Rituximab for treatment of severe renal disease in ANCA associated vasculitis

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Abstract:

Background: Rituximab (RTX) is approved for remission induction in ANCA associated vasculitis (AAV). However, data on use of RTX in patients with severe renal disease is lacking.

Methods: We conducted a retrospective multi-center study to evaluate the efficacy and safety of RTX with glucocorticoids (GC) with and without use of concomitant cyclophosphamide (CYC) for remission induction in patients presenting with e GFR less than 20 ml/min/1.73 m^2. We evaluated outcomes of remission at 6 months (6M), renal recovery after acute dialysis at diagnosis, e-GFR rise at 6M, patient and renal survival and adverse events.

Results: A total 37 patients met the inclusion criteria. The median age was 61 yrs. (55 to 73), 62% were males, 78% had new diagnosis and 59% were MPO ANCA positive. The median (IQR) e-GFR at diagnosis was 13 ml/min/1.73 m2 (7 to 16) and 15 required acute dialysis. Eleven (30%) had alveolar hemorrhage. Twelve (32 %) received RTX with GC, 25 (68 %) received RTX with GC and CYC and seventeen (46%) received plasma exchange. The median (IQR) follow up was 973 (200 to 1656) days. Thirty two of 33 patients (97%) achieved remission at 6 M and 10 of 15 patients (67%) requiring dialysis recovered renal function. The median prednisone dose at 6M was 6 mg/day. The mean (SD) increase in e-GFR at 6 months was 14.5 (22) ml/min/m2. Twelve patients developed ESRD during follow up. There were 3 deaths in the first 6 months.

When stratified by use of concomitant CYC, there were no differences in baseline e GFR, use of plasmapheresis, RTX dosing regimen or median follow up days between the groups. No differences in remission, renal recovery ESRD or death were observed.

Conclusions:

This study of AAV patients with severe renal disease demonstrates that the outcomes appear equivalent when treated with RTX and GC with or without concomitant CYC.

Introduction:

Rapidly progressive glomerulonephritis and diffuse pulmonary hemorrhage are the most common severe disease manifestations of ANCA associated small vessel vasculitis (AAV). Renal involvement occurs in 20- 50% of patients at disease onset and in 70-80% of patients during the disease course. Immunosuppressive therapy is indicated even in patients with severe renal disease requiring dialysis at diagnosis as there has never been a report that clinical features or histologic features of disease presentation could demonstrate a “point of no return” where immunosuppression is considered futile(1). Published reports note that 55 to 90% of initially dialysis dependent AAV patients recover enough renal function to discontinue dialysis (1-4). Both morbidity and mortality are high in patients who remain dialysis dependent, with both age greater than 60 years and renal dysfunction associated with poor prognosis(5). Progression to end stage renal disease (ESRD) can be prevented by prompt diagnosis and timely initiation of therapy. Induction therapy with glucocorticoids and cyclophosphamide with or without plasma exchange is the standard therapy and is usually effective with greater than 90% of patients achieving remission. However, 50% of patients will relapse. In these relapsing patients, the cost of remission is substantial with 42% of patients developed some form of serious morbidity directly attributable to therapy(6). Despite strategies to minimize exposure to cyclophosphamide, analysis of recent trials show that 59% of early mortality in AAV is attributable to therapy related events(7). The anti-CD20 monoclonal antibody

rituximab depletes B cells and has been approved for remission induction in AAV (8). Fourteen studies have examined rituximab use for remission induction(9). The remission rates after rituximab have varied from 62 to 90%, with differences in remission definitions influencing the results; in particular, the lower response rates were observed in the two randomized trials, which employed more stringent remission definitions(10, 11).

Patients with severe renal disease were excluded from many of the observational studies and from the RAVE trial because insufficient equipoise existed at the launch of RAVE trial to justify the randomization of patients with advanced renal dysfunction to an investigational treatment (10, 11). The RITUXVAS trial enrolled patients with severe renal disease. However, patients randomized to the rituximab arm received two pulses of intravenous cyclophosphamide (11). Furthermore, the KDIGO guidelines recommend use of rituximab for initial treatment only in absence of severe renal disease(12). The purpose of this retrospective multicenter study is to evaluate the efficacy and safety of using rituximab for remission induction in patients with AAV and severe renal involvement defined as, estimated eGFR less than 20ml/min/m^2. This eGFR was chosen to represent severe renal disease since patients become eligible to be placed on transplant wait list and accrue waiting time once the eGFR is at or below 20 ml/min.

Material and Methods:

Study Population:

The study population consisted of patients from a retrospective cohort from six different sites in United States and Europe (Johns Hopkins vasculitis center, U.S.A., Columbia University, U.S.A., Charles University, Prague, Linkoping University, Sweden, University of Birmingham, U.K. and Cambridge University Hospital, U.K.). Patients with a diagnosis of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) with active glomerulonephritis who met the following inclusion criteria were studied: 1) eGFR less than 20 ml/min/m^2; 2) remission induction therapy with glucocorticoids and rituximab with or without concomitant cyclophosphamide; and 3) follow up until remission or death. Patients were allowed to have had plasma exchange. There was no set protocol and as such the administration of cyclophosphamide and plasma exchange was dependent on the practice pattern of the physicians. The study protocol was approved by the Institutional Review Board at each institution

Data Acquisition:

Clinical data:

Demographic and clinical data at the time of diagnosis including age, gender, disease phenotype, ANCA type, new versus established diagnosis, clinical features at presentation, eGFR at presentation and six months, occurrence of disease relapse, need for renal replacement therapy at the time of presentation and at last follow up and details of induction immunosuppression including the dosing of rituximab, formulation and duration of cyclophosphamide use and number of sessions of plasmapheresis were extracted from review of clinical source documents. Adverse events including

rituximab infusion reaction, episodes of leukopenia (WBC less than 4.0) and infections requiring hospitalization were recorded.

Laboratory data:

Peak serum creatinine, erythrocyte sedimentation rate and C - reactive protein at the time of diagnosis were recorded. Available data on urine protein quantification data based on a spot urine sample or a 24 hour urine collection at the time of diagnosis was recorded. ANCA testing was done by standard indirect immunofluorescence assay on ethanol fixed neutrophils for cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (p-ANCA). PR3 and myeloperoxidase (MPO) testing was done by direct enzyme linked immunosorbent assay (ELISA) with commercially available kits at the local lab. If the testing for c-ANCA, p-ANCA, PR3 ELISA and MPO ELISA was negative, patients were labeled as having ANCA negative vasculitis. Patients were categorized as having cytoplasmic and/or proteinase 3-ANCA (thereafter referred to as PR3-ANCA) or perinuclear and/or myeloperoxidase-ANCA (thereafter referred to as MPO-ANCA). Renal biopsy was classified to the International Working Group of Renal Pathologists (IWGRP) class based on paper reports by the individual centers. Available data on B cell counts and presence of hypogammaglobulinemia were recorded.

Outcomes:

The principal outcomes of interest in this cohort were complete remission at 6 months and renal recovery after acute dialysis at diagnosis. Other outcomes included ESRD during follow up and death within the first 6 months.

Study definitions:

Disease phenotype was defined according to the Chapel Hill Consensus nomenclature. Renal function was measured using the 4 variable modification of diet in renal disease (MDRD) formula for estimated GFR (e-GFR) (13). Severe renal disease was defined as MDRD e-GFR of less than 20 ml/min/m^2. ESRD was defined by the ongoing need for renal replacement therapy. Hematuria was defined as urinary red blood cell count of more than 10 per high power field. Kidney involvement was defined by a diagnostic renal biopsy or with the presence of active urine sediment. Remission was defined as stabilization or improvement in serum creatinine, resolution of hematuria and absence of extra-renal signs of vasculitis for at least 1 month (1). Relapse was defined as occurrence of signs and symptoms of vasculitis in any organ requiring a change in immunosuppressive therapy after achieving remission. B cell reconstitution was defined as presence of more than 20 CD19 positive B cells per microliter. Depending on use of concomitant cyclophosphamide, Group A was defined as patients who received glucocorticoids and rituximab only and Group B was defined as patients receiving glucocorticoids and rituximab and concomitant cyclophosphamide either administered as oral or intravenous pulse cyclophosphamide.

Statistical Analyses:

Data were tabulated for the full sample, and also divided by treatment group. Continuous variables except for eGFR rise were summarized as median [interquartile range] and group differences were tested using non-parametric rank sum tests. The

variable eGFR rise was presented as mean (standard deviation) and group differences were tested using the t-test. Categorical variables were tabulated as number (percentage) and group differences were tested using Fisher exact tests. All tests of significance were two sided and differences were considered significant if the p-value was less than 0.05. All analyses were done using the Stata statistical software package (version 13; College Station, TX).

Results:

Patients:

In total, 37 patients with severe renal disease who met the inclusion criteria were identified (between March 2005 and April 2014). The baseline characteristics of the entire cohort are shown in Table 1. The median (IQR) age at diagnosis was 61 (55 to 73) years. Sixty two percent were male and all but one were Caucasian. Twenty two patients (59%) were MPO ANCA positive, 13 were PR3 ANCA positive (35%) and 2 were ANCA negative. Fourteen patients were categorized as GPA and remainder as MPA. The majority of them (78%) had a new diagnosis of AAV. The median (IQR) e-GFR at diagnosis was 13(7 to 16) ml/min/m^2 and 15 were dialysis dependent at presentation. Of the 27 patients that had a diagnostic renal biopsy, the IWGRP class was focal in 3 patients, crescentic in 6 patients, mixed in 12 patients and sclerotic in 6 patients. The remaining 10 patients were clinically diagnosed. Twenty five patients (68%) had extra-renal disease (15 with lung, 7 with sinus, 7 with joint, 5 with ear, 4 with

eye, 4 with peripheral nerve and 3 with skin involvement) Eleven (30%) had alveolar hemorrhage. Twelve patients (32%) received rituximab and glucocorticoids (Group A) and twenty five patients (68%) received cyclophosphamide, rituximab and glucocorticoids (Group B). Glucocorticoid dosing included pulse steroids for 3 days and oral prednisone starting at 1 mg/kg/day and weaned according to local protocol. Seventeen patients (46%) received plasma exchange. The dosing of RTX was 375mg/m^2 once a week for 4 weeks in 18 patients (49%) and 1000 mg every 2 weeks for 2 doses in 19 patients (51%). The median (IQR) follow up was 973 (200 to 1656) days.

When stratified by use of concomitant CYC, twelve patients received rituximab and glucocorticoids (Group A) and twenty five received cyclophosphamide, rituximab and glucocorticoids (Group B). Seven patients received oral cyclophosphamide and 18 received pulse cyclophosphamide. The median number of pulses in the pulse CYC group was 2 (range 1 to 4) and the median duration of CYC use in oral CYC group was 21 days (range 7 to 60 days). The baseline characteristics of both groups are shown in Table1. There were no differences in median age (64 yrs vs. 60 yrs, p=0.65), median (IQR) baseline e GFR [12 (6 to 16) vs. 13(7 to 16), p = 0.62], the RTX dosing regimen used (375 mg/m^2 x 4 or 1000 mg x2), use of plasma exchange (33% vs. 52%, p = 0.3) or median follow up days between the groups (652 vs. 1050, p = 0.59). Renal biopsies categorized by IWGRP class were: Group A (focal in 1 patient, mixed in 4 patients, sclerotic in 4 patients and remaining with no biopsy) compared to Group B (focal in 2 patients, crescentic in 6 patients, mixed in 8 patients, sclerotic in 2 patients and

remaining with no biopsy). Eleven patients had alveolar hemorrhage (3 in Group A and 8 in Group B). Twelve (2 in Group A and 10 in Group B) did not have extra-renal involvement (p=0.26).

Outcomes:

Thirty two of 33 patients with a minimum follow up of 6 months (97%) achieved disease remission at 6 months. The single refractory patient responded to mycophenolate mofetil. Among the 15 dialysis dependent patients 10 (67%) experienced renal recovery to stop dialysis. The mean (SD) rise in e-GFR at 6 months was 14.5 ml/min/m^2 (22). The median prednisone (IQR) dose at 6 months was 6 mg (5 to 10).Rituximab was well tolerated in both groups and no infusion reactions were reported. A total of 5 (13%) patients (1 in Group A and 4 in Group B) did not complete the RTX course, 2 due to lack of medical insurance, in two patients RTX was not given due to a ruptured aortic aneurysm and transition to palliative care due to CMV viremia and in one patient the fourth dose of RTX was not given due to dapsone induced hemolytic anemia. In 18 patients (49%) with available B cell data, all showed depletion at 6 months. At 12 months, 2 patients showed B cell reconstitution and the remaining 16 were B cell depleted. Among 19 patients who had immunoglobulins checked, 9 had low immunoglobulin levels and 10 had normal levels. There were 4 episodes of leukopenia in 4 patients. A total of 10 patients (27%) experienced infections requiring hospitalization. Six patients reached ESRD within the first 6 months and twelve (32%) patients reached ESRD during follow up. Among these 12 patients, 5 were dialysis

dependent at presentation, 4 had progressive disease, 2 had disease relapses and 1 had refractory disease.

There were no differences in outcome when groups were stratified according to use of concomitant CYC. All 12 patients in Group A achieved remission compared to 21 of 22 patients who achieved remission in Group B (p=1.0). There was no significant difference in the percentage of dialysis dependent patients who achieved renal recovery between the two groups (71% vs. 62%, p=1.00). The mean (SD) rise in e-GFR at 6 months in Group A was 17 (20) ml/min/m^2 compared to 13ml/min/ m^2 (24, p=0.6). The median prednisone dose at 6 months was 5 mg in Group A compared to 7.5 mg in Group B (p-0.04). There were no differences in number of patients reaching ESRD during the follow up time or death at 6 months between the groups. There were no deaths in Group A. There were 3 deaths in Group B in the first 6 months, one due to ruptured aortic aneurysm after 1 month of diagnosis, one due to CMV infection and the cause was unknown in one patient.

Rituximab was well tolerated in both groups and there were no infusion reactions reported. There were no differences in episodes of leukopenia or infections requiring hospitalization between the groups during the follow up (Table 2). Among 12 patients in Group A, one patient suffered from bacterial pneumonia and another patient had herpes zoster. Among 25 patients in Group B, 4 patients had bacterial pneumonia, 1 patient had sepsis, 1 patient had candida pneumonia, 1 patient had herpes zoster and 1 patient had CMV infection. Two episodes of leukopenia occurred in each group.

Discussion:

This retrospective analysis of AAV patients with glomerulonephritis and severe renal disease treated with rituximab and glucocorticoids for remission induction demonstrates that outcomes are equivalent to those treated with rituximab and glucocorticoids and a short course of concomitant cyclophosphamide.

AAV patients with severe renal disease pose special challenges due to poor response to therapy and increased burden of side effects from immunosuppressive therapy. The severity of renal dysfunction at diagnosis of AAV portends a poor prognosis for renal survival and patient survival. The one year mortality of AAV patients is 11%(7). The majority of these early deaths are attributed to therapy related adverse events rather than to active vasculitis. The severity of renal dysfunction is the principal predictor of therapy related adverse events and mortality. Individuals with impaired renal function develop episodes of leukopenia while receiving cyclophosphamide therapy suggesting that dose reduction of CYC is required based on GFR. Despite the widespread use of CYC in this setting, dose alterations based on GFR are controversial. Strategies that eliminate or reduce the use of CYC are needed in patients presenting with severe renal dysfunction. Rituximab has been shown to be non-inferior to CYC for remission induction in RAVE trial. However, this trial excluded patients with severe renal dysfunction. RITUXVAS enrolled patients with severe renal dysfunction but the rituximab arm received 2 pulses of IV CYC. Although RAVE and RITUXVAS did not show a safety benefit of RTX, there is no convincing evidence that RTX increases the frequency of severe infection in AAV and has in fact been used successfully for remission induction in the setting of severe infection (14).

Our cohort is enriched with patients with MPO-ANCA and patients had more severe renal disease at baseline with a significant percentage of them requiring dialysis at entry compared to randomized trials using rituximab for inducing remission with comparable remission rates. The degree of renal impairment at baseline was similar to MEPEX trial patients (15). One third of patients in our cohort had alveolar hemorrhage. Renal recovery in dialysis dependent patients in this series is similar to other reported series using either a rituximab based regimen or cyclophosphamide based regimen (2, 11, 16) and better compared to Chinese cohort of predominantly MPO ANCA patients treated with cyclophosphamide and glucocorticoids(17). In this context, it should be noted that despite the presence of severe renal disease, only 46% of patients in our cohort received plasma exchange. The median prednisone dose at 6 months in our cohort is comparable to RITUXVAS and was significantly lower in the group that received rituximab only. About a third of patients in this cohort experienced infections requiring hospitalization which is higher than reported in RAVE and RITUXVAS (11, 18). This may be related to the severity of renal disease in this cohort and use of standard doses of glucocorticoids. The mortality is lower compared to other reported series which included AAV patients with severe renal disease(2, 11, 17) and similar to another series using intravenous cyclophosphamide and plasma exchange for dialysis dependent AAV patients(16). The lower mortality may be due to minimization or avoidance of cyclophosphamide.

Our study is limited by its retrospective design and small sample size. There is significant heterogeneity in treatment regimens with regard to use of plasma exchange and dosing of glucocorticoids and CYC across centers. Due to relatively short follow up,

the duration of sustained remission and impact on long term renal function is not evident from this study. Although proteinuria is an important marker for damage in AAV, we did not have information on protein quantification for majority of patients. Not all patients in our cohort had biopsy confirmed GN and the renal biopsies were classified into the IWGRP class based on pathology reports and were not centrally read. We lack on our ability to comment on the nature of cell infiltrates due to lack of data on immunostaining for markers of B cells, T cells and plasma cells. This is relevant in light of recent study from RITUXVAS patients which correlates renal outcome at one year follow up with T cell tubulitis and the possibility that B cell targeted therapy may not control this arm of the pathogenesis(19).

This retrospective multi-center study demonstrates no added benefit of a short course of CYC for remission induction in AAV patients with glomerulonephritis and severe renal disease treated with a single course of rituximab and glucocorticoids. An open-label, randomized, controlled study is under way (PEXIVAS; NCT00987389), which aims to determine the role of plasma exchange and glucocorticoid dosing in severe AAV. In this trial, enrolled participants have an e-GFR less than 50 ml/min/m^2 and rituximab is permitted for remission induction and therefore the trial may provide additional data on efficacy and safety of rituximab. Further prospective randomized trials are needed to confirm these findings in this cohort of AAV patients with severe renal disease who are at risk for early mortality from therapy related adverse events.

Table1: Baseline characteristics of AAV patients with severe renal disease stratified by use of cyclophosphamide

	Entire cohort (n=37)	Group A(n=12)	Group B(n=25)	P value
Age at diagnosis (yrs), median(IQR)	61(55 to 73)	64(37 to 73)	60(55 to73)	0.65
Gender ,M:F	23:14	7:5	16:9	1.0
ANCA type: n PR3 MPO Negative	 13 22 2	 4 6 2	 9 16 0	0.19
New diagnosis, n (%)	29 (78)	11 (92)	18 (72)	0.23
e-GFR at entry (ml/min) median (IQR)	13 (7 to 16)	12 (6 to 16)	13 (7 to 16)	0.62
Dialysis dependent at entry (n) (%)	15 (40%)	7 (58%)	8 (32%)	0.16
Use of PLEX, n (%)	17 (46%)	4 (33%)	13 (52)	0.32
Extra-renal disease, n (%)	25 (68%)	10 (83%)	15 (60%)	0.26
Alveolar hemorrhage, n (%)	11 (30%)	3 (25%)	8 (32%)	1.0
RTX dosing 375 mg/m^2 q week for 4 weeks, n (%) 1000 mg x 2 doses, n (%)	 18(49) 19 (51)	 6(50) 6 (50)	 12 (48) 13 (52)	 1.0

Cyclophosphamide use Oral(n) Pulse(n)	 7 18	 NA	 7 18	
Clinical site*: 1 2 3 4 5 6	 11 2 4 7 7 6	 4 1 0 1 3 3	 7 1 4 6 4 3	
Follow up time, median days (IQR)	973 (200 to 1656)	652 (325 to 1518)	1050 (135 to 2367)	0.59

*1=Johns Hopkins, Baltimore, U.S.A., 2=Columbia University, New York, U.S.A., 3=Charles University, Prague, 4= Linkoping University Sweden, 5=University of Birmingham, U.K., 6=Cambridge University hospital, U.K.

Table2: Outcomes of patients with severe AAV treated with RTX + GC (Group A) vs. RTX+ CYC +GC (Group B)

Outcomes	Group A(n=12)	Group B (n=25)	P value
Remission n (%) (n=34)	11(100%)	21 (95%)	1.0
Median 6 month Prednisone dose (mg)(range)	5(0 to 6)	7.5 (5 to 10)	0.04
Mean GFR rise at 6 months (SD)	18(20)	13 (24)	0.6
Renal recovery, n %(n=15)	5 (71)	5 (62)	1.0
Infections, n (%)	2 (17)	8 (32)	0.44
Leukopenia, n (%)	2 (17)	2(8)	0.58
ESRD, n (%)	4 (33)	8 (32)	1.0
Death in the first 6 months	0 (0)	3(12)	0.54

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