A novel glucocorticoid free maintenance regimen for ANCA associated vasculitis

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ADS, CDP, MAL, RJP, TDC and SM devised the protocols and instituted the enrollment of patients, supervised their care and their follow up.
SH, AB, SMM, DK MG, JBL, JG, and JS supervised the protocol compliance and collected the clinical data.
SG, RBJ and DJ collected and coordinated the comparison of our cohorts with the EUVAs control groups.
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Key Messages:

1. This is the first time an extreme glucocorticoid avoidance regimen has been attempted in ANCA associated vasculitis, demonstrating its feasibility
2. Brief exposure to glucocorticoids with combined cyclophosphamide and rituximab results in similar remission rates to standard therapy, but with fewer infections and lower rates of diabetes
3. Glucocorticoid avoidance may allow effective remission with reduced adverse effects in both short and long term and should be tested in a formal clinical trial

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ABSTRACT

Objectives

Glucocorticoids (GC) are a mainstay of treatment for patients with anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV), but are associated with significant adverse effects. Effective remission induction in severe AAV using extremely limited GC exposure has not been attempted. We tested an early rapid GC- withdrawal induction regimen for patients with severe AAV.

Methods

Patients with active MPO- or PR3-ANCA vasculitis or ANCA negative pauci-immune glomerulonephritis were included. Induction treatment consisted of two doses of rituximab, three months of low dose cyclophosphamide, and a short course of oral GC (for between 1-2 weeks). Clinical, biochemical and immunological outcomes as well as adverse events were recorded.

Results

A total of 49 patients were included with at least 12 months of follow up in 46. All patients achieved remission, with decreases observed in creatinine, proteinuria, C-reactive protein, ANCA level and Birmingham Vasculitis Activity Score (BVAS). Three patients requiring dialysis at presentation became dialysis independent. Two patients required

introduction of maintenance GC for treatment of vasculitis. Overall outcomes were comparable to those of two matched cohorts (n=172) from previous European Vasculitis Society(EUVAS) trials, but with lower total exposure to cyclophosphamide and glucocorticoids ($p<0.001$) and reduced rates of severe infections ($p=0.02$), compared to RITUXVAS trial). We found no new cases of diabetes in the first year compared to historic rates of 8.2% from EUVAS trials ($p=0.04$).

Conclusions

Early GC withdrawal in severe AAV is as effective for remission induction as standard of care, and associated with reduced GC-related adverse events.

INTRODUCTION

Survival in patients with AAV has improved since the introduction of cyclophosphamide and GC-based treatment regimens [1-3]. However, patients within the first year of diagnosis are at greater risk of death from adverse events rather than active vasculitis. Important drivers of early mortality include infection and leucopenia with both renal impairment and older age being significant predictors of these adverse events [4]. In an attempt to reduce this early morbidity, treatment regimens have been refined in the belief that limiting cyclophosphamide exposure would have a positive impact on outcomes. However, despite minimizing, or completely substituting, cyclophosphamide with rituximab in induction regimens, no difference in adverse events has been found [5, 6]. In rituximab-based trials conventional dosing of intravenous and oral GC was mandated for the induction of disease remission. However, GC tapering has been used successfully in combination with rituximab alone[7] or with combined rituximab and low-dose cyclophosphamide[8, 9], in cohort studies of patients with mild and moderate renal involvement respectively. With rituximab alone reduced adverse effects, but greater relapse rates were found[7], while combined cyclophosphamide and rituximab resulted in both fewer relapses and adverse events [8, 9]. These data suggest that total GC exposure plays a major role in mediating serious adverse events. In addition to infectious

risks, prolonged high dose GC use is responsible for osteoporosis [10], weight gain, cataracts [11], hyperglycaemia and diabetes [12] and cardiovascular events[13], with a clear relationship between adverse events as well as cumulative damage assessed by the Vasculitis Damage Index (VDI) and extent of GC exposure, [11, 14]. This problem is not limited to AAV, as GC are used ubiquitously in the management of autoimmune rheumatological diseases; in patients with rheumatoid arthritis, GC use is associated with a dose-dependent increase in mortality with a threshold daily dose of 8mg [15], while both the dose, and cumulative exposure to GC result in an increased risk of myocardial infarction [16]. In lupus nephritis, lower GC doses were associated with fewer serious adverse events [17]. Until the recent PEXIVAS trial, the dose and taper of GC during induction treatment in AAV has not been subjected to analysis, with previous trials all using high dose GCs alongside cytotoxic or biological agents [18-20].

Beyond induction therapy, the use of maintenance GC to prevent relapse is controversial, but frequently employed. A meta-analysis suggested that patients in trials with a non-zero GC end point suffered fewer relapses compared with those enrolled in trials with a predefined GC withdrawal [21]. By contrast, others have shown that use of GC therapy beyond six months from diagnosis is associated with an increased risk of infections, but no reduction in relapse [22].

Early GC withdrawal or avoidance has been successfully introduced in renal transplantation, [23] [24], and reported in treatment of lupus nephritis [25]. More recently, in AAV, a phase 2 induction trial demonstrated that the use of Avacopan, a C5a receptor inhibitor, was effective in replacing high dose GC alongside cyclophosphamide or rituximab [26], in patients with milder AAV disease followed for just 12 weeks.

We report the outcome of two separate cohorts of AAV patients with acute and severe disease treated with similar GC-sparing regimens, based on combined use of rituximab and low dose intravenous cyclophosphamide, which achieved excellent outcomes, comparable to standard GC based regimens.

METHODS

Patients

Two prospective groups of patients were included with minor differences in duration of oral GC; Group 1 treated at Imperial College Healthcare NHS Trust, and Group 2 treated at the Royal Free Hospital and Trinity Health Kidney Centre, Ireland. Patients were included with either a new diagnosis of AAV or with relapsing disease. The diagnosis was made based on a combination of relevant clinical features and positive PR3-ANCA or MPO-ANCA serology. ANCA negative patients with crescentic pauci-immune glomerulonephritis were included and considered to have renal limited vasculitis. Group 1 excluded but Group 2 included patients with severe disease, requiring dialysis dependency or with alveolar haemorrhage. However, patients with an anti-glomerular basement membrane antibody, and those on long-term GC therapy, were excluded.

Groups 1 and 2 were exposed to slightly different treatment regimens (Table 1). Both were based on a short course of prednisolone, with all in Group 1 and 65% of patients in Group 2 receiving intravenous methylprednisolone, alongside low dose cyclophosphamide and two 1g doses of rituximab. Group 1 aimed to treat patients with a total of 7 days of oral prednisolone, while Group 2 aimed for 14 days. Those presenting with dialysis-dependent renal failure were considered for plasma exchange.

Following six doses of cyclophosphamide, maintenance treatment was commenced with azathioprine or, if intolerant, mycophenolate mofetil (MMF), methotrexate or rituximab. The dose of azathioprine was 2mg/kg (maximum 150mg), or 1mg/Kg in those with reduced thiopurine methyltransferase levels. All patients were treated with co-trimoxazole for three months, gastric protection with a proton pump inhibitor and bone protection with calcium/vitamin D combinations. Patients from high-risk groups were also given prophylaxis against tuberculosis with isoniazid and pyridoxine.

Comparison with EUVAS trial patients

Patients were matched based on age, baseline eGFR-CKD staging criteria and ANCA specificity with patients (n=139) from 3 European Vasculitis Society (EUVAS) clinical trials (CYCAZAREM [27], CYCLOPS [28], and MEPEX [18]) in a ratio of 3:1 for case-control analysis. A separate comparison with the rituximab group from the RITUXVAS [29] trial which used a comparable cyclophosphamide and rituximab based regimen but with standard GC dosing.

Clinical assessment

We recorded the following parameters at baseline, and months 1, 3, 6 and 12: Birmingham Vasculitis Activity Score (BVAS version 3), serum creatinine (μmol/L), urine protein:creatinine ratio (mg/mmol) and ANCA titre (IU/ml). B cells were considered depleted if the peripheral CD19 cell count was ≤10 cells per μl. Additionally, we recorded potential GC-related adverse effects including incidence of new onset diabetes, weight gain and infectious complications. Severe infections were defined as those requiring intravenous antibiotics and/or hospital admission.

Statistical analysis

Where three or more groups were analysed, non-parametric one way ANOVA using Kruskal-Wallis test was applied. A p value of $p<0.05$ was considered significant. ANCA negative patients were considered as MPO-ANCA positive for the purpose of case-control matching. Continuous variables were expressed as mean with 95% confidence intervals or medians with 25^{th} and 75^{th} quartiles within brackets. Categorical variables were presented as percentages and frequencies. Chi-square test or Fisher's exact test was used for comparison of categorical variables. Independent t-test or Mann-Whitney test was used for comparison of continuous variables between two groups. Data were analysed

using SPSS version 23, the R software (R foundation for Statistical Computing, Vienna, Austria) version 3.1.2, or Graphpad Prism 7.0.0.

Results

Baseline characteristics

The demographic features and baseline clinical characteristics are summarised in Table 2. There were 23 patients in Group 1 and 26 in Group 2 all except three (who died after 7 and 9 months) with at least 12 months of follow up. Both groups included PR3- or MPO-ANCA positive patients, and a limited number (n=3) of ANCA-negative patients. 44/49 (90%) patients had a new presentation of AAV, the remainder had relapsing disease. All except one had renal involvement, which was biopsy-proven in 44/49(90%); In those not biopsied, glomerulonephritis was inferred from deteriorating renal function in association with new urinary abnormalities. Four patients (8%) presented with pulmonary haemorrhage and three (6%) were dialysis dependent at enrolment.

Treatment

Group 1;n=23

All patients received 2 x 1g doses of rituximab. Twenty one (91%) patients received concomitant cyclophosphamide; in two patients with relapsing disease, cyclophosphamide was withheld due to concerns about cumulative prior exposure. Deviations from GC dose protocol resulted from variations in steroid use at other units prior to referral. The median dose of intravenous methylprednisolone and oral prednisolone was 750mg [range 0-4000] and 210mg [range 0-1155] respectively. The maximum duration of GC treatment was three weeks.

During the first year of follow up, four patients required introduction of GC treatment after initial protocol treatment for the following reasons: (i) at week four due to symptoms of active vasculitis (myalgia, fatigue); (ii) at week six due to symptoms of active vasculitis (pleuro-pericarditis); (iii) at month six for treatment of severe palmoplantar

psoriasis, and (iv) at month nine due to the development of azathioprine-induced interstitial pneumonitis.

Group 2;n=26

All patients received 2 x 1g doses of rituximab (except one who received 0.6 g). All received cyclophosphamide, with the exception of one patient presenting with extra-renal relapse. 17/26(65%) patients were treated with intravenous methylprednisolone [median dose 500mg (range 125-1500)]. All 26 patients were treated with prednisolone. The median total cumulative dose of oral prednisolone was 735mg (range 280-1800) and median duration of prednisolone treatment was 15 days (range 10-142). Combining the methylprednisolone and prednisolone exposure, total median dose of GC exposure was 1235mg (range 280-3940). Five patients received more than 30 days of oral prednisolone for the following reasons: (i) three had additional GC due to misunderstanding of the protocol (total of 70, 54 and 42 days); (ii) two had suspected on-going vasculitis activity (one patient treated with 50 additional days of prednisolone, one received an additional 126 days of prednisolone with a slow withdrawal). No patients were taking regular GC at month 6. Maintenance therapies are shown in Table 2.

Response to treatment and outcomes

In all patients, there was an improvement in BVAS by month 1 [Figure 1(i)]. This was sustained in the two groups over 12 months (Group 1: baseline v all subsequent time points $p<0.0001$; Group 2 baseline v all subsequent time points $p<0.0001$). Similarly, there was a decrease in CRP from month 1 onwards [Figure 1(ii)], (Group 1: baseline v month1 $p<0.05$, month 3 $p<0.001$, month 6 $p<0.01$, month 12 $p<0.01$; Group 2 baseline v month 3 and subsequent time points $p< 0.0001$).

At six months, 47/49(96%) patients were in disease remission without additional GC. Both patients from Group 1 that required re-introduction of GC at weeks 4 and 6 for symptoms of active vasculitis, achieved remission by month 6. At 12 months, 44/49

(90%) patients had a sustained remission without addition of further GC, (there were three deaths at months 7, 9 and 9 and two relapses at months 7 and 12).

Kidney function in both groups improved by three months, and was sustained in 47/49 at 12 months (two patients had renal relapse at months 7 & 12 resulting in loss of renal function)[Figure 1(iii)]. Median creatinine at time of entry was 179μmol/L [range 62-469] and 174μmol/L [range 89-999], and at month 12 109 μmol/L [range 64-423] and 113μmol/L [range 64-216], in Groups 1 and 2 respectively. In both groups, the decreases in creatinine were statistically significant, (Group 1 Baseline v month 12 $p<0.05$; Group 2 Baseline v month 3 $p<0.05$, month 6 $p<0.01$, and month 12, $p< 0.001$).

There were similar reductions in proteinuria (uPCR) from month 3 onwards (Figure 1(iv)]. The median uPCR at time of entry was 140 mg/mmol [range 42-1150] and 197 mg/mmol [range 11-611] decreasing to 33 mg/mmol [range 0-533] and 32mg/mmol [range 0-476] at month 12, in Groups 1 and 2 respectively. In both groups, the reduction in proteinuria was significant from baseline to month 3 (Group 1 $p <0.05$, Group 2 $p<0.001$), month 6 (Group 1 $p<0.01$, Group 2 $p<0.0001$) and month 12 (Group 1 $p<0.05$, Group 2 $p<0.0001$).

All three patients in Group 2 who initially required dialysis became dialysis independent after 11, 36 and 53 days, and had a median 12 month creatinine of 132 μmol/L (range 95-133) and a median urine protein creatinine ratio of 34 mg/mmol(range 20-64) at month 6. The patient requiring dialysis for 53 days also received seven plasma exchange sessions. During follow-up, no patient returned to dialysis or developed end-stage renal failure.

A Vasculitis damage index (VDI) was calculated for all the patients at 12 months. In both groups the median VDI was 1 with ranges 0-3 and 0-5 in groups 1 and 2 respectively.

B-cells and ANCA

All patients achieved B-cell depletion by 1-3 months (missing data on 1 patient in both groups). At 6 months, five patients in Group 1 and three in Group 2 had B-cells >10 cells

per µl. Both groups demonstrated a significant reduction in ANCA levels, from baseline to month 3 (Group 1 $p < 0.05$, Group 2 $p < 0.01$), month 6 (Group 1 $p < 0.01$, Group 2 $p < 0.001$) and month 12 (Group 1 $p < 0.01$, Group 2 $p < 0.0001$). Eleven patients in both groups became ANCA negative at 12 months.

Relapse

Two patients (9%) in Group 1 and one (4%) in Group 2 experienced disease relapse. One (who had required re-introduction of GC at week 6) experienced multi-system flare at seven months, which was treated with rituximab and oral GC, with resultant sustained remission until 12 months. One, with relapsing PR3-AAV, had a further relapse at 12 months, successfully treated with rituximab and cyclophosphamide without addition of GC. One patient in Group 2 had an extra-renal relapse at month 8 in the context of B-cell reconstitution and a positive PR3-ANCA.

Adverse events

These data are summarized in Table 4. There were two deaths in Group 1 (one at month 9 as a complication of bronchoscopy; one sudden cardiac death at month 9) and one in Group 2 (at month 7 from fungal pneumonia). There were no new cases of diabetes. There was one hip fracture but this patient had received no long-term maintenance steroids. A total of five patients developed severe infections, (three in Group 1; two in Group 2). In Group 1, there were four severe respiratory infections in three patients, all of whom had pre-existing airway disease. In Group 2, one patient who had a prolonged course of steroids due to disease activity developed recurrent sepsis and received numerous courses of intravenous antibiotics.

Comparison with GC-treated trial patients

The cases included in this study were compared with patient data from previous EUVAS trials summarised in table 5. The patients in this study received less GC and

cyclophosphamide therapy ($p<0.001$ for each) than historic controls, but achieved similar rates of remission, with similar improvements in renal function and reduction in BVAS. There were no new cases of diabetes at one year, compared with 8.2% in EUVAS studies. Importantly, we found fewer severe infections, requiring hospitalization or IV antibiotics, in our cases (12.2%) compared with those induced with a rituximab/cyclophosphamide regimen used in RITUXVAS (30%, $p=0.02$) in which the median cyclophosphamide dose was 1720mg [range 980-2265], .

DISCUSSION

This study reports a novel extreme GC minimization regimen for patients with severe AAV with high remission rates and good patient outcomes. It suggests that rapid GC-withdrawal, within two weeks, when used in conjunction with a rituximab/ cyclophosphamide based induction regimen is feasible. A previous study has demonstrated that a rituximab with low dose cyclophosphamide and standard dose prednisolone regimen is a safe and effective treatment in patients with severe AAV not requiring dialysis [8, 9], while rituximab and eight weeks of GC is also effective in patients with mild disease [7]. It is noteworthy that despite minor differences in the GC component of the protocols between the two groups, the outcomes were similar. This suggests that lower doses of GC delivered, as pulsed intravenous or oral therapy over one or two weeks, are equally effective.

Although this study was restricted to just 12 months of follow-up, this is the period of most intense immunosuppression, with the highest conventional doses of GC, and highest treatment-related mortality. During this period, we did not observe significant side effects associated with GC.

A prior study in patients with AAV implicated GC use in the development of damage [14] as recorded by VDI, which has been shown to be predictive of mortality [30] [31]. In keeping with lower GC exposure, our patients at 12 months had very low VDI scores. A

review of the adverse events in published EUVAS studies demonstrated that 8.2% of patients developed GC-induced diabetes during the first year after diagnosis [4]. Additionally, 20% of patients have been shown to gain over 10kg of weight, with this weight gain sustained for over 12 months [32]. We found no new cases of diabetes, but no statistical difference in weight gain compared to the EUVAS and RITUXVAS cohorts. It is important to note that weight gain is often poorly recorded and may also be influenced by renal impairment, fluid retention and dialysis prescription. Patients with AAV report a poorer quality of life (QOL) compared to the general population, and high GC doses represent a potentially modifiable factor that is related to a poor physical component score when assessing QOL in AAV patients [33]. This is not just due to disease activity affecting QOL and necessitating the use of GC, but is also likely to be due to the direct effects associated with the GC themselves, such as depression. Therefore, strategies that decrease long-term GC exposure could significantly impact on long term patient morbidity and mortality, which may not be apparent with only 12 months of follow up.

B-cell depletion therapy with rituximab may allow for discontinuation of other immunosuppressant agents, including GC. The RAVE trial aimed to completely stop prednisone by 5.5 months if the patient was in remission. These data demonstrated that rituximab was effective in the induction of remission, with a low risk of relapse as long as B-cells and ANCA remain undetectable [19] [34]. In addition, regular B-cell depletion during maintenance therapy has been used as a strategy that allows the weaning of other immunosuppressant medication [35].

Importantly, we enrolled patients with severe disease, including some who were dialysis dependent or had pulmonary haemorrhage, all of whom were successfully managed with early GC withdrawal. Compared to standard of care treatment as used in previous EUVAS trials, our strategy resulted in similar remission rates, without excessive levels of damage or persistent inflammatory markers. However, there are limitations of this study which include its non-randomised design and potential bias for patient selection. Patients were

recruited in a small number of expert centres who are likely to have the best outcomes for their patients and results may be weaker in a broader based study. EUVAS trial comparators included data collected up to 22 years ago and improved outcomes for ANCA vasculitis have been reported during this time.

Based on these encouraging pilot data, we propose an international randomized study to compare such a GC-minimisation regime against the current standard of care as induction treatment in AAV.

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Table 1: Summary of treatment protocols: Group 1 and Group 2

Induction therapy		
	Group 1	**Group 2**
Rituximab	2 x 1g Day 0, 7	2 x 1g Day 0, 14
Cyclophosphamide	6 x pulses 500-750mg Weeks 0, 2, 4, 6, 8, 10	6 x pulses 500mg Weeks 0, 2, 4, 6, 8, 10
Corticosteroids		
• Methylprednisolone	2 x 250mg-500mg Day 0, 7	250mg to 1g (n=15)
• Oral Prednisolone	0.5mg/kg (max 30mg) od Days 2-6 inclusive	60mg 1 week 45mg 1 week
Maintenance: From week 12		
• First Line	Azathioprine 1-2mg/kg od	Azathioprine 1-2mg/kg od
• Alternatives	MMF, MTX, RTX	MMF, RTX
MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab		

Table 2: Demographic features, clinical characteristics and delivered treatment in Group 1 and Group 2. 1 patient in Group 2 died before reaching 12 month follow-up.

Demographics	**GROUP 1 (n=23)**	**GROUP 2 (n=26)**
• Age	65 (16-85)	66 (43-83)
• Male : Female	14:9	10:16
ANCA Status		
• anti-MPO	13 (57%)	18 (69%)
• anti-PR3	9 (39%)	6 (23%)
• ANCA negative	1 (4%)	2 (8%)
Disease Status		
• New Disease	19 (83%)	25 (96%)
• Relapsing	4 (17%)	1 (4%)
Pre-existing Diabetes	4 (17%)	7 (27%)
Disease Activity		
• BVAS	17 (12-29)	16 (7-24)
• Creatinine, umol/l	179 (62-469)	174 (89-999)
• Urine protein: creatinine ratio	140 (27-1150)	197 (11-611)
Renal Biopsy Class		
• Focal	5/21 (24%)	9/23 (39%)
• Crescentic	3/21 (14%)	5/23 (22%)
• Mixed	12/21 (57%)	5/23 (22%)
• Sclerotic	1/21 (5%)	2/23 (9%)
• Too few glomeruli to classify		2/23 (9%)
Treatment Administered: Induction		
Rituximab, g	2	2 (0.6-2g)
Cyclophosphamide, g	3.2 (0-6.5)	3 (2.5-5.4g)
Total steroid dose including MP (mg)	1000 (80-4000)	1235 (280-3940)
CS duration, days	7 (0-21)	15 days (10-142)
Treatment Administered: Maintenance at 12 months		
Azathioprine, n (%)	16(70)	15(58)
MMF, n (%)	2(9)	7(27)
Other, n (%)	1 MTX(4); 3 RTX(13)	1(4)
None, n (%)	1(4)	2(8)

Continuous variables reported as median (±range). ANCA, anti-neutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase 3; BVAS, Birmingham Vasculitis Activity Score; eGFR, estimated glomerular filtration rate.

Table 3 Baseline and follow-up parameters.

	Group 1 (n=23)			Group 2 (n=26)		
Median/range	**Baseline**	**Month 6**	**Month 12**	**Baseline**	**Month 6**	**Month 12**
BVAS	17 (12-29)	0	0	16 (7-24)	0	0 (0-6)
CRP (mg/L)	47 (1-269)	8 (0-121)	7 (0-55)	52 (2-247)	2 (1-30)	2 (1-12)
Creatinine (µmol/L)	179 (62-469)	108 (56-358)	109 (64-423)	174 (89-999)	111 (76-257)	113 (64-216)
Protein:creatinine ratio (mg/mmol)	140 (27-1150)	42 (0-343)	33 (0-533)	197 (11-611)	39 (0-455)	32 (0-476)

Table 4 Adverse effects.
(PJP *Pneumocystis jirovecii* pneumonia, LRTI lower respiratory tract infection, UTI urinary tract infection, GI gastrointestinal, HTN hypertension, AKI acute kidney injury, ALI acute liver injury, Aza azathioprine)

Adverse events	Group I (n=23)	Group 2 (n=26)
Infections		
Severe (Grade III)	3 patients -1x PJP -3x Bacterial LRTI (two in the same patient)	2 patients -recurrent sepsis -Fungal & bacteria LRTI
• Non-severe	Total 13 (11 pts) 9 LRTI (7pts) 2 UTI 2 GI	Total 10 5 LRTI 6 UTI
Hypoglobulinaemia • Transient • Prolonged	 0 2	 4 4
• **GC-related adverse events**		
New onset diabetes	0	0
• Cardiovascular events	1	0
• Osteoporosis/fracture	1	0
• ESRD	0	0
• Deaths	2 (bronchoscopy; sudden cardiac)	1 (infection)
Malignancy	0	0
Other	-Post biopsy bleed -Accelerated hypertension x2 -Aza induced pneumonitis x1 -Aza induced neutropenia x1	-AKI and ALI secondary to blood transfusion -Drug Reaction to Septrin -1 Phaeochromocytoma -Relapse of pre-existing psychiatric illness

Table 5 Comparison of cases with matched patients from 3 previous published vasculitis trials(n=139)(a) and with patients from the rituximab arm of the RITUVAS trial (n=33)(b). The following statistical tests were used: * (Fisher's exact test,) @ (Independent t-test), $ (Chi-square test) and^ (Mann-Whitney test).

	Cases (n=49)	**EUVAS trial patients (a)(n=139)**	**P value**	**RITUXIVAS patients(b)(n=33)**	**P value**
Age (median-IQR)	65 (56.5-70.5)	63.9 (57.8-72.4)	0.92@	68 (56-68)	0.95@
Sex (M:F)	23:26	75:64	0.39$	16:17	0.82$
ANCA MPO	31/49 (63.3%)	90/139(60%)	0.72$	13/33 (39.4%)	0.007*
ANCA PR3	14/49 (28.6%)	42/139(30%)		20/33(60.6%)	
eGFR entry (median)	28.9 (14.6-46.9)	28.3 (12.7-44.3)	0.56^	24.9 (12.2-55.3)	0.50^
eGFR 12m (median)	52.2 (34.9-71.4)	46.6 (32.5-62.2)	0.15^	64.7 (24.5-71.9)	0.51^
Delta eGFR (mean)	16.9 (9.7-24.2)	10.3 (7.1-13.6)	0.10@	21.3 (6.9-35.6)	0.67@
Urine proteinuria at entry (median)	146.5 (77-297)	103 (50-165)	0.003^		
BVAS at entry (median)	16 (12.3-20.8)	16 (11.5-23)	0.53^	19 (14-24.5)	0.06^
BVAS at 12m (median)	0 (0-0)	0 (0-0)	0.25^	0 (0-0)	
In remission at 12m (BVAS=0)	45/46 (98%)	121/130 (93%)	0.46$	24/27 (88%)	0.14*
CRP entry (median)	48 (13.7-108.3)	46 (14.0-111.0)	0.94^	32 (12.5-87)	0.43^
CRP at 12m (median)	5.0 (5.0-7.9)	5.0 (5.0-6.25)	0.71^	5.0 (5.0-5.0)	0.08^
Cumulative corticosteroid dose in grams (median)	1.1 (0.9-1.5)	6.7 (6.0-7.8)	<0.001^		
Cumulative cyclophosphamide dose in grams (median)	3.0 (3.0-3.2)	13.4 (8.7-22.0)	<0.001^		
Weight gain in kg (median)	-2.4 (-2.1-7.3)	3.9 (0.0-8.3)	0.41^	3.0 (0.4-9.1)	0.67^
Grade 3 infections: proportion of patients (1 or more episodes)	5/49 (10.2%)	11/139 (7.9%)	0.36*	10/33 (30%)	0.02$
Mortality at 12m	3/49 (6.1%)	16/139 (11.5%)	0.41*	6/33 (18.2%)	0.15*

ESRF within 12m	1/49 (2%)	5/139 (3.6%)	0.99*	1/27(3.7%)	0.99*

Figure 1.

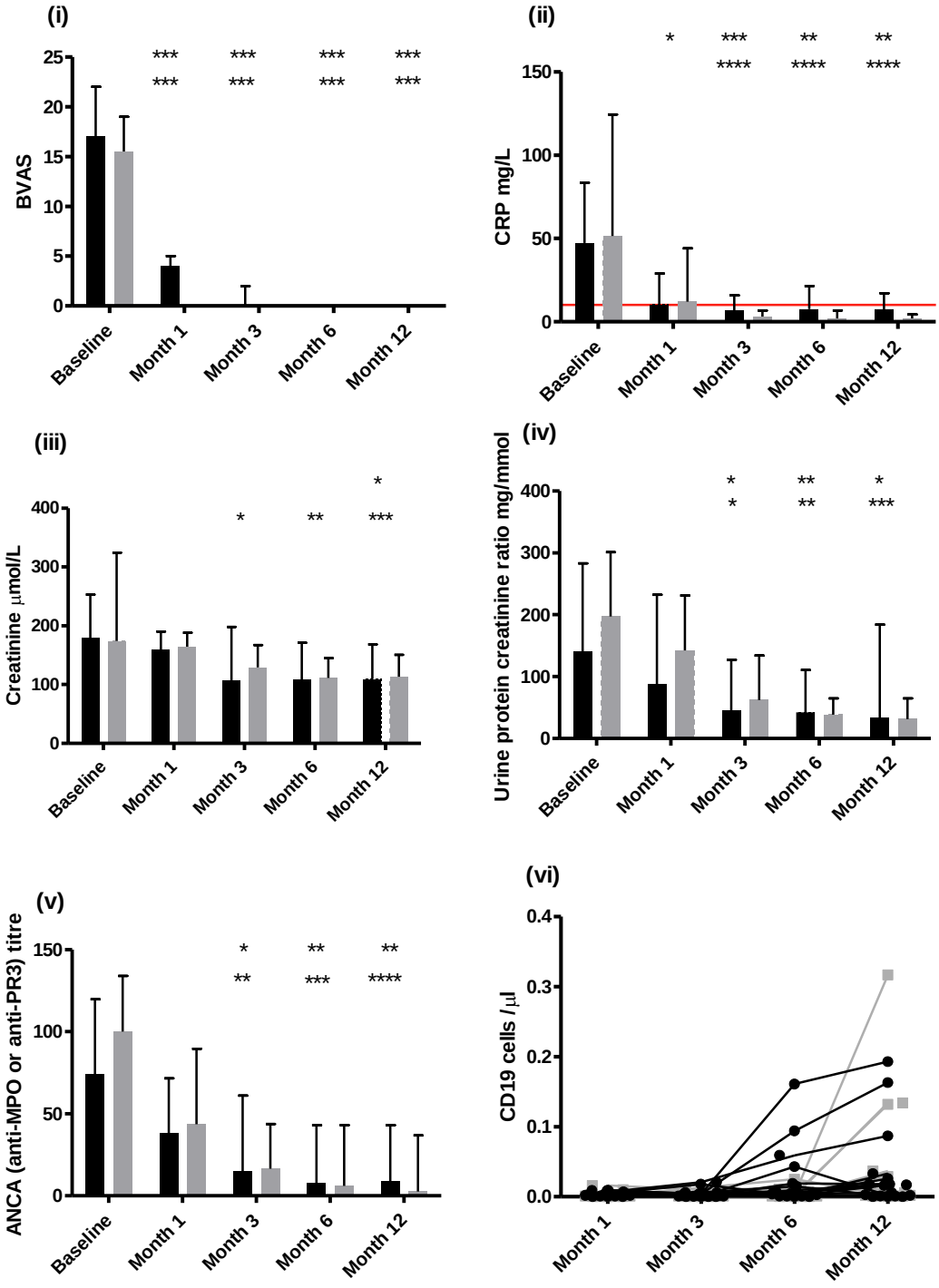

Figure 1 Clinical, biochemical and immunological outcomes for Group 1 (black) and Group 2 (grey); (i) median and IQR of BVAS at baseline and follow up; (ii) changes in CRP with treatment. Red line indicates the upper limit of normal range; (iii-iv) serum creatinine and proteinuria (UPCR); (v) changes in ANCA titre with treatment; (vi) changes in CD19 counts in individual patients (black line Group 1, grey line Group 2).