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Plasmapheresis rescue therapy in progressive systemic ANCA-associated vasculitis: single-centre results of stepwise escalation of immunosuppression.

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ABSTRACT

Objective

we evaluated 26 patients with antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) with progressive disease despite treatment with cyclophosphamide and steroids treated with additional plasmapheresis and compared outcome with 50 matched-disease controls.

Methods

patients diagnosed with AAV and treated with cyclophosphamide from January 1990 until December 2009 (n= 272) were included when plasmapheresis was not started at diagnosis but added for progressive disease during initial standard therapy (n=26). We selected controls equal for age, Birmingham vasculitis activity score and creatinine at diagnosis. Primary endpoint was estimated glomerular filtration rate (eGFR) or death.

Results

plasmapheresis was added 18 days (range 5 to 41) after start of therapy. In 11 patients, a rise in serum creatinine > 30% led to plasmapheresis; insufficient response to induction (n=11), progressive pulmonary disease (n=3) or progressive necrotic lesions (n=1) were other indications. In the plasmapheresis group, six patients needed renal replacement therapy (RRT), and three controls. Five years after diagnosis, four patients had died in the plasmapheresis group against eight controls (P=0.94).

At baseline, mean eGFR was 44 ml/min/1.73m2 in plasmapheresis group versus 43 ml/min/1.73m2 in controls. At start of plasmapheresis, eGFR was 26 ml/min/1.73 m2 (P=0.003), at 6 months mean eGFR had significantly improved to 44 ml/min/1.73m2 (P=0.0003), comparable to eGFR in controls, 48 ml/min/1.73m2. During long-term follow-up there was no difference in renal function between the groups.

Conclusion

AAV patients with progressive disease despite standard induction therapy in whom plasmapheresis was added, had significant improvement in renal function and similar long-term outcome in both renal survival and patient survival as matched disease controls.

INTRODUCTION

Antineutrophil cytoplasmic autoantibody (ANCA) associated vasculitides (AAV) are rare, potentially fatal diseases, usually with multi-organ involvement. Nowadays, therapy with cyclophosphamide and prednisolone results in disease remission in 80-90% of patients; however, those patients who present with advanced renal failure or pulmonary haemorrhage have significantly worse outcomes (1-3). Thus, in these patients stepwise introduction of more aggressive immunosuppressive induction therapy might be beneficial.
As ANCA are nowadays deemed pathogenic, their removal by plasmapheresis is rational (1-6). Elimination of circulating ANCA may stop the pathological process until corticosteroids and cyclophosphamide suppress inflammation and autoantibody production (4-6). In addition, removal of other pro-inflammatory factors could contribute to and augment the clinical effects of plasmapheresis (1-4,6-8).
Although plasmapheresis has been shown to be of benefit in patients with rapidly progressive glomerulonephritis caused by anti-glomerular basement membrane (GBM)-antibodies and in vasculitis patients with pulmonary haemorrhage, evidence for the use of plasmapheresis in AAV is limited (1,3,5,8). Based on previous studies, present recommendations for plasmapheresis or plasma exchange in vasculitis are limited to severe renal disease with creatinine > 566 umol/d (although one study suggested to start earlier with creatinine levels > 2.85 mg/dl based on positive effect on preservation of renal function), dialysis dependency and pulmonary haemorrhage or disease refractory to traditional therapy (1,3-8).
In our hospital, plasmapheresis is also used as rescue therapy in AAV patients when response to initial induction therapy is insufficient and when clinical condition or renal function worsens due to on-going vasculitis disease activity. We retrospectively evaluated a single-centre cohort of AAV patients undergoing plasmapheresis for so-called 'extended criteria' to evaluate outcome of these patients.

PATIENTS, MATERIALS AND METHODS

Patients

Between January 1990 and December 2009, 272 newly diagnosed patients with AAV started induction therapy with cyclophosphamide and prednisolone. In 22 patients, plasmapheresis was added to initial induction treatment as these patients presented with severe renal failure (dialysis dependency and/or serum creatinine > 566 umol/dl) or pulmonary haemorrhage. In 26 of the remaining 250 patients, plasmapheresis was added as rescue therapy following an unsatisfactory response to initial induction therapy with cyclophosphamide and prednisolone with persistent vasculitic activity and progressive clinical signs or symptoms. From the remaining cohort (n=224), we selected two controls

that were equal in age (range ± 5 years), Birmingham vasculitis score (BVAS; range ± 5) and serum creatinine (range ± 50) at diagnosis for every patient who received plasmapheresis as rescue therapy. Two plasmapheresis rescue patients could only be matched to one instead of two controls (due to age at diagnosis and limited number of patients in that age range), resulting in a control group of only 50 instead of 52 patients.

Patients data and follow-up

When at diagnosis, a positive ANCA was found in indirect immunofluorescence (IIF), its specificity was confirmed by antigen-specific enzyme-linked immune-absorbent assay (ELISA) (9). Different forms of AABV were classified using the Chapel Hill Classification criteria with the modification of Watts et al (10-12). After diagnosis, all patients were followed intensively with frequent evaluation of disease activity, complications and other events, whether admitted to the hospital or as outpatient. Baseline data included renal function (serum creatinine, creatinine clearance, proteinuria, urinary sediment), C-reactive protein (CRP), ANCA and assessment of BVAS. Monitoring of therapy response included also these latter measurements which were performed at least weekly for the first 6-8 weeks. Data extracted from the patients records included the baseline data (start of therapy), the data at the moment of start of added plasmapheresis (and the matching time point in the matched controls) and every 3 months during the first year and yearly thereafter.

Renal function was assessed as eGFR (ml/min/1.73m2) using the modification of diet in renal disease (MDRD formula).

During follow-up, complications possibly related to therapy were recorded. Relapses of vasculitic disease activity were assessed as time of relapse was defined as the moment institution of renewed/intensified immunosuppressive therapy for active vasculitis disease. All patients were followed until death (n=24), loss of follow up (n=2) or June 30th 2012 (n=246).

Treatment: immunosuppressive protocol and plasmapheresis.

Induction treatment consisted of oral cyclophosphamide (2 mg/kg, adjusted to 1.5 mg/kg in case of age > 65 years or signs of bone marrow insufficiency) and prednisolone (1 mg/kg; maximum dose 60 mg/day). In both the groups, five patients with severe disease at diagnosis were also treated with intravenous high-dose methylprednisolone (1000 mg) during three consecutive days. Doses of cyclophosphamide were adjusted to maintain the white blood cell count above 4 x 10*9/L. Biopsies were only performed when diagnosis was doubtful or when no response to treatment was observed. After 4-6 weeks of stable remission, in both groups the prednisolone dose was tapered by 10 mg every 2 weeks until the dose reached 30 mg and thereafter by 5 mg every 2-4 weeks.

Plasmapheresis (45 ml/kg/day), filtration method, was performed against albumin 5% every other day for nine sessions in 3 weeks in total (6,13). As fresh frozen plasma is far

more expensive, has potential transmission/contamination risks and no proven advantage, it was only used instead of albumin 5% to restore clotting factors in case of bleeding complications or planned invasive procedures. When no response was observed and a (second) renal biopsy showed on-going active disease, another nine plasma exchanges in 3 weeks followed.
During 1990-1996, maintenance therapy consisted of oral cyclophosphamide with tapering of the daily dose by 25 mg every 3 months starting after 3 months of stable remission on cyclophosphamide (n=117). From 1996, patients were switched to azathioprine maintenance therapy (1.5-2 mg/kg body weight daily) after 3 months of stable remission on cyclophosphamide (n=165). From 1 year after diagnosis, azathioprine was tapered by 25 mg every 3 months.

Statistical analysis.
Groups were matched in 2: 1 manner. Data were analysed using SPSS16 and Graph Pad Prism version 5.01. Values are given as median and range. Groups were compared using unpaired t-test or chi-squared test. For paired data, a paired Student's t-test was used. Relapse-free survival was assessed with actuarial survival curves, calculated using Kaplan-Meier estimates for survival distribution. Differences between groups in survival were analyzed with log-rank test. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics and renal course in plasmapheresis group.
Mean time to start plasmapheresis as rescue therapy after diagnosis was 18 days (range 5-41); most patients underwent nine plasmapheresis sessions (range 4-18). Of the 26 patients who started plasmapheresis, three patients had to be treated because of worsened pulmonary symptoms, one patient started plasmapheresis for worsening symptoms of necrotic acra and the remaining 22 patients started because of insufficient response or deterioration in renal function. In 15 of these patients, a renal biopsy showed on-going vasculitis-activity, while in seven patients a renal biopsy could not be performed due to contraindications; six of these 22 patients needed renal replacement therapy (RRT) when renal function deteriorated.
Mean eGFR in all the 26 patients decreased from 44 ml/min/1.73m2 at time of diagnosis and start of standard induction therapy to 26.4. ml/min/1.73m2 ($P= 0.003$). After starting plasmapheresis, eGFR improved to 43.3 ml/min/1.73m2 at 6 months after diagnosis and 48.4 ml/min/1.73 m2 at 12 months after diagnosis. During long-term follow-up, eGFR did not decline: 5 and 10 years after diagnosis mean eGFR was 60 and 54 ml/min/1.73 m2, respectively.

Of the six patients who started RRT, five patients became dialysis-independent within 3 months after diagnosis following addition of plasmapheresis rescue therapy and only one continued RRT. During long-term follow-up, two additional patients developed end stage renal disease (ESRD); one of them had been treated with RRT during the first month after diagnosis.
Two patients died within 4 months after diagnosis and treatment with plasmapheresis, both due to septic condition and respiratory insufficiency caused by pulmonary aspergillosis and pneumocystis jirovecii pneumonia (as an exception to our local protocol, no prophylaxis had been initiated because of a known allergy to co-trimoxazole).

Plasmapheresis versus controls

Baseline

Clinical characteristics of patients in plasmapheresis group and controls are given in Table 1.
Only mean CRP levels at baseline differed significantly between both groups, 143 vs 105 mg/l (P=0.045). Granulomatosis with polyangiitis and microscopic polyangiitis were equally distributed over the groups. Twenty-one patients (81%) in plasmapheresis group were proteinase 3 (PR3)-ANCA positive against 33 controls (66%).

Mortality

During long-term follow up, 27 patients (36 %) died, 6 (23 %) in the plasmapheresis group and 21 (42 %) in the controls (P=0.10). Mortality in the plasmapheresis group at 1, 5 and 10 years was 92%, 80% and 72% respectively and 88%, 83% and 67% in the controls ([HR 0.81; 95%CI 0.31-2.00; P=0.66] for death during long-term follow-up, Fig 1). No difference in causes of death were found between the groups (Supporting Information). Patients in the plasmapheresis group had no higher risk for dying of infectious diseases (P=0.49).

Renal function

At diagnosis mean eGFR in both groups did not differ, 44 ml/min/1.73m2 (range 12-122) in plasmapheresis group and 43 ml/min/1.73m2 (range 8-110) in controls (Fig.2). In the plasmapheresis group, mean eGFR significantly deteriorated from baseline to time of start plasmapheresis to 26.4 ml/min/1.73m2 (range 9-110) while in the same period, eGFR in controls had slightly improved (P=0.0004).
After treatment expansion with plasmapheresis, renal function improved significantly in the plasmapheresis-group and became comparable to renal function in controls (Fig. 2). Also long-term renal function remained comparable in both groups.
Six patients in the plasmapheresis group as well as three controls had to start RRT. During long-term follow-up, two patients in the plasmapheresis group reached ESRD, while only one control started RRT.

Table 1 clinical characteristics at baseline: differences between 26 patients treated with plasmapheresis and 50 controls (C).

	Plasmapheresis	Controls	p-value
Number (n)	26	50	
Age mean (range	56 (26-81)	56 (20-78(	0.95
Sex (m): nr (%)	16 (62)	28 (56)	0.64
Diagnosis			
GPA: n	20	31	0.73
MPA/NCGN: n	5/1	13/6	0.43/0.24
ANCA-specificity			
PR3: n	21	33	0.18
MPO: n	5	14	0.40
ANCA neg: n	0	3	0.20
ENT: n (%)	15 (58)	43 (86)	0.37
Pulm: n (%)	13 (50)	27(54)	0.74
Ren: n (%)	26 (100)	47 (94)	0.20
Creat: mean (range)	224 (54-431)	221 (40-483)	0.52
Creat < 125: nr (%)	10 (38%)	19 (38%)	0.92
Creat 125-299: nr (%)	7 (27%)	15 (30%)	0.83
Creat >300: nr (%)	9 (35%)	16 (32%)	0.77
BVAS: mean (range)	20 (12-32)	22 (15-30)	0.83
CRP mean (range	143 (29-312)	205 (8-307)	0.045

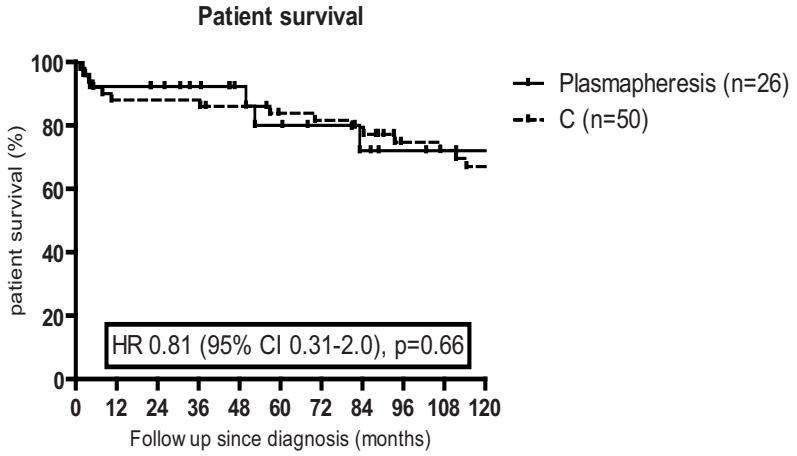
GPA: granulomatosis with poly-angiitis, MPA"microscopic poly-angiitis, NCGN: necrotizing and crescentic glomerulonephritis. PR3: proteinase 3, MPO, myeloperoxidase, ENT: ear nose and throat, Pulm: pulmonary, Ren: renal, Creat: serum Creatinine.

Relapses, Course in ANCA-titre and CRP

Fifteen patients (58%) in plasmapheresis group and 20 patients (40%) in controls experienced a relapse (P=0.009; HR, 2.9; 95% CI, 1.3-6.4) (Fig 3).

At baseline, 100% of patients in plasmapheresis group and 94% in controls were ANCA positive. Significantly more patients became ANCA-negative in plasmapheresis group compared to controls at 3 and 6 months (P<0.0001)(Fig 4). Beyond 6 months, ANCA titres became and remained positive in >50% of patients, irrespective of former treatment.

As CRP is regarded as a marker for active disease, its course was evaluated during and after the start of plasmapheresis. In both groups, the highest CRP levels were found at baseline. In the controls, levels of CRP declined and remained stable during follow-up, while in the plasmapheresis group, CRP decreased to a mean value of 43 mg/l at start of



No at risk	0	6	12	60	96	120
Plasmapheresis	26	24	24	13	7	5
C	50	46	44	38	29	26

Figure 1 Patient survival in months during long term follow up.

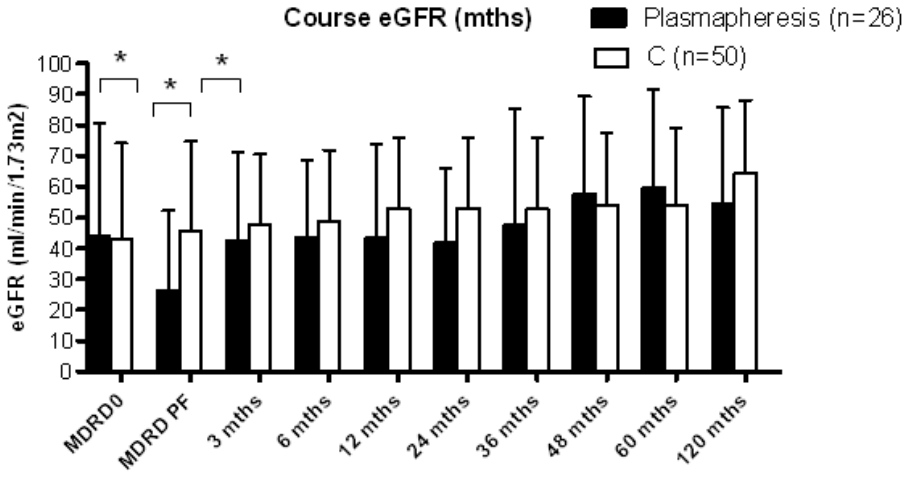
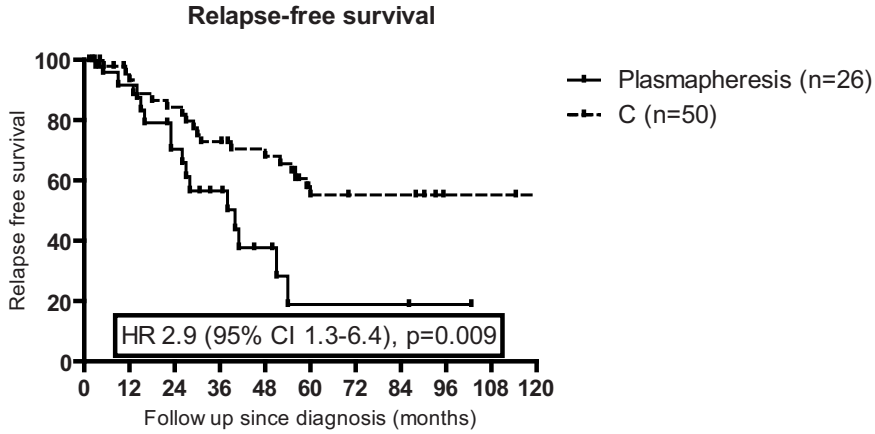


Figure 2 Renal function in MDRD during long term follow up.



No at risk	0	6	12	60	96	120
Plasmapheresis	26	23	22	2	1	0
C	50	45	42	21	15	14

Figure 3 relapse-free survival in months during long term follow up.

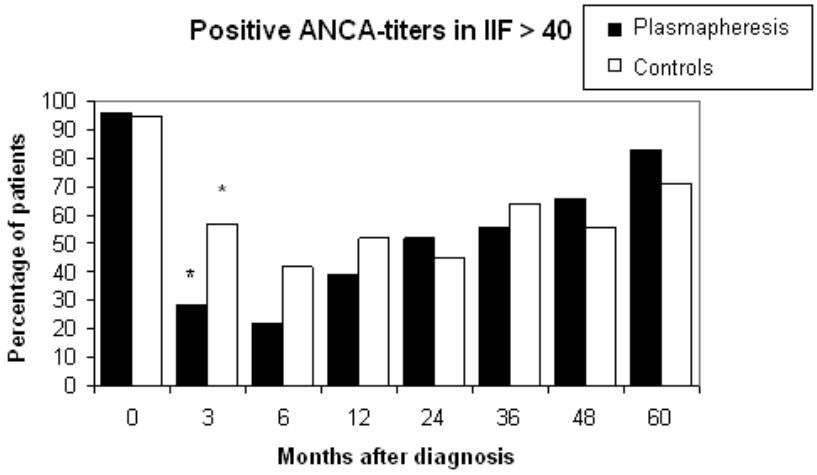


Figure 4 Percentage of patients with positive ANCA titres in IIF after diagnosis (months)

plasmapheresis and fluctuated at low levels over the following weeks. Given the course of clinical parameters and renal function, this may have been related to infectious episodes and not due to active vasculitis.

Adverse events: infectious diseases and others.

All adverse events are given in Table II. Nearly all infectious events occurred within the first month after starting treatment (35 periods, bacterial n=16, viral n=19). No significant difference for bacterial infections was found between the groups (P=0.62), while a trend was found toward more overall viral infections in the plasmapheresis group (P=0.07). For CMV-infections alone, the difference was significant (P=0.03).

Leucopenia was the most prevalent other adverse event in plasmapheresis group which was both statistically significant for mild (< 4.0* 10E9/L) leucopenic episodes (P=0.010) as well as severe (<1.5*10E9/L; P=0.001) compared to controls.

Table 2 Adverse events within 3 months after diagnosis for plasmapheresis- and control-groups.

	Plasmapheresis	Controls	p-value
Number (n)	26	50	
Infectious events	15	17	0.053
Bacterial: n (%)	6 (24)	9 (19)	0.62
Viral: n (%)	9 (36)	8 (17)	0.07
CMV: n (%)	6 (24)	3 (6)	0.03
Leucopenia: n (%)	21 (84)	25 (53)	0.0096*
Severe (< 1.5): n (%)	8 (32)	2 (4)	0.0012*
Diabetes mellitus: n (%)	3 (12)	4 (9)	0.63
Gastro-intestinal: n (%)	5 (20)	1 (2)	0.009*
Thrombosis: n (%)	4 (16)	4 (9)	0.034*
Haemorrhages: n (%)	1 (4)	3 (6)	0.067
Others: n (%)	6 (24)	2 (4)	0.011*

DISCUSSION

Plasmapheresis has been shown to be of benefit in AAV with renal failure and in patients presenting with alveolar haemorrhage (1-8). Two recent studies from Denmark reported better short-term and long-term renal survival in AAV patients who were treated with plasmapheresis added to standard immunosuppressive therapy at diagnosis (7,14).
Our study aimed to proof benefit of addition of plasmapheresis in patients who did not qualify for plasmapheresis therapy at diagnosis but deteriorated clinically while being treated with standard immunosuppressive treatment: until today, only anecdotal evidence existed for this stepwise approach (7).
In our cohort, plasmapheresis was started on average 18 days after diagnosis and start of standard therapy and this addition changed the course of disease. Renal function improved in almost all patients after starting plasmapheresis, was comparable to the controls at 6 months after diagnosis and followed the same course during long-term follow- up, even when added up to 5 weeks after diagnosis and initial treatment. Within 3 months after diagnosis, five of six patients who started RRT were independent of RRT. During long-term follow- up, only two patients reached ESRD.
Surprisingly, relapse-free survival was higher comparing the plasmapheresis group to controls, while maintenance therapy did not differ between the groups. Maybe this was caused by over-representation of PR3-positive patients, well known for higher relapse rates, in the plasmapheresis group (15). However, because we only studied a relative small number of patients, further studies need to be done to verify whether the population of patients selected for plasmapheresis indeed experience a higher relapse rate.

In the plasmapheresis-group, ANCA-levels decreased faster than in the controls, but increased again after 6 months. One could assume a rebound effect of increased production of auto-antibodies after removal, but this should be prevented by cyclophosphamide and prednisolone. Maybe the initial worsening course of disease in the plasmapheresis group suggests a more aggressive phenotype, with faster decline of ANCA after start plasmapheresis but a rebound of ANCA production after the end of this therapy and also more relapses. If this is true, increasing the total burden or lengthen the course of immunosuppressive therapy would maybe result in less frequent relapses.
One could probably attribute part of the adverse events (i.e. infections or haemorrhages) to the immunosuppressive regime and plasmapheresis itself. However, the combination of both therapies was not at the expense of more infectious adverse events. Although a trend was found toward more viral infections in the plasmapheresis group, especially in CMV-infections (P=0.03) during the first month of treatment, no significant differences were found between plasmapheresis group and controls. Other serious adverse events

did occur: more episodes of leucopenia were found in the plasmapheresis group, which more often led to an adjustment in immunosuppressive therapy.
Our study has limitations. It is a retrospective analysis, encompassing more than two decades of clinical observation in which treatment regimens and start of plasmapheresis were not yet fully standardized. In our hospital, biopsies are not taken routinely and only performed when diagnosis is unclear. Data on plasmapheresis and course of clinical symptoms or laboratory parameters may ne underreported.
We compared the plasmapheresis group to controls, in which the patients were broadly equal in age, creatinine and BVAS at diagnosis. These groups were not randomized and had a different initial disease course. Furthermore, the groups are small and in the subgroups even smaller. Therefore, we do recognize that comparing these groups has some major limitations. Nevertheless, this is the one of the first studies to address the significance of plasmapheresis in AAV especially without renal failure, added in the course of disease when response to standard induction therapy is lacking.
Future randomized studies should identify whether patients with AAV would benefit from adding plasmapheresis without renal failure or alveolar haemorrhage, especially since a recent report on long-term follow-up showed no beneficial effect of plasma exchange added as induction therapy compared to intravenous methylprednisolone (19).
On the basis of our finding, one could await initial response for at least 2-3 weeks, but optimal timing of adding plasmapheresis should be studied further. Although current treatment regimens are recommended for those with severe renal involvement, it is also still unclear whether all recommendations can be translated to patients who are dialysis dependent, as lessening toxicity to reduce infectious complications especially seems important in these patients (17,18). At last further studies could be aimed, next to plasmapheresis, at alternative treatment regimens like rituximab, which in prior studies has already been used successfully in refractory disease (19,20).

CONCLUSION

Our study showed a significant improvement in renal function after adding plasmapheresis as rescue therapy, which was not at the expense of higher mortality or increase of serious infectious episodes. Overall, no significant difference was found in development of ESRD during long-term follow-up after diagnosis. Therefore, next to present recommendations, adding plasmapheresis, even after 1 month of initial induction therapy, should be considered in those patients who show insufficient response to standard initial induction therapy.

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