 10% improvement in the controls.

Based on this trial, prosorba was admitted for the treatment of signs and symptoms of active and refractory disease by the US Food and Drug Administration (FDA) and subsequently by other health authorities worldwide. However, radiographic criteria of joint destruction has not been investigated and immunoadsorption is therefore considered as a last-resort treatment when DMARDs and biologicals have failed.

The removal of Igs cannot sufficiently explain the evident clinical effects that lasted for a median of 34 weeks in those patients who responded to treatment. The classical understanding of immunoadsorption does not apply to this particular device. In contrast to biologicals or DMARDs, humoral markers of inflammatory activity such as C-reactive protein (CRP) remained elevated and patients usually experienced a flare after the first adsorptions. Improvement showed only gradually after eight to ten weeks of treatment. In the second half of every adsorption, cryoglobulins could be detected in the patients' plasma. These disappeared hours after treatment.

These phenomena were first explained by a hypothesis. It is based on the biological properties of the IgG1 rheumatoid factor, a small dimer that does not bind complement and therefore escapes both

routine laboratory tests and physiological clearance mechanisms in the body. This dimer is able to cross-link the Fcγ3 receptor on the surface of monocytes and macrophages, thus leading to the production of tumour necrosis factor (TNF)-α, the key cytokine in the inflamed joints. IgG1 binds well to protein A on the surface of the adsorber and, unlike the condition in the bloodstream, becomes immobilised for a short moment before complexing with its antigen and other rheumatoid factors. The adsorber therefore acts as a catalyst to the formation of bigger aggregates of these molecules, which are subsequently torn from the surface of the adsorber and carried back into the patient's circulation, where they can be detected as cryoglobulins for some time afterwards.

Larger immune complexes bind complement and are therefore opsonised for clearance in the reticuloendothelial system, a classical inflammatory way of removal that could explain the elevated humoral markers and the flares experienced by patients after prosorba treatment. According to this hypothesis, the device would induce specific intracorporeal inflammatory clearance of pathogenic rheumatoid factors, rather than eliminate them in the extra-corporeal circulation. The delay of clinical improvement would reflect the time it takes to gradually recruit joint deposits of rheumatoid factors into the circulation, where they can be complexed and then cleared. If this hypothesis proved to be true, prosorba immunoadsorption would be the only non-immunosuppressive treatment available. In this respect, it clearly distinguishes itself from any biological or DMARD treatment, as well as from quantitative immunoadsorption or therapeutic plasma exchange, both of which have the disadvantage of the extracorporeal depletion of Igs. This would open new options for this particular treatment. It could be aimed at those patients who are contraindicated for immunosuppression as well as at those who fail to respond to DMARDs and biologicals.

Many questions still remain to be answered. For example, whether immunoadsorption is able to slow down or (as biologicals appear to) even halt bone destruction. Furthermore, if quantitative immuno-adsorption were carried out at larger intervals in order to allow for the recruitment of joint deposits of immune complexes, the question is whether it would continue to yield similar efficacy. Despite these queries, with good evidence and a mode of action based on the immunological understanding of inflammation, immunoadsorption moves a step nearer the status of biologicals and the newer DMARDs in meeting at least some of the current requirements for sound clinical decision-making. This broadens the treatment repertoire, particularly for those patients who are hardest to treat. ■