Effects of Prosorba® Column Apheresis in Patients with Chronic Refractory Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Since the approval of Prosorba® column apheresis therapy (PCT) for rheumatoid arthritis (RA) in 1999 there have been multiple requests for additional information on the response rate of PCT used commercially in rheumatology practice settings.

Methods. Data were collected in a noninterventional prospective fashion on patients with RA who qualified for the PCT treatment per the package insert. There were 91 patients who completed the 12 prescribed treatments. There was no washout of other drugs [i.e., disease modifying antirheumatic drugs (DMARD), biologics]. An initial baseline assessment was performed prior to first treatment and then up to 4 additional assessments were performed at Weeks 9, 16, 20, and 24. Criteria for ACR20 were noted in order to assess response rate, and commercial adverse event reporting was used to record serious/unanticipated adverse events.

Results. There was a response rate of 53.8% (measured as ACR20 response or better) in these patients with previously refractory RA. The individual criteria showed a much greater improvement than reflected by ACR20; for example, this response included a 52% improvement in joint tenderness, 40% improvement in swelling, 42% improvement in patient's pain, 38% improvement in patient's global response, and 48% improvement in physician's global scores (76% of responders had measured ACR20 by Week 16 and 100% by Week 24). The actual measurement of an ACR response generally occurred during assessments at Week 16; however, most patients who respond will state they felt improvement some time between Weeks 8 and 12. There were no assessments between Weeks 9 and 16 so the actual week of improvement could not be identified by ACR criteria. Some patients stated that they felt improvement began closer to the 6th week. Most responders were concurrently taking biologics or DMARD, e.g., methotrexate and etanercept, despite previously inadequate RA response to those medications.

Conclusion. This postmarketing study of PCT used commercially in 59 rheumatology practice settings supports the safety and efficacy of this treatment regime in selected patients with RA and compares favorably with the initial sham controlled clinical trial. PCT is a relatively underutilized choice for the management of active, aggressive RA. (J Rheumatol 2004;31:2131–5)

Key Indexing Terms:
PROSORBA COLUMN APHERESIS REFRACTORY RHEUMATOID ARTHRITIS

Since approval of Prosorba® column apheresis therapy (PCT) in 1999 for use in patients with rheumatoid arthritis (RA), over 2000 patients have undergone over 20,000 PCT treatments for RA[1]. During this same interval, several new biologics and disease modifying medications have become available to rheumatologists for usage in this RA population[2]. There have been outcome reports of benefits from these new medications in the treatment of RA[3]. However, there have been reports of serious adverse events from the US Food and Drug Administration (FDA)[4]. A significant rate of infectious episodes and the activation of latent tuberculosis have been associated with the sustained immunosuppression common to these medications[5]. Multiple sclerosis and lymphoma have generated special reports associated with this type of immunosuppression[6,7]. There have also been warnings of hepatic toxicity associated with one of the drugs[8].

In contrast, the experience with PCT has not been associated with any increased potential for infection or malignancy, except for infections related to central venous catheters. The Phase III study revealed no evidence of immunosuppression[1]. Consistent with the 12 years' experience of Prosorba therapy for approved treatment of idiopathic thrombocytopenic purpura (ITP), the experience in refractory RA has been relatively safe and nontoxic[9].

MATERIALS AND METHODS

Fresenius HemoCare (Redmond, WA, USA) has been collecting data as part of a post-approval market surveillance study in a population of patients with severe RA comparable to that studied in a randomized, double-blind, sham controlled, Phase III clinical trial[9] that resulted in FDA approval. Data were collected in a prospective noninterventional fashion on RA patients who qualified for the PCT treatment following instructions in the product package insert. Authorization for PCT required inadequately controlled RA after or with use of multiple biologicals/disease modifying

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antirheumatic drugs (DMARD) or when potent immunosuppressive therapy was contraindicated. There was no washout period of other drugs (i.e., DMARD, biologics). There were 59 sites participating, with a total of 131 patients enrolled in the study. The patients treated had severe active disease (63.8% class III) and an average of 4 + 2.3 prior DMARD regimens had failed. Those patients who decided not to initiate treatment or did not complete all 12 treatments were not included in the final analysis of 91 patients who completed all 12 treatments. Patients' demographic details are shown in Table 1. Patients received treatments weekly for 12 weeks. Assessments were performed at baseline and at Weeks 9, 16, 20, and 24.

RESULTS

Efficacy results were based upon American College of Rheumatology (ACR) outcome criteria for RA[10] on the 91 evaluable patients as indicated in Figures 1 and 2.

Study results revealed a response rate of 53.8% (measured as ACR20 or greater) in these patients with previously refractory RA. The individual criteria showed a much greater improvement than reflected by ACR20; for example, this response included a 52% improvement in joint tenderness, 40% improvement in swelling, 42% improvement in patient's pain, 38% improvement in patient's global response, and 48% improvement in physician's global response scores.

During the study, most patients who responded stated that they felt improvement some time between 8 and 12 weeks. Anecdotally some patients stated that they felt improvement begin close to the 6th week.

Results in this postmarket surveillance study revealed an even greater response rate than seen in the pivotal study, a randomized, double-blind, sham controlled phase III trial[9]. The overall response rate was 53.8% as measured by the ACR20. As shown in Figure 1, 17.6% of these responders qualified as ACR50 responders.

Unlike the FDA regulated clinical trial[9], 51% of the responders in this study continued taking biologics/DMARD to which they had been inadequately responding prior to initiation of PCT. The top 4 DMARD used were methotrexate, hydroxychloroquine, leflunomide, and etanercept. It was recommended that these medications not be tapered until the PCT response was achieved per the physician evaluation (Figure 3). Information regarding tapering of these medications is limited due to the design and length of the study/data collection.

Adverse events. Of 133 patients enrolled, 127 patients received at least one treatment; 6 patients did not begin treatment. The most anticipated side effect that occurs with PCT in the patient with RA is arthritis flare in the early weeks posttreatment. Patients are informed that this is a likely side effect and therefore it is not usually reported to the company as an adverse effect.

Table 1. Patients' demographic details.

Characteristic	Mean ± SD
No. of subjects	91
Age, years	56 ± 13.3
Female, %	76.7
Prior disease duration, mean years (range)	16.6 ± 11.2 (4–42)
Class III stage, %	68.9
Prior DMARD regimens failed	4 ± 2.3

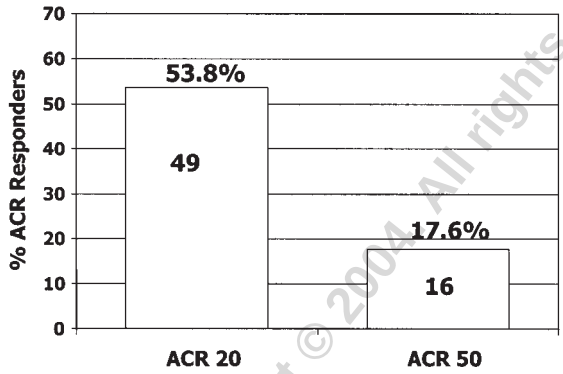

Figure 1. Responses to ACR outcome criteria in the 91 evaluable patients.

The most common serious adverse event reported was cutaneous vasculitis or rash, which occurred in 6 patients. Five of these occurred after the 1st, 2nd, or 3rd treatments, with one occurring after the 9th treatment. In each of these cases treatments were stopped and the rash resolved. These patients did not continue treatment. Two of the reports of rashes were in patients who previously had similar reactions to a biologic treatment. Fresenius HemoCare now recommends that treatments be stopped with the appearance of a rash or possible vasculitis. Renal laboratory results should be checked and, if normal, the treatments can resume once the rash has resolved. Based on adverse event reports to the company in the last 2 years, in most of these cases, treatment has been resumed without recurrence of the rash and patients have been able to complete the prescribed number of treatments. There were also 2 reports of hypotensive/bradykinin types of side effects, which resolved when treatments were stopped.

More severe adverse events included: (1) Two patients whose vasculitis reaction included renal involvement. No further treatments were performed. (2) One patient with a history of 6 myocardial infarctions developed significant congestive heart failure after his 4th treatment. No further treatments were done. (3) A female patient with concurrent systemic lupus erythematosus (SLE) developed chest pain 1 hour after her 9th treatment. She was admitted to hospital the next morning and diagnosed with a myocardial infarction. She stated she had indigestion and heartburn prior to the Prosorba treatment. An angiogram revealed single vessel coronary artery disease and a stent was placed. (4) One patient who was also diagnosed with SLE developed a pulmonary embolism after his 6th treatment. It was later reported that this patient had an existing deep venous thrombosis,

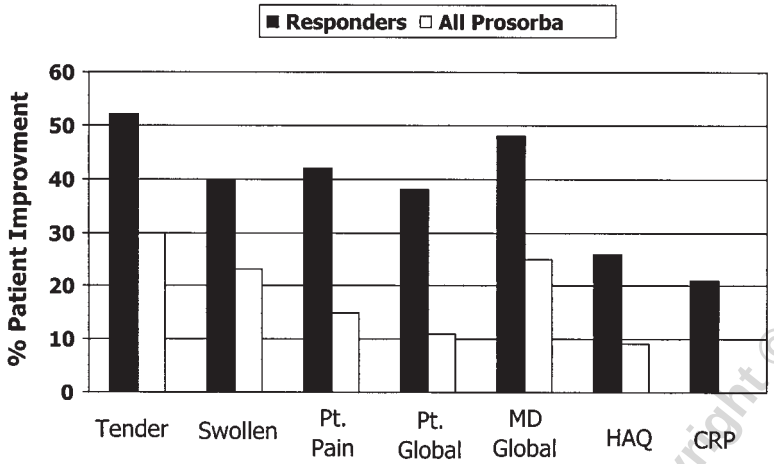

Figure 2. Completer categorical responses compared to intent-to-treat group. HAQ: Stanford Health Assessment Questionnaire; CRP: C-reactive protein.

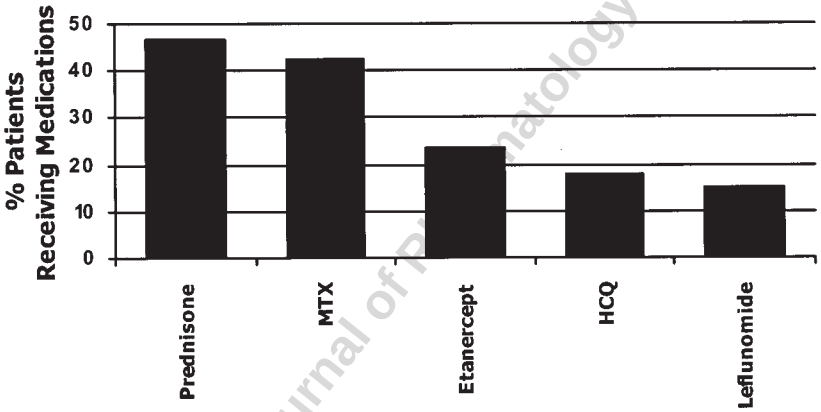

Figure 3. Patients' use of other therapies. MTX: methotrexate; HCQ: hydroxychloroquine.

which would have contraindicated the use of Prosorba therapy. No further treatments were done.

Hypercoagulability associated with thrombotic events has been reported in the Cypress Bioscience/Fresenius HemoCare complaint database[1] more frequently in the RA population than in the patients with ITP treated since 1987. Patients with moderate to severe RA are more susceptible to thrombosis due to factors such as increased platelet count, decreased mobility, and possible antiphospholipid antibodies[11]. There is a contraindication for use of Prosorba in patients with a known hypercoagulable state or who have history of a thrombotic event. These events appear to be very susceptible to simple platelet aggregation suppression as occurs with an 81 mg daily dosage of aspirin. Thrombotic events have been dramatically reduced (none reported in 2002 and one in 2003 in the Fresenius HemoCare complaint database[1]) since Fresenius HemoCare began recommending the use of this simple prophylaxis during the weeks of treatment.

Central line infections, which were a problem in the early stages of the pivotal trial, were not reported in this study. Data were not collected on the number of participating patients in whom central lines were utilized. The product package insert cautions against the use of central lines due to risk of infection or thrombosis. This is especially important in patients who are unable to adequately care for them. Peripheral access is the preferred method for these treatments and can generally be achieved in most of the patients who present for these treatments.

DISCUSSION

Despite the severity of adverse events seen with the presently available biologics/DMARD, those therapies are approved for all stages of RA without preconditions for stages of RA including early onset RA. PCT as a form of induction therapy is judged under very different and challenging clinical circumstances. It also must be admitted that a further prejudice overshadowing the choice of PCT for RA is that it has been confused with plasma exchange. Plasma exchange was studied and judged a therapeutic failure in

RA, and yet plasma exchange and PCT are 2 distinctly different treatment modalities[9]. Past difficulties in obtaining PCT have been greatly resolved. With the approval by over 90% of private insurance providers and a national coverage decision by the Centers for Medicare and Medicaid Services (Washington, DC, USA), reimbursement coverage is available. In regard to the patient experience, a Prosorba treatment is very similar to a volunteer platelet donation and takes about the same amount of time as an infliximab infusion, 2 hours.

The current theory regarding the mechanism of action of the Prosorba column may assist in understanding the adverse events that were seen, but also in understanding why Prosorba therapy has such a dramatic effect on those patients who respond. It has never been thought that the removal of a maximum of 1 g of IgG/complexed IgG is in itself the only mechanism of action that results in the responses seen in patients with ITP and RA. Cox and Wiesenhutter described increases in cryoglobulins in 3 patients treated with Prosorba therapy[12]. These increases were transient and occurred during and disappeared soon after several or most of the patients' treatments. Based on this evidence it is thought that as IgG and immune complexes bind to protein A in the columns during treatment, they may attract and bind to other antibodies, immune complexes, and also complement and actually restructure these molecules into larger immune complexes. As treatment progresses these larger immune complexes are "bumped" off their binding sites and reenter the patient's circulation as cryoglobulins. The positive effect of this modulation of the circulating immune complexes is that they are now identified as abnormal and destroyed by the immune system, which may account for the response in the patient. It may also be responsible for some side effects, such as flare and the rarer occurrence of vasculitis and thrombosis, in some patients.

Discussion about the mode of action also includes a theory regarding activation of complement during Prosorba column treatment. It is thought that complement fragments that are capable of solubilizing immune complexes return to the patient's circulation. There the complement fragments may be reentering the joint space, which results in mobilization of the immune complexes there. Once solubilized, these complexes are able to move out of the joints and into either the circulation or the lymphatics.

Since the definitive etiology of RA remains unknown, we are presently limited to identifying mediators and empirically describing clinical outcomes based on modifying their activity. This is true for all present DMARD and biologics, as it is for basic PCT research. Currently, work is being done to identify both the positive and negative aspects of this therapy.

The demands of PCT therapy on the patient, including the requirement for venous access and 2-hour outpatient treatments, with efficacy often delayed for 8–12 weeks, and the concept of extracorporeal intervention, have presented some critical lessons (Table 2).

Table 2. Experience with column apheresis therapy.

- Peripheral access is strongly recommended. Patient must have at least one antecubital vein that can tolerate venipuncture with an 18 gauge needle. Return of blood can be accomplished through an 18 gauge needle or intracath elsewhere in the forearm, if necessary.
- Patients should be prepared with information regarding likeliness of arthritic flaring after each of the first 4–6 treatments and that response is usually delayed until the later third of treatment.
- Patient selection is an important factor in reducing complications from side effects and therefore ensuring that patients will be able to complete the suggested 12 treatments. Contraindications (e.g., history of thrombotic events) and cautions such as significant cardiac disease should be strongly considered. A cardiology consult may be helpful in determining a cardiac patient's ability to tolerate the apheresis procedure.
- Treatments should be stopped with the appearance of a rash or possible vasculitis. If renal data remain normal and rash resolves, treatments may be resumed.
- Cost equivalent to current RA biological infusion therapy.
- PCT effective in majority of RA patients refractory to multiple biologics/DMARD.
- PCT immunomodulatory alternative when major immunosuppression is contraindicated.
- Therapeutic/toxicity ratio favorable even in refractory RA.

Bruce and Fries recently published an excellent update on outcome assessment in intervention for serious diseases such as RA[13]. In its most active stages, RA is the most crippling of all chronic diseases. It has accelerated mortality associated with its unchecked state[14]. It creates enormous direct and indirect financial burdens through loss of income and also healthcare and management costs[15,16]. Patients considering PCT must be carefully selected and well informed of the reasons they may benefit and the difficulties they may face during the treatment period. Efficacy may not be achieved if the 12-week course is not completed. PCT is not associated with the reward of early symptomatic benefits, as with biologics or corticosteroids; however, it is also not associated with as much potential for serious adverse events in the population with moderate to severe RA. Patients with RA at risk for recurrent chronic infections, septic joints, or a personal or family history of malignancy, or those contemplating pregnancy now have an alternative to biologics/DMARD with PCT. Further, during the therapy, symptomatic medication interventions were common and useful in maintaining compliance.

This postmarketing study of Prosorba column apheresis therapy used commercially in a rheumatology practice setting supports the safety and efficacy of this treatment regime in selected patients with RA, and compares favorably with the initial sham controlled clinical trial. PCT provides a unique choice as a potent non-immunosuppressive therapy for RA, a disease in which infection remains the leading cause of death.

REFERENCES

1. Fresenius HemoCare PCT. Internal files. Fresenius HemoCare, Redmond, WA, USA.
2. Roth S. Arthritis therapy: A better time, a better day [editorial]. Rheumatology Oxford 2001;40:603-6.
3. Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus on biologic agents for the treatment of rheumatoid arthritis and other rheumatic diseases. Ann Rheum Dis 2002;61 Suppl II:ii2-ii7.
4. Arthritis Drugs Advisory Committee. Safety update on TNF-a antagonists: infliximab and etanercept. Internet [cited June 23, 2004] Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3779b2.htm
5. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis alpha-neutralizing agent. N Engl J Med 2001;345:1098-104.
6. Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ 1998;317:180-1.
7. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occuring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001;44:2862-9.
8. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: A double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 1999;353:259-66.
9. Felson DT, LaValley MP, Baldassare AR, et al. The Prosorba column for treatment of refractory rheumatoid arthritis: a randomized double-blind, sham-controlled trial. Arthritis Rheum 1999;42:2153-9.
10. Felson, DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
11. Fort JG, Cowchock FS, Abruzzo JL, Smith JB. Anticardiolipin antibodies in patients with rheumatic diseases. Arthritis Rheum 1987;30:752-60.
12. Cox DA, Wiesenhutter CW. Immunoadsorption with Staph A protein columns (Prosorba®) induces marked cryoglobulinemia in patients treated for rheumatoid arthritis [abstract]. Arthritis Rheum 2002;46 Suppl:S168.
13. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: A review of its history, issues, progress and documentation. J Rheumatol 2003;31:167-78.
14. Wolfe F, Mitchell D, Sibley J, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481-94.
15. Callahan LF, Pincus T, Huston JW 3rd, Brooks RH, Nance HP Jr, Kaye JJ. Measures of activity and damage in rheumatoid arthritis: depiction of changes and predictions of mortality over five years. Arthritis Care Res 1997;10:381-94.
16. Yelin E, Meenan R, Nevitt M, Epstein W. Work disability in rheumatoid arthritis: effects of disease, social, and work factors. Ann Intern Med 1980;93:551-6.