Drugs 2006; 66 (15): 1903-1908
0012-6667/06/0015-1903/$44.95/0

Role of Apheresis in Rheumatoid Arthritis

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Abstract

Apheresis, a therapeutic procedure that has been available for decades, has recently been added to the long-term management of rheumatoid arthritis (RA). It is a procedure whereby blood is removed from the body and divided into its various components. With the development of specific instrumentation, it has become possible to target the specific cellular or humoral components to be removed or altered.

RA is a destructive, chronic progressive disease with high morbidity and significant mortality if it is not treated. Recently, combinations of disease-modifying pharmacotherapeutic agents have successfully been brought to bear on this serious disease. This approach of combining potent anti-inflammatory, disease-modifying antirheumatic drugs (DMARDs), chemotherapy and biologicals continues with some success but not without significant dangers of severe adverse toxicity, including the risks of sepsis, immunopathology and malignancy. In the setting of RA, various apheresis procedures, with and without these combination modalities, have been tested with variable success. This article reviews that experience as an overall approach to better, safer RA disease management.

Drug therapy of rheumatoid arthritis (RA) in modern times began with symptomatic treatment with aspirin and evolved through close to 100 NSAIDs, absent any important disease-modifying benefit or the analgesic potency afforded by the spectrum of opioids.[1] The selective cyclo-oxygenase (COX)-2-inhibitory NSAIDs that followed were not determined to be any more potent and all shared end-organ toxicities. Although corticosteroids have been the most successful of all anti-inflammatory agents used in the symptomatic therapy of RA, hormonal toxicities limit their use.[2]

Gold salt therapy, followed by penicillamine and sulfasalazine, were found to be somewhat useful in RA disease suppression, but are now rarely used alone and have their own specific toxicities that may limit long-term use.[3] Accordingly, chemotherapy has been found to be a more reliable disease-modifying therapy, alone or in combination. Methotrexate has been the anchor of present anti-metabolite drug therapy programmes, although azathioprine, and less often cyclophosphamide, have had limited selective roles.[4]

Biologically derived and immune messenger active agents now dominate the most potent therapy for severe and crippling RA, led by infliximab and etanercept.[5] More follow, but as the list grows, so do the reports of serious sepsis, malignancies and death from profound sustained immunosuppression.[6-8] As various apheresis procedures continue to develop, a potential option for safer treatment of RA is emerging. These non-pharmacological alternatives alone and in combination with established biological treatments may provide relief from seri-

ous adverse events typical of immunosuppressive therapy. Their effectiveness is currently being evaluated in controlled clinical trials.

1. Apheresis Therapy

1.1 Evolution of Apheresis in Rheumatoid Arthritis

In medieval times, RA, regarded as caused by "the falling of the humors", may have been treated by ancient bloodletting. Interestingly, blood transfusions for RA were in vogue as late as the mid-20th century. Indeed, some arthritis centres included a blood transfusion unit, which corrected the common anaemia, fatigue and malaise of RA. However, more sophisticated understanding of the basis of these complaints (abnormal iron handling, hypoalbuminaemia, acute phase reactants), as well as fears of risk of hepatitis or AIDS associated with transfusions, have relegated this empirical practice to the dusty back shelves of history.

1.2 Plasmapheresis

Plasma exchange became the first form of apheresis practiced in the treatment of RA. At present, plasma exchange using centrifuge or filter-based technologies may remove autoantibodies (anti-DNA, anti-cardiolipin) and influence T-cell ratios.[9] Since plasmapheresis was first used for RA in 1962, multiple trials have failed to demonstrate a lasting clinical benefit.[9] As a result, plasmapheresis has not found a role in RA treatment.

1.3 Prosorba® Column Therapy

Immune complex and dysimmunoglobulinaemia are part of the RA pathogenesis puzzle. The Prosorba® [1] protein A-silica adsorption column (Fresenius HemoCare, Redmond, WA, US) is a medical device containing purified staphylococcal protein A bound to a silica grid in conjunction with a plasmapheresis machine. Blood cells are separated from the plasma in the machine, and the plasma is passed through the column and returned directly to the patient. There is no plasma exchange involved as there is in plasmapheresis. Ongoing research into the mechanism of action of Prosorba® has resulted in the following: the mechanism is proposed to be "an adsorbed catalyzed conversion of small, tissue-penetrating, scarcely detectable, non-complement-binding, proinflammatory IgG-rheumatoid factor (RF)-based immune complexes (IC) into the more readily phagocytosed species of IC: intermediate-sized, partially cryoprecipitable, non-tissue penetrating IC that are opsonized with complement. These IC are rather short-lived and could quickly be cleared by the body's scavenging system".[10] In simpler terms, exposure to protein A appears to cause restructuring of immune complexes that enter the column. It is the return of these complexes to the body that stimulates the body's own immune response to destroy those larger, more recognisable complexes. This is quite different to plasma exchange in that bulk removal of plasma does not utilise the body's own defense mechanisms to selectively remove immune complexes. The stimulation of the normal immune response that takes place is likely to be the reason that response to Prosorba® is generally quite durable versus the short-lived response to plasma exchange that is sometimes seen. Recently, the Prosorba® column was approved by the US FDA as the first use of apheresis for RA in the US.

Prosorba® column therapy (PCT) has been used for over a decade in the treatment of idiopathic thrombocytopenic purpura, a severe autoimmune disorder of platelets. It was assumed that PCT acted against immune complex formation because of the high affinity of protein A for IgG and IgM complexes.

PCT was initially tested in a pilot study of 11 RA patients, in which 9 responded.[11] This was supported by a subsequent pilot study of 15 patients, in which 10 responded according to Paulus criteria.[12] Efficacy in RA was further supported by a randomised, double-blind, multicentre trial with sham pheresis versus PCT.[13] The trial was halted in

1 The use of trade names is for product identification purposes only and does not imply endorsement.

mid-course >1 year later when an interim safety committee discovered proof of efficacy and determined that allowing the sham group to deteriorate would be unethical (both groups were off all second-line DMARDs during the trial). The intention-to-treat analysis demonstrated that 31.9% of the PCT group improved by American College of Rheumatology (ACR) criteria versus only 11.4% of the sham group ($p = 0.019$). In a subsequent long-term follow-up, the response rate to open-label PCT therapy in patients with advanced refractory RA was 53.8% (49 of 91).[14] This study led to the FDA approval of PCT in the treatment of RA.

Table I lists serious adverse events (SAEs) that occurred in a recent US market-based study of experience with PCT.[15] Note that thrombotic events were felt to represent increased platelet agglutination from PCT. Thus, prophylaxis with antiplatelet agglutination therapy (i.e. aspirin) during PCT may be indicated.

Post-marketing data suggest the efficacy and relative safety of PCT in refractory RA without the risks of profound immunosuppression associated with powerful biological therapy in patients at high risk for infection or malignancy. This treatment regimen as approved requires once-weekly PCT for 12 weeks and then a return to the previous regimen for ≥6 months. This could act as a 'rest pulse' from previous immunosuppression. Another possible approach to maintenance therapy could be based on the gold salt therapy model of monthly doses after induction PCT (12 weekly doses). The long-term data on this model are not yet available.

1.4 Cytapheresis: Adacolumn® and Cellsorba™

The vast panoply of targets for RA disease expression includes various genetic factors, triggering events, symptoms and target organs. The unifying feature of RA, therefore, is that the full spectrum of the cellular and humoral immune system is somehow activated. However, the nature of the antigen, whether self or foreign, remains unknown.[16]

In 1977, Paulus et al.[17] demonstrated that lymphocyte depletion via a surgically created fistula in the thoracic duct was capable of decreasing the

Table I. Prosorba® column therapy in rheumatoid arthritis (RA): unanticipated serious adverse events (SAEs)[15]

SAE	Events/no. of patients[a]	Patients (%)	Aggravating conditions
Bradykinin reaction	1	0.8	Facial flushing, vasodilation
Hypotension	1	0.8	
Rash	2	1.6	One patient with history of rash as a reaction to infliximab
Vasculitis (cutaneous) without renal involvement	4	3.1	Occurrence always after second treatment; improvement after corresponding intervention (corticosteroids)
Vasculitis (cutaneous) with renal involvement	2	1.6	Occurrence with APGN after second treatment (patient 1); occurrence after ninth treatment, and development of RPGN 7 days later (patient 2); improvement after corresponding intervention, both renal involvements completely resolved
Myocardial infarction	1	0.8	Contraindicated: patient with history of cardiac disease, 75 years old, advanced cancer of prostate receiving chemotherapy, pemphigus, hypertension and RA medication; occurrence during fifth treatment; reconstitution
Pulmonary embolus	1	0.8	Contraindicated: patient 53 years old, SLE, existing deep venous thrombosis, chronic varicose, obesity; occurrence after sixth treatment; reconstitution after anticoagulation
Congestive heart failure	1	0.8	Contraindicated: patient 69 years old, history of six MI, chronic congestive heart failure, hypertension; occurrence after fourth treatment

a Of the 133 patients enrolled, 127 patients received at least one treatment, 6 patients did not begin treatment.

APGN = acute proliferative glomerulonephritis; **RPGN** = rapidly progressive glomerulonephritis; **SLE** = systemic lupus erythematosus; **MI** = myocardial infarction.

number of tender joints and decreasing the duration of morning stiffness in patients with rheumatoid arthritis. Subsequently, two randomised, controlled studies using lymphapheresis and lymphoplasmapheresis demonstrated similar benefit in reducing articular involvement.[18,19] Combining the results from these trials, one can conclude that the relative value of lymphocytapheresis and lymphoplasmapheresis cannot be assessed, but the antirheumatic effect is relatively rapid in onset (1–2 weeks) with approximately 40–50% of patients having marked improvement for up to 3 months.

Unique to the pathogenesis of RA is intense activation of monocytes/macrophages.[16] Granulocyte counts in RA patients are twice the level of those in healthy people.[20] Immune complexes and other chemicals/proteins, including rheumatoid factor itself, are deposited in and around the joint spaces and in the serum early in the disease process. This facilitates the accumulation of granulocytes in arthritic joints. The granulocytes phagocytose these complexes and adhere to the cartilage, where they release enzymes that digest bone and cartilage. This causes joint tissue destruction, with misshaping and malalignment of the involved joints and ultimately the familiar symptoms of RA. Granulocytes also contribute to an excess of synovium in RA patients. Importantly, activated granulocytes and monocytes produce a large amount of inflammatory cytokines, thus initiating and perpetuating the inflammation in RA.[21,22]

Accordingly, an extracorporeal leukocytapheresis device that selectively adsorbs granulocytes and monocytes from the peripheral blood using cellulose acetate beads was developed and first tested in a rabbit autoimmune model, with encouraging results.[23] Called Adacolumn® (JIMRO Co. Ltd, Takasaki, Japan), this selective granulocyte and monocyte adsorptive apheresis device was subsequently tested successfully in patients with inflammatory bowel disease.[24] The Adacolumn® is designed for selective depletion of myeloid leukocytes (granulocytes, monocytes and macrophages) by perfusing 1800mL of peripheral blood through the column. Blood is primed with heparin prior to the treatment.[25]

The clinical benefits of cytapheresis in RA have been detailed in the past decade, for the most part in Asian populations, primarily via observational studies rather than randomised controlled trials.[20,23,26,27] Thus, wider outcomes and more definitive data from Western countries are awaited. With some exceptions, almost all of the clinical studies were small, non-blinded, and short in duration. They ranged from three to five treatments over 3–4 weeks. RA activity was assessed according to ACR20 or Ritchie indices, including joint swelling, tenderness, limitation of function, acute phase reactant levels and global outcomes. As is usual with this therapy, there were exquisite measurements of immune cellular and cytokine levels and few, if any, descriptions of severe negative outcomes or serious adverse effects. These reports, then, are based for the most part on testimonial reporting without evidence-based, blinded, randomised controls.

In addition, cytapheresis studies were usually conducted in patients with severe, refractory RA. One study of leukocytapheresis (LCAP) using Cellsorba™ (Asahi Medical, Tokyo, Japan) included nine patients with serious complications of associated rheumatoid vasculitis, in whom the stigmata of polyneuritis, skin ulcerations, nodules and digital gangrene were said to have shown "substantial improvement" after column therapy of up to seven treatments.[21] A small sham-controlled study of Cellsorba™ documented an increase in activated T cells in the peripheral blood at the same time as a reduction in T cells in the synovial fluid.[28] The investigators postulated a possible "redistribution of activated cells from affected joints into the circulating blood" as a result of the procedure.

In another double-blinded, sham-controlled study of Cellsorba™ in RA, 25 patients receiving active and 7 patients receiving sham apheresis received three procedures over a 3-week period.[29] By ACR criteria, the active treatment group had a statistically significant improvement in outcome over the sham group. The procedure was well tolerated, with no major adverse effects reported.[29,30] More recent-

ly, a sham-controlled study of Adacolumn® in six healthy volunteers carefully documented cytokine and immune cellular outcomes, and treatment was well tolerated.[30] However, it is not possible to simply extrapolate this basic information to RA.

Recently, 27 patients with refractory RA were treated in a multicentre, open-label, pilot study with five treatments of Adacolumn® on a once-weekly basis, and were carefully monitored using ACR and laboratory criteria.[25] Response to therapy was monitored from weeks 5, 7, 12 and 20. Of the 27 patients, 81.5% were women with long-term RA who had not responded to therapy with multiple DMARDs and biologicals. Of the intent-to-treat group, 40.7% achieved ACR20 by week 20. Treatment was well tolerated by all patients. The importance of this unblinded observational study is that the salutory results were reported in a non-Asian population in contrast to the primarily Asian bias of previous outcome reports with this procedure.[25]

The role of phagocytic cells in RA pathogenesis is still conjecture and remains to be confirmed, although the positive direction of related clinical outcomes with Adacolumn® is encouraging.

2. Conclusions

The effective therapy of rheumatoid arthritis has come a long way – from symptomatic anti-inflammatories and corticosteroids to biologicals, with or without methotrexate and combined DMARD 'fellow travellers'. Although the cause of RA is still unknown and none of these therapies represents a 'cure', functional disability and suffering are often relieved and/or the disease halted in its tracks with these newer therapeutic models. But for how long? And at what price, in terms of dollars as well as serious toxicities and threats of new SAEs?

To answer these questions, we wait upon even more specific therapies, pharmacogenomic data and research breakthroughs beyond current empirical impressions. Table II gives currently available therapeutic choices – from pharmacotherapy, with its potential for drug dependence, tolerability and toxicity, to the non-immunosuppressive steady-state restorative intervention of apheresis.

Table II. Currently available therapeutic choices in rheumatoid arthritis therapy: pharmacotherapy versus apheresis

Therapy	Mechanism	Outcomes
Pharmaco-therapy	Prescription of pills and/or injections	Drug-dependent efficacy vs tolerability/time or drug toxicity
Apheresis	Removal of selective pathogenic compromisers (PMNs, macrophages, immune complexes)	Return to steady-state absent drug or biological toxicities

PMNs = polymorphonuclear leukocytes.

For RA, a crippling disease that often requires lifelong therapy, the new apheresis option is a welcome addition to the treatment armamentarium. With infection, the primary cause of RA deaths, the chronic potent immunomodulation produced by the chemotherapy agents and biologicals that are the mainstay of current therapy represents a less than optimum situation. The concern about malignancies and serious infections associated with the popular anti-tumour necrosis factor antibody therapy has been substantiated.

Effective immunomodulation achieved by apheresis does not carry the serious risks of chronic potent immune suppression. Not only is it an alternative to mainstay therapy, it can also offer 'rest periods' from these therapies to lessen the danger of immune suppression for those at risk. Our oncology colleagues have already demonstrated this in their use of flexible treatment models in the face of such challenges, whereby they substitute alternative treatment options while patients are 'off chemotherapy'.

Unfortunately, the long-term apheresis data and outcomes are merely anecdotal and not yet controlled, as required in evidence-based medicine and in accordance with cost-effectiveness standards. However, that necessary work is in progress, and it suggests that the current heated love affair with the new biologicals can allow some room for 'companionship'.

Acknowledgements

The author would like to thank the Board members of the Academy for Immunomodulation Through Apheresis (AITA) for scientific review and the AITA secretariat for editorial assistance. No sources of funding were used to assist in the

preparation of this review, and the author has no conflicts of interest directly relevant to the content of this review.

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