

# Apheresis Treatment of Recurrent Focal Segmental Glomerulosclerosis After Kidney Transplantation: Re-Analysis of Published Case-Reports and Case-Series

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A systematic re-analysis of published cases was performed to better define the role of plasmapheresis in the treatment recurrent focal segmental glomerulosclerosis after renal transplantation. Forty-four cases were identified, of which 32 responded to apheresis. The median number of treatments to response was 9. There was no difference between responders and nonresponders in the total number of treatments performed. The presence of sclerosis on biopsy predicted treatment failure. Relapse after first successful treatment was reported in 10 cases. The median number of treatments received was less and the time from diagnosis to first treatment was greater for patients who relapsed than for patients in whom relapse was not reported, but the differences were not statistically significant. On the basis of this analysis, we recommend early treatment after diagnosis with a regimen of three daily plasmapheresis treatments followed by 6 treatments on an every other day basis. *J. Clin. Apheresis* 16:175–178, 2001. © 2001 Wiley-Liss, Inc.

**Key words:** plasmapheresis; renal failure; biopsy; proteinuria

## INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) may recur after kidney transplantation and can result in renal failure. There is evidence that FSGS is due to the presence of a circulating factor that causes increased glomerular filtration [1]. Plasmapheresis has been shown in a number of uncontrolled series and case reports to be effective in treating recurrent FSGS after transplantation [1]. However, there is little consensus on the appropriate plasmapheresis protocol. In order to better rationalize the treatment of recurrent FSGS, we conducted a systematic re-analysis of published case reports.

## DATA COLLECTION AND ANALYSIS

Published reports meeting the following criteria are included: renal transplantation for chronic renal failure due to FSGS, recurrence of FSGS after transplantation, and treatment by plasmapheresis after diagnosis of recurrence. Series in which only aggregate data or qualitative results were reported were excluded. Cases in which there was a secondary diagnosis, such as allograft rejection, in conjunction with recurrent FSGS were included. Cases in which there was a diagnosis other than FSGS were not included. The following data were collected: interval from transplant to diagnosis of recurrent FSGS, interval from diagnosis to initiation of plasmapheresis, apheresis regimen, response to apheresis, number

of apheresis treatments before response, total number of apheresis treatments, transplant biopsy results before apheresis, and presence or absence of second relapse. In cases where there was more than one recurrence of FSGS treated with apheresis, we examined only the first recurrence.

Recurrent FSGS was defined as new onset of nephrotic range proteinuria or biopsy diagnosis. Criteria for biopsy diagnosis of FSGS were the presence of mesangial hypercellularity, epithelial foot process fusion, or glomerulosclerosis. Response was defined as a decrease in proteinuria to less than 50% of the pretreatment level. When serial determinations of proteinuria were reported, the day at which protein excretion dropped below 50% was considered the time of response. When only the post-treatment level of proteinuria was reported, the time of response was considered to be the last day of treatment.

## RESULTS

Forty-four cases satisfying inclusion and exclusion criteria were identified [1–12]. The interval from transplant to diagnosis was reported in 30 cases. The

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Received 4 May 2001; Accepted 15 September 2001

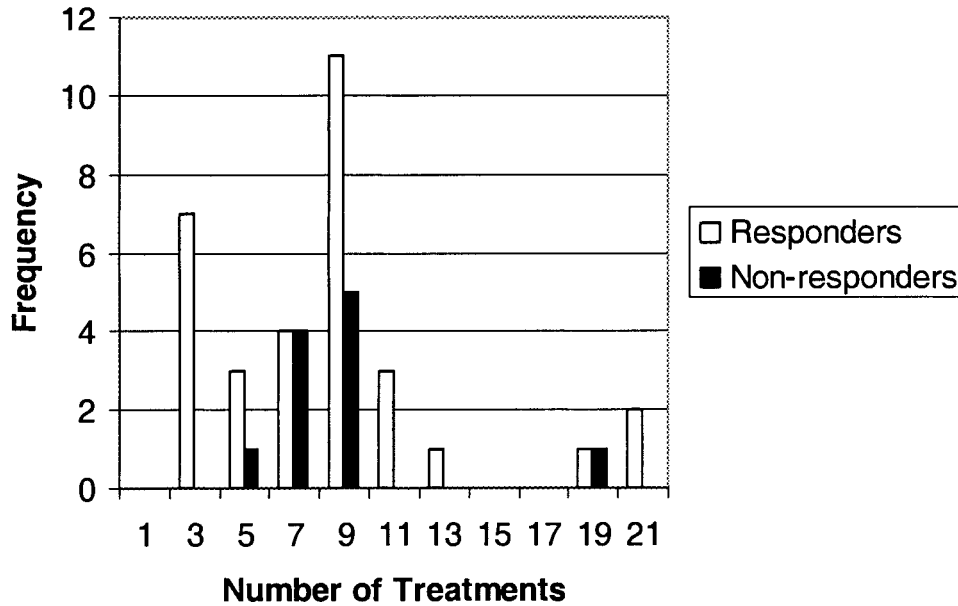


Fig. 1. Comparison of the number of apheresis treatment until clinical response or termination of apheresis therapy (non-responders).

median time from transplant to recurrence was 21 days, with a range of 1 to 2,100 days. The interval from diagnosis of recurrent FSGS to initiation of apheresis was reported in 27 cases. The median time from diagnosis of recurrence to initiation of apheresis was 9 days, with a range of 0 to 91 days.

Among all cases, there were 32 positive treatment responses and 12 treatment failures. There was no difference in the number of treatments performed between responders and nonresponders (Fig. 1). Among responders, the median number of treatments to response was 9 with a range of 2 to 20. Twenty-six of 32 patients (81%) responded in 9 or fewer treatments. Ten patients received additional treatments after a positive response. The median total number of treatments received by responders was 9 with a range of 3 to 20. Among nonresponders, the median number of total treatments was 9, with a range of 6 to 32. There was no statistically significant difference in number of treatments received by responders vs. nonresponders (Mann-Whitney U test = 0.71).

The median interval from diagnosis of recurrence to first plasmapheresis was 10 days for responders as compared to 19.5 days for nonresponders. This difference was not statistically significant (Mann-Whitney test = 0.34). However, the interval from diagnosis to first apheresis treatment was available in only 4 out of 10 cases of nonresponders. The median time from transplant to first plasma exchange was 20 days for responders, as compared to 21 days for nonresponders (Mann-Whitney U test = 0.95).

Relapse of FSGS after successful apheresis treatment was reported in 10 cases. The time from last

apheresis treatment to recurrence ranged from 7 days to 13 months. The median number of total treatments received by patients who subsequently had relapse of FSGS was 6, compared to 9 for patients in whom relapse was not reported (Fig. 2). However, this difference did not achieve statistical significance (Mann-Whitney U test = 0.069). There is no difference in total number of treatments received by patients who relapsed within one month compared to patients who relapsed later.

The median time from diagnosis to first apheresis treatment was 9 days for patients who had an initial positive response and did not relapse, as compared to 27 days for patients who did subsequently relapse. However, this difference was not statistically significant (Mann-Whitney U test = 0.067).

A pretreatment biopsy was obtained 36 cases. In two cases, the biopsy was inadequate for evaluation of FSGS due to insufficient numbers of glomeruli. The presence of glomerulosclerosis or an inadequate biopsy was predictive of treatment failure. Nine out of 10 biopsied nonresponders had sclerosis or inadequate material, compared to three out of 26 biopsied responders (Chi square test < 0.05). The most frequent finding on biopsy patients who responded to apheresis was epithelial foot process fusion.

Eleven different treatment regimens were among the 12 reports. The most commonly used regimen consisted of 3 treatments performed on consecutive days followed by six treatments performed on an every other day basis. The most intensive protocols consisted of daily treatment for 10 days followed by weekly treatments for 7 to 8 weeks. The least intensive

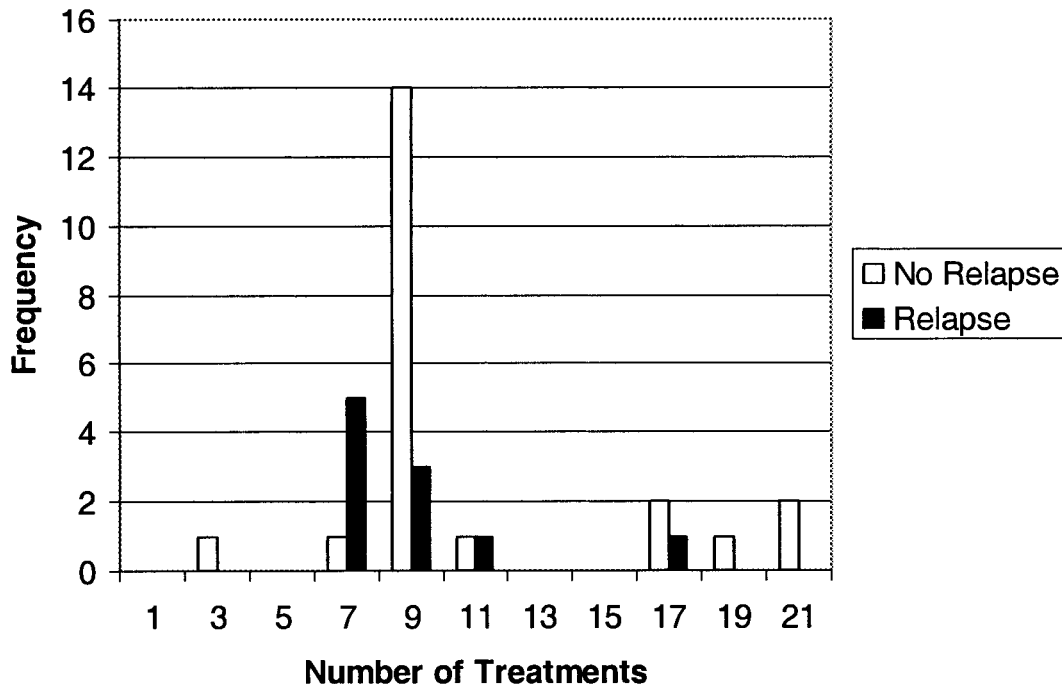


Fig. 2. Comparison of the total number of apheresis treatments received by patients with an initial response to apheresis grouped by the presence or absence of subsequent relapse.

protocol was six treatments performed on an every other day basis. The diversity of regimens reported precluded statistical analysis. However, an initial period of intensive plasmapheresis may be associated with less chance of subsequent relapse. Five of ten patients with relapse after treatment had an initial treatment on an every other day basis, compared to 5 of 22 patients who did have subsequent relapse.

## DISCUSSION

Analysis of published cases is limited by data collection and reporting. We endeavored to identify as many published cases as possible by searching Medline and through references in relevant publications. However, this does not assure that all case reports meeting the inclusion criteria were identified. It is possible that inclusion of more cases would alter the results of this analysis. In addition, reporting bias may influence the current results. Unsuccessful treatments tend to be reported less frequently than successful treatments. We limited this analysis to treatment of the first recurrence of FSGS in renal transplant patients. These results may not be directly applicable to other situations. It is possible that FSGS in the native kidney would respond differently. In particular, it may not be diagnosed at an early stage because the patient may not be monitored as vigilantly as after transplantation. There are few data on treatment of second or third recurrence of FSGS in

the transplant kidney. However, several case reports indicate that response to apheresis in subsequent relapse may be as good as with first relapse [4,10,13].

The strongest predictor of good response to apheresis is the presence of epithelial cell foot process fusion and lack of sclerosis on renal biopsy. Positive response tends to be fairly rapid with approximately 80% of patients responding within nine treatments. There is a suggestion that early treatment is associated with positive response although statistical significance could not be demonstrated at the 0.05 level. It seems prudent to initiate apheresis as soon as possible after the diagnosis of the recurrence of FSGS is made.

Relapse after initial successful treatment by apheresis is not clearly associated with the total number of apheresis treatments, although there is a suggestion that patients who relapsed early may have received fewer treatments than patients in having relapse was not reported. Similarly, there is a suggestion that a longer interval from time to diagnosis to first plasma exchange may be associated with relapse. It seems prudent to suggest early apheresis treatment and a total of at least nine procedures, since this appears to be less associated with relapse. However, we do not know the final outcome of all patients. It is possible that late relapse is underreported.

There is no clear consensus on the best apheresis regimen for the treatment of recurrent FSGS. However, the experience from these cases suggests that a

regimen consisting of three daily treatments followed by six treatments on an every other day basis is associated with good response and perhaps a lesser chance of relapse. If a significant reduction of proteinuria is not achieved within nine treatments, then further apheresis treatment is unlikely to be successful. In such cases, consideration should be given to other causes of inadequate graft function.

Consolidation therapy, in which apheresis is continued after successful response has been achieved, is not supported by these data. Consolidation therapy does not prevent relapse. In addition, apheresis appears to have a long-term positive effect. Protein excretion can continue to decline even after conclusion of apheresis [6,12,13]. However, it is important to adapt the apheresis regimen to the patient's clinical response.

## CONCLUSIONS

Despite the absence of controlled studies, our review of the available case-reports and case-series permits us to offer certain recommendations for the management of patients with recurrent FSGS after renal transplantation. We recommend early plasmapheresis treatment of patients with FSGS who have proteinuria or evidence of recurrence on biopsy with a course of three daily treatments followed by 6 treatments on an every other day basis. We do not recommend plasmapheresis if there is sclerosis on the biopsy. We do not recommend continuing plasmapheresis beyond nine treatments if a positive clinical response is achieved. Failure to achieve a clinical response in nine treatments should prompt evaluation for other causes of allograft dysfunction.

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