Analyses of registry data of patients with anti-GBM and antineutrophil cytoplasmatic antibody-associated (ANCA) vasculitis treated with or without therapeutic apheresis

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ABSTRACT

Therapeutic apheresis (TA) as a treatment for antibody-associated vasculitis (AAV) was questioned by the PEXIVAS although the MEPEX study favored TA. The aim of this study was to evaluate the efficacy of TA to improve renal function in patients consecutively included in the WAA-apheresis registry versus patients not treated with TA.

Materials and methods: Included were 192 patients that suffered from anti-glomerular basement membrane disease (anti-GBM, n = 28) and antineutrophil cytoplasmatic antibody-associated vasculitis of MPO or PR3 origin. Of these 119 had performed TA and the other 73 had not performed TA for these diagnoses (CTRL).

Results: Elderly had an increased risk to die within 12 months (p = 0.002). All 28 anti-GBM had renal involvement, 21 dialysis dependent. At 3 month ninety (36 %) did not need dialysis. Baseline data regarding renal function of AAV patients, subtype MPO and PR3, were worse in the TA groups than in CTRL. Recovery out of dialysis was better for the PR3-TA group compared with 1) the controls of MEPEX (RR 0.59, CI 0.43–0.80) and 2) the MPO-TA patients (RR 0.28, CI 0.12–0.68). The MPO-TA recovered similarly as the MEPEX-CTRL. Renal function improved most for TA-patients from baseline during the first 3 months (MPO-TA and PR3-TA) and stabilized thereafter and less for MPO-CTRL and PR3-CTRL.

Conclusion: PR3-TA patients seem to have best chances to get out of dialysis. PR3-TA and MPO-TA improved residual renal function better than CTRL. The present study recommends reconsiderations to use TA for AAV especially those with PR3-vasculitis with severe renal vasculitis.

1. Introduction

Patients with antibody mediated vasculitis and renal involvement develop various clinical pictures. Therapeutic apheresis (TA) has been used as an additional therapeutic effort to immunosuppressive drugs in antibody mediated diseases such as anti-glomerular basement membrane disease (anti-GBM) and antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV) [1]. ANCA can be specific for myeloperoxidase (MPO) or proteinase 3 (PR3). AAV is clinically subdivided into microscopic polyangiitis, granulomatosis with polyangiitis,
and eosinophilic granulomatosis with polyangiitis [2]. Approximately 20 % are treatment resistant while 30–60 % relapse with 20–40 % ending up with end stage renal disease (ESRD) [2]. Besides initial TA, the treatment of AAV subtypes is divided into two phases, i.e. induction and maintenance therapy with aim to reduce antibody titers and to avoid relapses [2].

Although previous studies indicated benefits using TA to recover kidney function [3–8], other studies stated that there was no benefit using TA in these patients [9,10] inducing a pro and con debate [11–13]. The studies included aggregated patients of both MPO and PR3 positive AAV.

The aim of the present study, based on registry data, was to investigate recovery out of dialysis and renal function in a group of patients performing TA in regard to a non-TA group, suffering from either anti-GBM, MPO or PR3 vasculitis.

2. Materials and methods

The study included 192 patients that suffered from ANCA or anti-GBM associated vasculitis. The investigation focused on recovery out of dialysis and change in renal function in a group of patients performing TA compared to a non-TA group. One hundred nineteen patients were included as they had performed apheresis (included from the WAA apheresis register from 2011 until 2019) TA as part of the therapy (Groups: TA). The other 73 patients constituted a non-apheresis control group (Group: CTRL) that suffered from ANCA or anti-GBM associated vasculitis. Those patients were collected from Swedish hospitals that did not perform TA. The registry includes data that is part of the Swedish quality assessment system, supported by Swedish health authorities (Swedish Association of Local Authorities and Regions, the National Board of Health and Welfare in Sweden, and Personal data ordinance, PUL).

To find control patients, that were registered at hospitals not performing apheresis but included in the National Data Base for Diagnoses a search was made for patients with the following diagnoses coded by the ICD-10 system: M310, M313, M317, M318, M319. All diagnoses were clinically confirmed by the local physician as based on elevated anti-ICD-10 system: M310, M313, M317, M318, M319. All diagnoses were included aggregated patients of both MPO and PR3 positive AAV.

The study included 192 patients that suffered from ANCA or anti-GBM associated vasculitis. The investigation focused on recovery out of dialysis and change in renal function in a group of patients performing TA compared to a non-TA group. One hundred nineteen patients were included as they had performed apheresis (included from the WAA apheresis register from 2011 until 2019) TA as part of the therapy (Groups: TA). The other 73 patients constituted a non-apheresis control group (Group: CTRL) that suffered from ANCA or anti-GBM associated vasculitis. Those patients were collected from Swedish hospitals that did not perform TA. The registry includes data that is part of the Swedish quality assessment system, supported by Swedish health authorities (Swedish Association of Local Authorities and Regions, the National Board of Health and Welfare in Sweden, and Personal data ordinance, PUL).

The same questionnaire was used in centers that performed TA and in centers which did not (CTRL).

Physicians at the various centers were asked to fill out baseline and follow up data on the patients. Data collected included if and how many TA procedures were performed and if available data of replacement fluid, gender, age, diagnosis, and antibody titer levels against MPO, PR3 and anti-GBM. One question included tobacco habits since tobacco habits have been suspected to interfere with vasculitis [14]. A question included information of immunosuppressive therapy. Since this varied over time no doses in relation to body weight were requested. Collection of data of pulmonary hemorrhage was sparse and if given the grade of severity was not given. These data were therefore not included in the analysis.

The study lacks precise data of the individual apheresis technique used and individual volumes exchanged.

The patients were divided into subgroups including those who needed dialysis during baseline therapy or had a serum creatinine >500 μmol/L (Group: HD). These criteria were similar to those used by Jayne et al. in their randomized trial (MEPEX) [6]. MEPEX was a randomized controlled trial where TA was compared to methyl prednisolone pulses (Dose). We compared our data with the control group of the MEPEX study. Data on renal function (creatinine and eGFR, based on the MDRD formula) were collected at baseline (at admission) and during follow-up at 3, 6 and 12 months. This included data whether belonging to the HD group and if the patient was alive or not. For patients in hemodialysis imputations were then done regarding eGFR that was set at 5 mL/min/1.73 m² during the first 3 months and at 4 mL/min/1.73 m² after ≥6 months, since established dialysis patients have an expected drop in GFR.

Centers where TA was not established as baseline therapy were investigated for their consecutive patients in a similar manner. We were not able to collect individual information of the dosage of immunosuppression.

However, since most patients derived from Sweden, most physician treated according to the Skåne guideline protocol for AAV treatment. This is in line with recent Cochran recommendations [15].

The induction protocol adjusted medication after disease, severity, eGFR and age (>75 years) of the patient. Options for oral cyclophosphamide (1.5–2 mg/kg bow/day) and pulse (doses if pulse 7.5–15 mg/kg bow/pulse based on eGFR and age), solumedrol pulse (250–500 mg 1–3 dose initially) and in parallel oral prednisolone (1 mg/kg bow) were recommended and doses tapered over time. Rituximab pulse doses recommended were 1 g each with 2 doses within 2 weeks. Maintenance doses recommended were initiated after approximately 5–6 months and the use of i.e., azathioprine where recommended as 2 mg/kg bow and day initially, tapered to 1 mg/kg bow and day at 24 months and then recommended reevaluation if to be continued or not.

Statistical analyses included Fishers and Mantel Haenszel test for rates, group comparisons using t-test and for non-parametric data Mann-Whitney U test Paired comparisons were made using Wilcoxon non-parametric analyses. Correlation analyses were performed with Spearman test. Multiple logistic regression analyses were performed with death as dependent factor and variable gender, age and induction therapy cyclophosphamide versus rituximab. A two-tailed p-value less than 0.05 was considered significant. Analyses were performed with SPSS IBM statistic program version 25.

3. Results

A total of 192 patients (mean age 62 years ±17, range 11–88 years, 57 % men, see Tables 1 and 2) were included in the study. Of these 119 were treated with TA performing plasma exchange in addition to pharmacological therapy (Group TA) while the other group had been treated by pharmacological therapy only (Group CTRL). All anti-GBM and ANCA patients had elevated antibodies. In 18 of 28 anti-GBM patients also ANCA antibodies were measured. Seven of these (39 %) had elevated ANCA antibodies in addition to anti-GBM (Table 1).

The number of apheresis performed within the various groups are given in Table 3. The choice of replacement fluid was registered for most of the TA patients. Mainly albumin was used (versus mainly plasma) in 59 % (10/17) of those treated with TA for anti-GBM, 28 % (7/25) of those with MPO-ANCA, and 38 % (16/42) for PR-3-ANCA. The other proportion of patients were mainly supplemented by fresh frozen plasma.

Seventy-three suffered from MPO-positive vasculitis (MPO) and 91 from PR3-positive vasculitis (PR3). A total number of 63 patients were in need of dialysis during the initial hospital stay (59 of them were treated with TA) while 133 patients did not need HD at baseline or later except one patient (anti-GBM) that progressed into HD within 3 months.

Twenty-seven of the Anti-GBM patients received pharmacological therapy (Pharma) and TA while one 80 year-old man received Pharma but not TA. He needed dialysis and stayed with dialysis until he died 5 months later. These 28 were grouped together into anti-GBM (GBM).

The other patients were grouped as those with TA (MPO-CTRL and PR3-CTRL) or as controls without TA (MPO-CTRL, PR3-CTRL).

The median number of apheresis performed by each patient is shown
Table 1  
Distribution of data of anti-GBM patients at start and follow up. Data is given as median (25 and 75 % quartiles), in numbers and proportion (n, %), ‘Lost to follow up’ (Ltfu) and either not dialysis dependent (Not- Dialysis Dep.) or dialysis dependent (Dialysis Dep.). ANCA analysis besides anti-GBM was performed in 18 of the patients.

<table>
<thead>
<tr>
<th>All anti-GBM patients</th>
<th>Within 1st month (n = 28)</th>
<th>At 3 months (n = 28)</th>
<th>At 6 months (n = 27, Lfu = 1)</th>
<th>At 12 months (n = 24, Lfu = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive (n = 28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Median IQR, years</td>
<td>63.5 (46–70)</td>
<td>61 (45–68)</td>
<td>75 (69–75)</td>
<td>61 (45–66)</td>
</tr>
<tr>
<td>Age &gt;60 years (n, %)</td>
<td>16 (57 %)</td>
<td>13 (52 %)</td>
<td>3 (100 %)</td>
<td>11 (52 %)</td>
</tr>
<tr>
<td>Male (n %)</td>
<td>13 (46 %)</td>
<td>10 (40 %)</td>
<td>3 (100 %)</td>
<td>9 (43 %)</td>
</tr>
<tr>
<td>Additional positive ANCA (n, %)</td>
<td>7/18 (39 %)</td>
<td>10/16 (63 %)</td>
<td>2/2 (100 %)</td>
<td>7/14 (50 %)</td>
</tr>
<tr>
<td>Dialysis (n, %)</td>
<td>21 (75 %)</td>
<td>16 (64 %)</td>
<td>2 (100 %)</td>
<td>14 (67 %)</td>
</tr>
<tr>
<td>Subgroup: Not-Dialysis Dep.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>27 (21–69)</td>
<td>29 (20–67)</td>
<td>29 (21–64)</td>
<td>44 (20–70)</td>
</tr>
<tr>
<td>Age &gt;60 years (n, %)</td>
<td>3 (43 %)</td>
<td>3 (33 %)</td>
<td>2 (9 %)</td>
<td>3 (50 %)</td>
</tr>
<tr>
<td>Male (n %)</td>
<td>3 (43 %)</td>
<td>3 (33 %)</td>
<td>3 (43 %)</td>
<td>3 (50 %)</td>
</tr>
<tr>
<td>Additional positive ANCA (n, %)</td>
<td>1/4 (25 %)</td>
<td>1/4 (25 %)</td>
<td>1/4 (25 %)</td>
<td>1/4 (25 %)</td>
</tr>
<tr>
<td>s-creatinine (μmol/L)</td>
<td>195 (189–340)</td>
<td>201 (101–271)</td>
<td>145 (92–239)</td>
<td>109 (84–301)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>30 (16–40)</td>
<td>39 (21–71)</td>
<td>43 (30–72)</td>
<td>60 (18–83)</td>
</tr>
<tr>
<td>Subgroup: Dialysis Dep.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Median IQR, years</td>
<td>64 (51–73)</td>
<td>64 (54–69)</td>
<td>64 (51–67)</td>
<td>63 (52–65)</td>
</tr>
<tr>
<td>Age &gt;60 years (n, %)</td>
<td>13 (62 %)</td>
<td>10 (63 %)</td>
<td>9 (64 %)</td>
<td>7 (64 %)</td>
</tr>
<tr>
<td>Male (n %)</td>
<td>10 (48 %)</td>
<td>7 (44 %)</td>
<td>6 (43 %)</td>
<td>5 (46 %)</td>
</tr>
<tr>
<td>ANCA-positive</td>
<td>6/14 (43 %)</td>
<td>4/11 (36 %)</td>
<td>4/9 (44 %)</td>
<td>4/7 (57 %)</td>
</tr>
</tbody>
</table>

Table 2  
Demographic data of patients who were treated with therapeutic apheresis (TA) or not (CTRL) with either MPO-ANCA (MPO) or PR3-ANCA (PR3) vasculitis. Data is given as numbers (N), percentage (%), mean (m) and standard deviation (±). Dialysis dependent or serum creatinine >500 μmol/L at admission. eGFR is given as mL/min/1.73 m².

**MPO + PR-3**

- Group TA
  - N = 92
  - Age, years: 62.2 ± 17.6
  - Dialysis dep. N = 39
  - Serum-creatinine: 496 ± 365 μmol/L
  - eGFR: 22.7 ± 28.0 mL/min/1.73 m²

- Group CTRL
  - N = 72
  - Age, years: 64.2 ± 13.4
  - Dialysis dep. N = 3
  - Serum-creatinine: 201 ± 148 μmol/L
  - eGFR: 49.1 ± 35.1 mL/min/1.73 m²

**MPO**

- Group TA
  - N = 35
  - Age, years: 63.8 ± 18.7
  - Dialysis dep. N = 19
  - creatinine: 510 ± 298 μmol/L
  - eGFR: 17.3 ± 21 mL/min/1.73 m²

- Group CTRL
  - N = 38
  - Age, years: 68.5 ± 11.0
  - Dialysis dep. N = 1
  - creatinine: 225 ± 127 μmol/L
  - eGFR: 36.3 ± 24 mL/min/1.73 m²

**PR3**

- Group TA
  - N = 57
  - Age, years: 61.2 ± 17.0
  - Dialysis dep. N = 20
  - creatinine: 487 ± 404 μmol/L
  - eGFR: 26.1 ± 31 mL/min/1.73 m²

- Group CTRL
  - N = 34
  - Age, years: 58.9 ± 14.2
  - Dialysis dep. N = 2
  - creatinine: 175 ± 167 μmol/L
  - eGFR: 63.4 ± 40 mL/min/1.73 m²

Antibody titers were analyzed as pairs only, since different methods were used at different hospitals. All antibody titers were significantly reduced within 3 months (by 67–84 %); while anti-GBM was further reduced up to 6 months in the TA group (p = 0.022).

3.1. Group differences

3.1.1. Anti-GBM

All anti-GBM patients (N = 28) had renal impairment. Of these 7 did not need dialysis during the initial hospital stay. The median numbers of apheresis/patient were 9 (IQR: 8–19); Serum creatinine at inclusion was at a median 578 μmol/L (133–1131 μmol/L). Induction therapy was cyclophosphamide oral or pulse in 27 and rituximab in one; all 28 received corticosteroids in addition.

None of the initial dialysis patients came off dialysis during initial hospital stay, while 4 of them came off dialysis until 3 months and another came off dialysis until 12 months (Table 1). One of the initial 7, not in dialysis during initial hospital stay, worsened renal function and needed dialysis within 3 months. Due to referral back to the local hospitals 1 patient was lost to follow up before 6 months and 4 more after 6 months.

At three months 5 of the 7 patients, not HD dependent during the admission period, stayed off dialysis (one died and one progressed into...
HD) while 4 of the initial 21 HD patients recovered out of HD.

One 80-year old man was not treated with TA. He died within 6 months from inclusion. The change in eGFR is seen in Table 1 for those not on dialysis and for the whole group in Fig. 1.

3.1.2. MPO and PR3 vasculitis (Table 4A and 4B)

At baseline there were more dialysis patients in the TA versus CTRL group, both in the MPO and the PR3 groups (p ≤ 0.004, Tables 2 and 3, Figs. 2 and 3). eGFR was lower at baseline in the MPO-TA and also in the PR3-TA than the respective CTRL group (Table 4A).

The change in eGFR from baseline to 3, 6, and 12 months was present that was similar for patients in the MPO-CTRL group and the MPO-CTRL group, although the baseline level was lower for the MPO-TA.

The percentage improvement from baseline was significantly better for the MPO-TA patients than for MPO-CTRL (p < 0.001).

For PR3 patients the improvement in eGFR from baseline to 3, 6, and 12 months was better for patients in the PR3-TA group versus the PR3-CTRL (p ≤ 0.011). For the PR3-CTRL group a significant reduction developed in eGFR from 3 months to 6 months (p = 0.029).

The percentage improvement from baseline to 3, 6, and 12 months was also better for the PR3-TA versus PR3-CTRL (p ≤ 0.012, Table 4A). The number of patients in dialysis at baseline and rate of recovery out of dialysis is shown in Table 4B.

3.1.3. TA groups without dialysis at baseline

Neither any of the non-dialysis patients at baseline of the MPO-TA (n = 16) nor the PR3-TA (n = 37) worsened to need dialysis later. Loss of patients due to death of these patients was present for the MPO-TA in 1 at 3 months, and 2 at 6 and 12 months and for PR3-TA in 2 at 3 months and 3 at 6 and 12 months. None was lost to follow-up in any of the groups.

3.1.4. Control groups with dialysis at baseline

In the control groups hemodialysis at baseline was necessary in 1 of the MPO patients and 2 of the PR3. The MPO patient recovered out of HD within 12 months. One of the PR3 patients died within 3 months while the other recovered out of HD within 6 months.

3.1.5. Control groups without dialysis at baseline

Neither any of the non-dialysis patients at baseline of the MPO-CTRL (n = 37) nor the PR3-TA (n = 32) worsened to need dialysis later. Loss of patients due to death of these patients was present for the MPO-CTRL in 2 at 3 months, and 3 at 6 and 12 months and for PR3-CTRL in none during 12 months. None was lost to follow-up in the MPO-CTRL and in the PR3-CTRL 2 at 3 months and 3 at 6 and 12 months.

3.1.6. Comparison of MPO-TA and PR3-TA with the MEPEX study

The number of patients on dialysis or with a serum creatinine >500 μmol/l is seen in Table 5 and 3. Comparison was made with outcome data of the MEPEX study (Table 4A, 4B, Fig. 4). In the MEPEX study there were 67 patients that were not treated with TA. Of these 33 recovered out of dialysis until 3 months follow up [6]. Comparison with the present study data showed that the recovery in the aggregated data of the MPO-TA and PR3-TA groups did not differ versus the control group of the MEPEX study.

When the PR3 and MPO groups were analyzed separately when patients on HD and death was included in analysis: the PR3-TA had a significantly better outcome than was found for the MEPEX control group (79 %, RR 0.59, CI 0.43–0.80; Table 5). A better outcome was also found when comparing PR3-TA with MPO-TA (RR 0.21, CI 0.07–0.68). In contrast there was no difference between the MPO-TA group and the MEPEX control group.

When disregarding those who died and analyzing only surviving patients at 3 months: there were 3 on HD of 19 of the PR-3 in the present study and 23 on HD of 56 alive patients in the MEPEX study (RR 0.38, CI 0.13–1.14, Fisher’s test p = 0.08).

3.1.7. Pharmacological therapy

The induction therapy was mainly based on cyclophosphamide (Cycl) and corticosteroids (CS) and less on rituximab and CS.

Maintenance therapy varied. Most patients were prescribed azathioprine and CS but differences were present.

Death during 12 months follow up occurred in 21 % of GBM, 15 % of MPO and 7% of PR3 (Table 3). Those who died were older (mean age 73 ± 14 vs 62 ± 16, p = 0.002) while there was no difference in gender or those who performed TA or not (CTRL). Neither was there a difference in survival between those who belonged to the initial HD groups versus those who did not. Comparing with the MEPEX trial, death within 3 months was lower in the PR3 group that received TA in the present study using Mid-P exact test (two tail, p = 0.046) but not Fisher’s test (p = 0.092).

The proportion of patients that died with rituximab as induction therapy was 33 % (5 of 15) versus 10 of 129 (8%) that received cyclophosphamide (RR 4.4, CI 1.70–10.9). Multiple logistic regression with death as dependent factor including variables age, gender and induction therapy exhibited age as the only significant variable (p = 0.009).

4. Discussion

4.1. TA effect on HD recovery

Patients in the TA group had significantly worse renal function at

![Fig. 1. Mean change (±SEM) of eGFR for one patient with GBM-CTRL (hatched line) and patients with GBM-TA (full line). eGFR is given as mL/min/1.73 m².](image-url)
baseline compared to the control group. TA groups included more dialysis patients and also patients with lower baseline levels of eGFR versus the MPO-CTRL and PR3-CTRL groups.

This difference was found upon analysis of data despite ambitions to collect similar control patients from centers treating patients solely with immune suppressive drugs. The data indicated that numerous of the most severely ill patients, even from ‘non-apheresis centers’, had been admitted to apheresis centers for TA. This included patients with both PR3 and MPO which is in line with previous ASFA guidelines for the period of inclusion [16]. In principle all anti-GBM patients were treated with TA, which is in accordance with present ASFA guidelines [1].

Due to lack of comparative control patients in the present study data were compared with the outcome of the MEPEX study [6]. When comparing the MEPEX control group with the merged MPO-TA and PR3-TA group there was no significant benefit of TA. However, when the analysis was divided the PR3-TA but not MPO-TA group showed significant improvements in comparison with the MEPEX-control group, similarly to the MEPEX apheresis group. The PR3-TA group had superior results than the MPO-TA group of the present study. These results indicated that PR3 respond better to TA than MPO. Different therapeutical effects have been described by others [17,18] reporting that the renal prognosis was better in the PR3-ANCA group versus MPO even
studies. An additional impact of environmental factors may be present.

Table 5
Analysis of patients with ANCA vasculitis (mixed group MEPEX) differentiated into MPO-ANCA (MPO) or PR3-ANCA (PR3) vasculitis. Included are the number of patients that had a baseline serum creatinine >500 μmol/l or were dialysis dependent and followed up after 3 months either off HD or still on HD or dead compared with the control group of the MEPEX study [6]. Given below is the relative risk (RR) and confidence interval (CI) for comparison.

<table>
<thead>
<tr>
<th></th>
<th>MEPEX</th>
<th>MPO + PR3</th>
<th>MPO</th>
<th>PR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>33 (49%)</td>
<td>20 (56%)</td>
<td>4 (24%)</td>
<td>16 (84%)</td>
</tr>
<tr>
<td>Maintain HD or dead</td>
<td>24</td>
<td>16</td>
<td>10 + 3</td>
<td>3 + 0</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>36</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>RR, CI</td>
<td>0.88, 1.51</td>
<td>0.57–1.35</td>
<td>1.06–2.15</td>
<td>0.11–0.90</td>
</tr>
</tbody>
</table>

Table 5 Analysis of patients with ANCA vasculitis differentiated into MPO-ANCA (MPO) or PR3-ANCA (PR3) vasculitis. Included are the number of patients that had a baseline serum creatinine >500 μmol/l or were dialysis dependent and followed up after 3 months either off HD or still on HD or dead compared with the control group of the MEPEX study [6]. Given below is the relative risk (RR) and confidence interval (CI) for comparison.

4.2. TA effect on eGFR recovery

In general, a beneficial effect of TA was also seen when analyzing the improvement of both eGFR and the percentage recovery in both the MPO-TA and the PR3-TA groups versus their control groups.

In addition, data indicated that patients treated with an increased number of TA had better improvement of eGFR, an effect that was also described by others [18]. There was no apparent difference between genders.

The present study and others [4,20,27] show that the main improvement in renal function appears during the first 3 months and in principle no further improvement in eGFR can be expected thereafter, except eGFR for anti-GBM-TA that seems to improve until 6 months. Overall the improvements in renal function indicate that time until need of eGFR even in patients not in HD at baseline, such as those with a residual renal function. This would support the concept to treat patients with TA even before they enter the stage of dialysis, as shown by others [7,8]. We agree with others that individual conditions have to be considered (such as degree of fibrosis/sclerosis at histology) and that there is still a space for TA [11,20]. We also want to emphasize that in the MEPEX study [6], and also in the recent study by Walsh [9], a considerable proportion of TA treated patients had a delay in progress into end stage renal disease and dialysis (HD) beyond 3 months of TA.

Antibodies seemed to be reduced to a similar degree for TA patients as for patients with combined therapy and those with immunosuppressive therapy only. However, a reason in favor of TA, besides of more rapid removal of antibodies, is a removal of various activators known to be crucially involved in the complex pathogenesis of ANCA associated vasculitis [11] such as C3a, C5a and sC5b-9.

In the present study induction pharmacological therapy was congruent with the recommendation of the CYCLOPS-study [28] and Cochran analysis [15]. The maintenance therapy was more in line with azathioprine, mycophenolate, methotrexate than prolonged cyclophosphamide [6,29–31]. Most patients were on prolonged maintenance therapy, as suggested by others [29,32]. When relapse develops activation of therapy may be necessary including TA [32]. In resistant cases the use of more potent drugs and immunoabsorption may lower antibody levels faster, which eventually can help to keep more patients out of the HD program [4].

The risk for severe side effects by apheresis is in the range of 5/10,000 procedures [33] while patients with AAV may be more prone to AEs [34]. In patients with an active disease, TA is recommended to continue until resolution of evidence of ongoing glomerular or pulmonary injury, which may be 10–20 days [1].

The present data showed a correlation of a better eGFR outcome with more frequent apheresis procedures, such as suggested by ASFA guidelines [1]. The MEPEX and PEXIVAS trials [6,9] did not address the question of repeated TA when relapse appeared.

**Limitation**: this was a retrospective, consecutive study including patients that in some cases could have a worse condition than patients being included in a randomized trial. Therefore, the effect of TA may be less pronounced than could have been expected otherwise.

Since antibody titer analyses differed between hospitals only paired analyses were performed and no comparisons were made between patients. We were not able to collect individual dosage information of the immunosuppression. However, most patients were treated in Sweden where guidelines are adopted by most physician.

Since only few severely ill patients were present in the control groups, although consecutive inclusion from specific hospitals, comparison on the effect on recovery from dialysis could not be done.

Recent interpretations of pro- versus con arguments for TA [35,36] were based on the PEXIVAS study [9]. That study showed a lack in survival and effect on end stage kidney disease between groups after a median follow-up time of 2.9 years. It is reasonable to argue against TA...
concluded that TA was effective in patients with severe acute kidney injury secondary to vasculitis. Pulse cyclophosphamide may result in an increased risk of relapse when compared to continuous oral use but a reduced total dose. Whilst cyclophosphamide pulse is standard induction treatment, rituximab and mycophenolate mofetil were also effective. Azathioprine, methotrexate and leflunomide were effective as maintenance therapy [13].

In conclusion the present study supports different pathophysiology of PR-3 and MPO ANCA vasculitis that may explain superior response of PR-3 ANCA to TA. Future studies will reveal the importance of renal biopsy for diagnosis and selection to TA based on renal damage such as extensive sclerosis and fibrosis. Both PR-3-TA and MPO-TA improved residual renal function better than controls. We suggest to reconsider the use of TA for AAV especially in regard to patients with PR3-vasculitis with severe renal disease. We also recommend differentiation of AAV when analyzing efficacy of TA.

CRediT authorship contribution statement

Monica Mortzell Henriksson: Conceptualization, Methodology, Writing, draft preparation, Data curation, Investigation, Analysis, Validation, Editing, Reviewing. Maria Weiner: Data curation, Validation, Editing, Reviewing. Wolfgang Sperker: Data curation, Validation, Editing, Reviewing. Berlin Gosta: Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. Maritn Segelmark: Conceptualization, Methodology, Validation, Editing, Reviewing. Alfonso Javier Martinez: Data curation, Validation, Reviewing. Audun Jønnesen Judita: Conceptualization, Methodology, Data curation, Editing, Reviewing. Griskevicius Antanas: Conceptualization, Methodology, Data curation, Editing, Reviewing. Elizabeth Newman: Conceptualization, Methodology, Data curation, Investigation, Reviewing, Milan Blaha: Data curation, Investigation, Validation, Editing, Reviewing. Vrieling Hans: Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. Witt Volker: Conceptualization, Methodology, Data curation, Investigation, Validation, Editing, Reviewing. Stegmayr Bernd: Conceptualization, Methodology, Writing, Data curation, Investigation, Analysis, Validation, Editing, Reviewing, Funding acquisition.

Declaration of Competing Interest

The authors report no declarations of interest.

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