Evidence analysis of Prosorba® to treat rheumatoid arthritis

Randomized controlled trial (RCT)

Keywords:
Reference: Felson DT, LaValley MP, Baldassare AR, et al. The Prosorba column for treatment of refractory rheumatoid arthritis. ***Arthritis & Rheumatism*** 1999;42:2153-59.

Study Type: Double-blind, multicenter, randomized controlled trial with 19-20 weeks of follow-up.

Outcomes

- *Primary:* American College of Rheumatology (ACR) defined improvement (response).[1] An ACR response means a 20% improvement in tender joint count and a 20% improvement in swollen joint count and 20% improvement in 3 of 5 other ACR core measures: patient and physician global assessment, pain, disability, and an acute-phase reactant (CRP for this study). The outcome studied was improvement 19 to 20 weeks after beginning 12 weekly treatments.
- *Secondary:* Adverse effects
- *Reviewer's comment:* Long-term remission, such as response 6-12 months after treatment was begun, was not studied. Thus, this study should be considered an evaluation of Prosorba's short-term efficacy in treating symptoms of RA.

Design

- *N* = 99 (The paper reported data for 91 patients, but an additional 8 patients completed 19-20 weeks of follow-up and are included in this analysis.) The results are not substantially different when those 8 patients are excluded.
- *Description of population:* Adults with rheumatoid arthritis (RA) of $\geq$ 12 months duration.
- *Inclusion criteria:* Adult, RA present $\geq$ 12 months duration, failed either methotrexate or at least two other disease-modifying agents, $\geq$ 20 tender joints, $\geq$ 10 swollen joints, significant pain, C-reactive protein $\geq$1.25 normal.
- *Exclusion criteria:* Patients for whom extracorporeal immunoadsorption might be medically contra-indicated (e.g., coagulation system abnormalities), patients taking ACE inhibitors, serious comorbid illness, serum creatinine > 130% the upper limit of normal, hematocrit < 27% or hemoglobin < 9 gm/dl, RA patients in RA functional class I and functional class IV.
- *Power:* N/A
- *Method of randomization:* Computer-generated randomization, stratified by site. Patient assignment was recorded in a closed envelope. At each site, an unblinded operator was only person with access to envelope, and s/he determined the treatment administered.
- *Intervention:* Once weekly for 12 consecutive weeks, patients randomized to receive active treatment had plasma filtered through the Prosorba immunoadsorption column. Patients randomized to receive sham apheresis had plasma transferred to a transfer bag instead of being filtered through a Prosorba column. Plasma was returned to patients through a leukocyte removal filter.
- *Blinding:* Double-blind. Each site had an operator who was unblinded. The operator adjusted stopcocks to route blood either to the Prosorba column or to the transfer bag. The column and bag were hidden behind a curtain while treatment took place.
- *Length of follow-up*: 19-20 weeks.

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[1] Felson DT, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727-35.

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- *Completeness of follow-up:* 30% of patients in each group did not complete the protocol, and were not evaluated 19-20 weeks after beginning treatment.

Validity

- *Is the study type appropriate for the questions being asked?* Yes, it is appropriate that it was a double-blind, randomized, placebo-controlled trial. It was of too short duration to evaluate Prosorba's effects on modifying disease or inducing remission.
- *Was the study population typical of patients with this disease?* Patients in this study had more severe RA than is typical of patients with RA.
- *Were the treatment/control groups comparable at baseline?* Not entirely. The sham group had a mean duration of RA that was 4.2 years greater than the Prosorba group. ($P = 0.02$) The Prosorba group also had better baseline status as measured by Health Assessment Questionnaire scores and physician and patient global assessments.
- *Was the intervention compared to placebo and/or best accepted intervention?* Yes, sham apheresis was used as a placebo control. No, it was not compared to best accepted intervention.
- *Was there compliance with the intervention?* Only 70% of patients completed the study.
- *Was there equal intensity of observation of study and control subjects?* Yes
- *Was the process of observation likely to effect the outcome?* No
- *Intention to treat analysis?* Yes, in fact it was discovered that one patient who improved and was assigned to the Prosorba group actually received sham apheresis. Data was analyzed as if he were in the placebo group, which was unfavorable to the Prosorba group.
- *Did conclusions about safety take into account the limited size of the study?* No
- *Conflict of interest disclosure:* This trial was funded in part by Cypress Bioscience, Inc., the manufacturer of Prosorba columns. A review of Cypress Bioscience's website reveals that some of the authors of this study (Drs. Felson (lead author), Fleischman, and Roth) serve on the Rheumatology advisory board of Cypress Bioscience, Inc. Dr. Gendreau, another author, is an executive vice-president and chief medical and scientific officer of Cypress Bioscience. (http://www.cypressbio.com/mapindex.html)
- **Conclusions regarding validity of methods:** The trial design is the correct one. However, the validity of this study is sub-optimal. The study size was small, treatment groups were not equivalent at baseline, and this study is inadequate to address the issue of long-term outcome. The baseline differences between the two groups would have favored the Prosorba group.

  In their presentation of the results, the authors do not present confidence intervals. Nor do they make clear, to my reading, what statistical method they used to calculate the *P* values they presented.

Results

- Quantified results (i.e., incidence/1000)
  - ❖ 27% in the Prosorba group had ACR-20 improvement when evaluated at 19-20 weeks. This represents 15 of 52 patients. This compares to 11% of patients in the placebo group. This represents 5 of 47 patients.
- Relative risk (RR) and 95% CI
  - ❖ 0.81 RR for failure to improve (95% CI: 0.68 to 0.99)
- Absolute risk reduction (ARR)
  - ❖ 16% more Prosorba patients improved (95% CI: 1 to 31)
- Number needed to treat (NNT), 95% CI, and time period
  - ❖ 6 patients would need to be treated with Prosorba for one to achieve an ACR-20 response 4 months after beginning treatment (95% CI: 3 to 74)
- P values (exact values if possible)
  - ❖ First, this caveat: I could not identify with certainty what statistical method was used to calculate *P* values by the authors of this study.

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- ❖ For difference in duration of RA at baseline: $P = 0.02$
- ❖ For different ACR-20 response rates, $P = 0.019$, adjusted for interim analysis (author's P value)
- ❖ $P = 0.03$ for ACR-20 responses in a retrospective analysis that attempted to control for the longer disease duration of the placebo group and the better baseline status regarding patient and physician global assessments and Health Assessment questionnaire scores of the Prosorba group (author's P value).

- Include adverse outcomes
  - ❖ Adverse outcomes were frequent, and commonly severe. They commonly occurred in both the Prosorba and placebo groups. The authors indicated that they believed that apheresis was the likely cause of the side effects and not the Prosorba device, per se. N.B., however that use of the Prosorba device entails apheresis, and hence adverse effects secondary to apheresis are part and parcel of Prosorba treatment. 62% of patients in the Prosorba group (29 of 47) experienced side effects designated as severe. 55% of patients in the placebo group (24 of 44) suffered side effects designated as severe. Common side effects included joint pain (88% Prosorba group; 78% placebo), continuous ($\geq$ 3 weeks) joint pain or swelling (21% Prosorba group; 29% placebo group, severe fatigue or weakness (the same side effect) (13% Prosorba group; 16% placebo group). The average hemoglobin, hematocrit, RBC count, and MCV dropped equally in both groups. The average decline in hematocrit was 6% (from 43 to 37%). Central venous lines (placed for IV access) were plagued by serious complications. Complications occurred in 5 of 9 patients with central lines. Three subjects suffered thromboses and there were 3 central line infections. Mid-way through the trial, the protocol was altered and only peripheral venous access was permitted.

Authors' Conclusions

"… apheresis with the Prosorba column is an efficacious treatment for patients with RA who have failed other treatments. The temporal association of side effects with apheresis treatment and the similar rate of side effects in the treatment groups suggest that most side effects were related to apheresis treatment. … Further work is necessary to delineate how long treatment remains efficacious and how often patients may need to be treated. Also, the cost-effectiveness of this treatment is unknown."

Reviewer's Conclusions

In a very small study with a large proportion of patients who did not complete the study, use of the Prosorba column was associated with improvement (ACR-20 response) in about 16% more patients than those assigned to placebo treatment. The number needed to treat for such modest effects is 6, with the 95% confidence interval extending to 74. Side effects were very common, and many were serious. It is, in my opinion, at least a toss-up whether the side effects from Prosorba treatment outweigh the benefit. Given the small study size and the frequency of adverse effects, this study fails to reassure me of the safety of Prosorba treatment. That the two groups were not equivalent at baseline in ways that would tend to favor the Prosorba group is troubling. This study provides no evidence that long-term results from Prosorba are improved over placebo. This study provides no data as to whether Prosorba is more efficacious than treatment with single or combination therapy using standard RA treatments, or that relief of pain is any greater than could be achieved by adding effective analgesics to standard RA treatment.

I conclude that this study provides unconvincing evidence that Prosorba *may* provide better symptom relief 19 to 20 weeks after beginning treatment than placebo for 1 out of 6 patients (95% CI: 1 out of 3 to 1 out of 74). This study does not confirm any long-term benefit or any benefit beyond that provided by currently available treatments for RA.

I do not feel that the evidence provided by this study warrants adopting Prosorba treatment for RA. However, I will briefly comment upon the cost-effectiveness. The cost to purchase 12 Prosorba columns, according to a recent *Medical Letter* review is about $11,000. For an NNT of 6 this would equal, in device costs alone, about $66,000 to benefit one patient. If the true number benefited is halfway between the point estimate of NNT and the outer bound of NNT, then the "true" NNT would be 40 and the Prosorba device cost to benefit one patient would be about $440,000.

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