Wide variation in glucocorticoid dosing in paediatric ANCA-associated vasculitis with renal disease: a paediatric vasculitis initiative study

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Abstract

Objective

High-dose glucocorticoids for remission-induction of ANCA-associated vasculitis are recommended and commonly used in adults, but recent studies suggest lower glucocorticoid doses can reduce toxicity without reducing efficacy. No paediatric-specific data exists to inform optimal glucocorticoid dosing in paediatric ANCA-associated vasculitis (pAAV). Our objectives were to describe glucocorticoid use in pAAV-related renal disease, and to explore associations between glucocorticoid dose, baseline patient characteristics and 12-month outcomes.

Methods

Youth <18 years with pAAV, biopsy-confirmed pauci-immune glomerulonephritis and 12-month follow-up data were included from an international paediatric vasculitis registry. Presenting features and 12-month outcomes (eGFR, glucocorticoid-related adverse effects), were compared between patients receiving no, low-moderate (≤90mg/kg) and high (>90mg/kg) cumulative intravenous methylprednisolone (IVMP), and low (<0.5mg/kg/day prednisone equivalent), moderate (0.5-1.5mg/kg/day) and high (>1.5mg/kg/day) starting doses of oral glucocorticoids.

Results

Among 131 patients (101 granulomatosis with polyangiitis, 30 microscopic polyangiitis), 27 (21%) received no IVMP, 64 (49%) low-moderate and 29 (22%) high-dose IVMP, while 9 (7%) received low, 75 (57%) moderate and 47 (36%) high initial doses of oral glucocorticoids. Renal failure at diagnosis (p=0.022) and plasmapheresis use (p=0.0001) were associated with high-dose IVMP. Rates of glucocorticoid-related adverse effects ranged from 15-31% across dose levels, and glucocorticoid dosing did not associate with 12-month outcomes.

Conclusion

Glucocorticoid dosing for pAAV-related renal disease was highly variable, and rates of adverse effects were high across all dosing groups. A significant proportion of patients received oral glucocorticoid or IVMP doses that were discordant with current adult guidelines. Higher glucocorticoid doses did not associate with improved outcomes.

Key words

paediatric vasculitis, glucocorticoids, vasculitis, granulomatosis with polyangiitis

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Introduction

ANCA-associated vasculitis (AAV) is a group of rare small-vessel vasculitides with high morbidity that includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Over 80% of paediatric AAV (pAAV) patients have renal disease at diagnosis (1). Patients with AAV-associated pauci-immune glomerulonephritis often present with acute kidney injury (AKI) and sometimes require acute renal replacement therapy; patients may progress to chronic kidney disease (CKD), end stage renal disease (ESRD), chronic renal replacement therapy or renal transplantation (2).

In pAAV patients with moderate to severe renal disease, glucocorticoids are considered the cornerstone of remission-induction treatment (3). This treatment frequently includes both high-dose pulses of intravenous methylprednisolone (IVMP) and a tapering course of high-dose oral glucocorticoids, together with cyclophosphamide or rituximab (4, 5). Although glucocorticoid toxicity is well-recognised (6), strategies to reduce glucocorticoid use are only recently being evaluated in adults (6, 7). Studies comparing 'use' *versus* 'non-use' of IVMP (8, 9) demonstrated non-inferior primary outcomes, but increased toxicity (infection frequency and development of new onset diabetes) within the first year in patients treated with even one dose of IVMP *versus* those with no IVMP. Similarly, a reduced-dose regimen of oral glucocorticoid that used 60% less cumulative prednisone over 6 months than the traditional regimens used in adult clinical trials and practice, showed no difference in primary outcomes but fewer infections in the first year (10). In view of these findings the Canadian Vasculitis research network (CanVasc) revised their 2016 AAV treatment guidelines to advise caution in the use of any high-dose IVMP, and both CanVasc and recent American College of Rheumatology (ACR) guidelines recommend a reduced-dose glucocorticoid regimen over a standard-dose glucocorticoid regimen for remission-induction therapy of AAV (11, 12). Short- and long-term side effects of glucocorticoids include hypertension, increased infection risk, osteopenia, glucose intolerance, weight gain, and avascular necrosis; additional toxicity in children include delayed growth and self-image disturbances (*e.g.* acne, striae, cushingoid facies and hirsuitism) (4, 13). Thus, glucocorticoid dosing in children with pAAV must balance the need to successfully treat active disease while minimising side-effects.

The primary objective of this study was to describe practice variation in glucocorticoid use in pAAV-related renal disease, and secondarily to explore associations between glucocorticoid dose, baseline patient characteristics and 12-month outcomes.

Materials and methods

This is an ambispective cohort study conducted with data from the web-based international paediatric vasculitis registry ARChiVe (A Registry for Children with Vasculitis). Established in 2007 to retrospectively collect time-of-diagnosis clinical data, the registry became incorporated into a prospective paediatric vasculitis initiative (PedVas) collecting both clinical and biologic follow-up data (4). There are currently 41 sites enrolling patients into PedVas.

PedVas collects data on demographics, diagnosis, presenting symptoms, clinical features, laboratory results, imaging and biopsy investigations, medications, hospitalisation, paediatric vasculitis activity scores (PVAS) and the paediatric vasculitis damage index (pVDI) (14, 15). Glucocorticoid-related adverse effects collected in the registry were defined as per the pVDI glossary (15): infections requiring hospitalisation, avascular necrosis, cataract, osteoporosis, new onset obesity, diabetes and growth failure.

Patients

Patient eligibility criteria, the registry dataset, and the strategy for establishing the time-of-diagnosis dataset have been described previously (4). Registry patients were diagnosed by the treating physician after January 1st, 2004 and before 18 years of age with a chronic

systemic vasculitis. Patient data was collected retrospectively for patients diagnosed from January 2004 to March 2007, and prospectively for those diagnosed March 2007 onwards. Enrolment is ongoing, and data reported here was extracted as of October 31, 2019.

To be eligible for this study, a diagnosis of pAAV, biopsy confirmed pauci-immune glomerulonephritis, and follow up data to 12-months after diagnosis were required.

Glucocorticoid dosing

The glucocorticoid dosing for remission induction was entirely at the discretion of the attending physician; there were no dosing guidelines or direction associated with registry participation.

IVMP pulses were recorded as mg/kg/pulse with a specified maximum of 1 gram per pulse. Cumulative doses of IVMP within the first 4 weeks of treatment was examined in three categories: no IVMP, low-moderate (≤90mg/kg), or high (>90mg/kg). These categories encompass the dose range for remission-induction of pAAV recommended in the 2019 European SHARE initiative guidelines for IVMP of 10-30mg/kg/day for 3 days (a 'triple pulse') (3).

Oral glucocorticoid starting dose was recorded in prednisone equivalents as low (<0.5mg/kg/day), moderate (0.5-1.5mg/kg/day), or high (>1.5mg/kg/day). The absolute starting dose was not recorded in the registry.

Renal function and disease activity

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine and patient height using the Schwartz formula (16). Patients' renal function was categorised according to eGFR based on KDIGO (Kidney Disease Improving Global Outcomes) 2012 chronic kidney disease guidelines as: 1. normal to mildly reduced (eGFR ≥60 ml/min/1.73m^2); 2. moderately to severely reduced (eGFR 15-59 ml/min/1.73m^2); 3. renal failure (eGFR <15 ml/min/1.73m^2) (17).

Disease activity was assessed using the Paediatric Vasculitis Activity Score (PVAS), a paediatric modification of the adult Birmingham Vasculitis Activity Score (BVAS) (14).

Table I. Demographics of the 131 patients with pAAV and biopsy-confirmed glomerulonephritis included in this study.

Baseline demographics and characteristics of pAAV renal cohort		
		Total (n=131 (%))
Diagnosis	GPA	101 (77)
	MPA	30 (23)
Gender	Male	40 (30)
	Female	91 (70)
Age (years)	Median (IQR)	14 (10,15)
Year diagnosed	2004-2007	27 (21)
	2008-2012	56 (43)
	2013-2017	48 (37)
Country of residence	CAN	48 (37)
	USA	61 (46)
	Other	22 (17)

pAAV: paediatric ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; CAN: Canada.

Outcomes

Outcome measures included glucocorticoid-related adverse effects according to pVDI (avascular necrosis, osteoporosis, cataract, new onset obesity, growth delay and diabetes), rates of hospitalisation in the first 12 months, rates of infection leading to hospitalisation, 12-month eGFR, and change in eGFR from diagnosis to 12-months. Change in eGFR from time of diagnosis to 12-months was categorised as 1) improved (>10ml/min/1.73m^2 increase in eGFR), 2) stable (change of <10 ml/min/1.73m^2) or 3) worsening (>10ml/min/1.73m^2 decrease). Patients that maintained normal eGFR (≥90ml/min/1.73m^2) over the 12-month period were deemed 'stable' irrespective of the amount of change within the normal range. Hospitalisation rates were expressed as number of patients who were hospitalised at least once in the year after diagnosis, as well as the total number of hospitalisations per 100 years of patient follow up.

Missing data

Data points that were missing included: eGFR at time of diagnosis for 13 patients (10%), and IVMP cumulative dosing data for 11 patients (8%). These patients were included in the analysis for where data was available, and omitted from the denominator for eGFR and IVMP percentage calculations.

Analysis

Descriptive statistics included medians and interquartile ranges (IQR). The Chi-square test and Fisher exact test were used to compare proportions for categorical variables, and the Kruskal-Wallis test was used for non-normally distributed continuous variables compared across >2 groups, using R software (v. 1.1.423, R collaborative group, www.rstudio.com).

Results

Patients

At the time of censoring in October 2019, there were a total of 400 children and youth with pAAV from 41 sites in the PedVas registry and among these, 222 had biopsy-confirmed glomerulonephritis. Of these, 131 patients had follow-up data to 12-months and were included in the study: 101 (77%) patients had GPA and 30 (23%) had MPA (Table I). No patients with EGPA met inclusion criteria. 64 patients (49%) had PR3 ANCA and 56 (43%) had MPO ANCA. The median age at diagnosis was 14 years (IQR 10, 15). Baseline demographic characteristics of this cohort are shown in Table I. The median duration of illness prior to presentation was 1 month (IQR 1, 3).

Multiple extra-renal organ systems were affected including respiratory (63%; n=83); musculoskeletal (58%; n=76); and ear, nose and throat (42%; n=55) (Fig. 1, Table II). Forty-two patients (32%) had pulmonary haemorrhage at time of diagnosis. The median PVAS at time of diagnosis was 20 (IQR

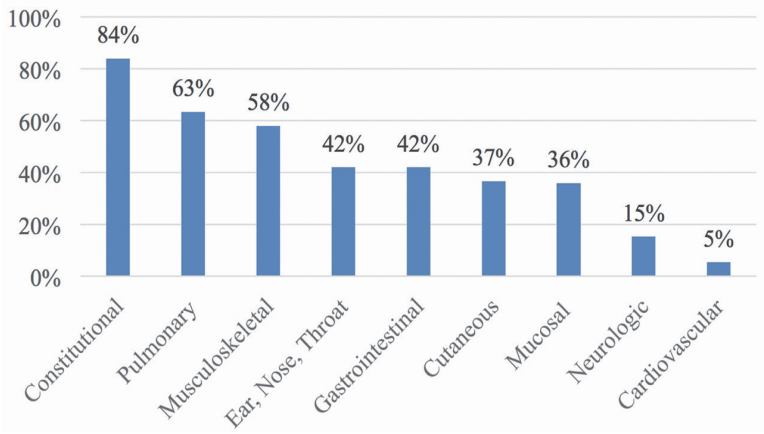

Fig. 1. Organ system involvement (%) in 131 paediatric patients with AAV-related renal disease at time of diagnosis.

Table II. The distribution of oral and IV glucocorticoid use in 131 patients with paediatric ANCA associated vasculitis (pAAV).

n (%)		Oral glucocorticoid (mg/kg/d) (n=131)			
		Low <0.5 (n=9)	Moderate 0.5-1.5 (n=75)	High >1.5 (n=47)	*p*-value
Cumulative IV glucocorticoid (mg/kg) (n=120)	None	3 (33)	15 (20)	9 (19)	0.511
	Low-moderate ≤90	4 (44)	35 (47)	25 (53)	
	High >90	1 (11)	16 (22)	12 (26)	
	Unknown	1 (11)	9 (11)	1 (2)	

17, 24). At diagnosis, 118 patients had eGFR data recorded - 46 patients (45%) had normal to mildly reduced eGFR, 32 (27%) had moderately to severely reduced eGFR, and 40 (34%) had renal failure. Twenty-eight patients (21%) required renal replacement therapy at diagnosis.

Glucocorticoid dosing

Among the 131 patients included in the study, 120 patients had complete IV glucocorticoid data recorded in the registry. IVMP use varied widely as 27 patients received no pulses, and 93 received a median of four IVMP pulses (range 1-14) as part of induction treatment. Individual pulse doses ranged from 10-30 mg/kg up to the specified 1 gram maximum. Cumulative IVMP dosing groups included: no IVMP for 27 patients (21%); low-moderate dose (≤90mg/kg) for 64 (49%); and high dose (>90mg/kg) for 29 (22%) (Fig. 2). 11 patients (8%) had no cumulative IVMP dosing recorded (Table II).

All 131 patients received oral glucocorticoid therapy: 9 (7%) received <0.5mg/kg/day, 75 (56%) 0.5-1.5mg/kg/day, and 47 (36%) >1.5mg/kg/day starting doses (Fig. 2). Within each of the 3 oral glucocorticoid dosing groups, the use of IV glucocorticoids was compared and no significant difference was found between the groups (p=0.822) (Table II).

Glucocorticoid dose and clinical features at presentation

IVMP dose groups differed significantly by country of residence (p=0.007) (Table III). In the group that received low-moderate IVMP, 41 patients lived in the United States (64%), and 16 (25%) lived in Canada. High dose IVMP was associated with lower eGFR at diagnosis (p=0.022), greater use of plasmapheresis (p=0.0001), pulmonary haemorrhage at diagnosis (p=0.0001) and shorter time to diagnosis (p=0.004). Twenty-two of the 42 patients receiving plasmapheresis had pulmonary haemorrhage (52%). Normal to mildly reduced renal function (eGFR ≥60) was significantly more common (65%) among those who received no IVMP at diagnosis compared to those receiving low-moderate IVMP (38%) and high IVMP dose (25%). Half of the patients who received high dose IVMP had eGFR < 15ml/min/1.73m^2 at diagnosis. Oral glucocorticoid starting dose was not associated with demographic or clinical features at diagnosis (Table III).

Glucocorticoid dose and 12-month outcomes

There were no statistically significant associations between IVMP dosing groups and 12-month eGFR (p=0.095) (Table IV). At 12-months, 84% (n=21) of those who received no IVMP, 63% (n=40) who received low-moderate dose and 48% (n=14) who received high dose IVMP had normal or mildly reduced eGFR. At 12-months, 8% (n=2) of patients who received no IVMP, 16% (n=10) who received low-moderate dose and 28% (n=8) who received high dose had renal failure. Across all IVMP dose categories, about 40% of patients from each group had improved eGFR compared to diagnosis (Table IV).

The proportion of patients with glucocorticoid-related adverse effects increased with increasing cumulative IV dose: 15% of patients who received no IVMP, 22% of patients who received low-moderate dose and 31% who received high dose. These differences were not statistically significant (p=0.259) (Table IV).

At 12-months, there was no association between oral glucocorticoid starting dose and outcomes; 6 (67%) patients who received low dose oral glucocorticoids, 48 (66%) patients who received moderate, and 25 (57%) patients who received high dose, had normal to mildly reduced renal function (Table IV). Glucocorticoid-related adverse effects were seen in 22% (n=2) of patients who received low dose, and 23% for both the moderate (n=17) and high dose (n=11) groups (Table IV).

There were no significant differences between oral or IV glucocorticoid doses with regards to hospitalisation rates over the first year following diagnosis, and specifically rates of infection were similar across all oral and IV glucocorticoid doses (Table IV). Approximately 30% of patients were hospitalised within the first year of diagnosis, and

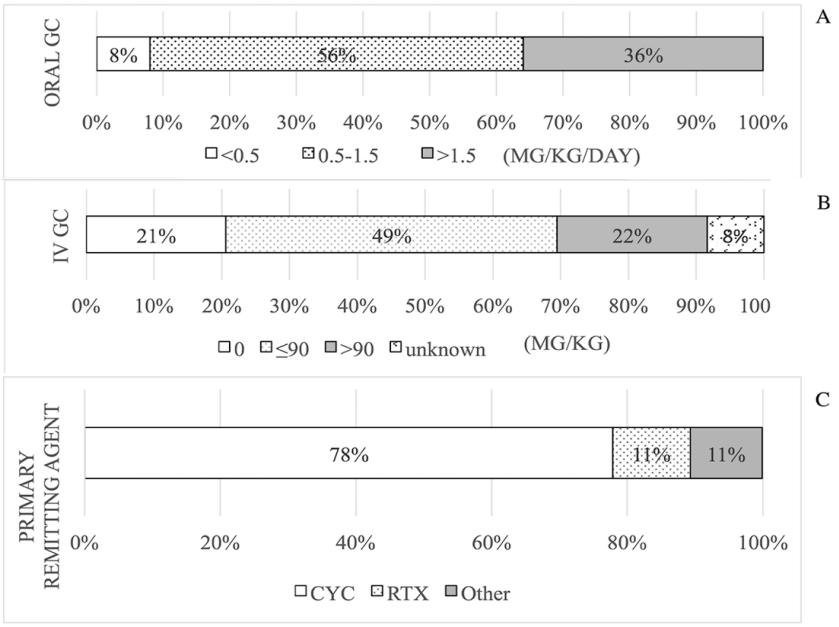

Fig. 2. Distribution of induction treatments for 131 patients with pAAV-related renal disease including oral glucocorticoid (GC) doses (**A**), cumulative IV glucocorticoid doses (**B**) and primary remitting agents (**C**). Oral glucocorticoid units are expressed in mg/kg/day. IV glucocorticoid units in mg/kg cumulative dose received over the first month of treatment.
CYC: cyclophosphamide; RTX: rituximab; other includes methotrexate, mycophenolate mofetil and the combination of both cyclophosphamide and rituximab.

reasons for hospitalisation included: infection, relapse, adverse effects of medication or reasons related to other health issues. Although not statistically significant, the rates of hospitalisation for infection were greatest in the groups receiving >1.5 mg/kg/day of oral glucocorticoid (19%) and >90 mg/kg total cumulative IV dose (28%) (Table IV).

Other induction agents

Cyclophosphamide (78%; n=102) and rituximab (11%; n=15) were the most common remission-induction agents used. Forty-six patients (35%) received oral cyclophosphamide, and 56 (43%) received IV cyclophosphamide. Rituximab was first used after 2008, with most patients (80%, n=12) receiving it after 2012. Other induction agents included methotrexate (n=3), mycophenolate mofetil (n=3) or a combination of cyclophosphamide and rituximab (n=8).

Discussion

This is the largest pAAV cohort published to date describing glucocorticoid use for remission-induction in renal disease. The 2019 European SHARE guidelines recommend 10–30 mg/kg/pulse for a total of 3 pulses in induction treatment of pAAV (cumulative dose 30–90mg/kg) (3). CanVasc recommends cautionary use of up to 3 IVMP pulses for AAV induction because of the known side effects and lack of proven efficacy (12). In our study, 23% of patients received more than 3 pulses and >90 mg/kg cumulatively in the first 4 weeks. On the other hand, 21% of patients did not receive any IV glucocorticoids.

We document a widespread variation in starting doses of oral prednisone with about one-third of patients starting with >1.5 mg/kg. Current European consensus recommendations on oral glucocorticoid use in pAAV suggest using 1–2 mg/kg/day up to a maximum of 60 mg/day of prednisolone (3), while both the EULAR/EUVAS and CanVasc adult vasculitis guidelines suggest use of 1mg/kg/day up to a maximum of 80mg/day of prednisolone in induction treatment (3, 11). The PEXIVAS trial described no impact on primary outcomes (death or end-stage renal disease) and fewer side effects with a prednisone starting dose of 1mg/kg, and a faster, non-traditional dose taper that resulted in a 60% decrease in cumulative dose (10).

Our findings suggest that children with more severe presentation received a greater cumulative dose of IV glucocorticoids; these patients had acute onset, significant renal impairment, pulmonary haemorrhage and received plasmapheresis more frequently. We speculate that IVMP use was based on the treating physician's belief that increased doses of glucocorticoids may improve outcome in these patients with severe disease.

No associations between oral glucocorticoid starting doses and baseline disease characteristics were found; a-priori it might be difficult to find associations between baseline characteristics and a starting dose that could not be simply explained by variations in institutional practice at the 29 different centres. However, the variation in starting doses was limited to three categories with just over half of the patients (56%) receiving 0.5–1.5mg/kg/day, and just over one third (36%) receiving >1.5mg/kg/day starting doses. These findings are relevant in that current CanVasc guidelines for adult treatment of AAV recommend an oral prednisone starting dose of no more than 1 mg/kg/day. New CanVasc guidelines also recommend an early initial first oral prednisone wean within 2 weeks, with a faster continuing wean than previous guidelines resulting in significantly reduced cumulative doses. Our dataset did not allow us to capture cumulative oral glucocorticoid dose.

For the cohort overall, renal function improved between time of diagnosis and 12-months; a normal or mildly reduced eGFR was found in only 35% of patients at diagnosis compared to 60% at 12-months. These findings of increased eGFR by 12-months were evident across all IVMP dose categories and are congruent with adult AAV studies in which there were no significant difference in rates of remission or degree of eGFR change at 12-months among patients who received and did not receive IVMP (8). Potential influences on eGFR change at 12-months that were not examined in this study may include other specific remission-induction treatments and the extent of patients' irretrievable baseline renal damage.

Table III. Distribution of oral and IV glucocorticoid dosing at diagnosis according to clinical features and other initial therapy in 131 patients with pAAV-related renal disease. Percentages denote the proportion within each glucocorticoid dosing category. Time to diagnosis refers to time since symptom onset to diagnosis (in number of months).

		Oral Glucocorticoid (mg/kg/d) (n=131)				Cumulative IV Glucocorticoid (mg/kg) (n=120)			
n (%)		Low <0.5 (n=9)	Moderate 0.5-1.5 (n=75)	High >1.5 (n=47)	*p*-value	None 0 (n=27)	Low-moderate ≤90 (n=64)	High >90 (n=29)	*p*-value
Diagnosis	GPA	7 (78)	60 (80)	34 (72)	0.589	19 (70)	48 (75)	25 (86)	0.337
	MPA	2 (22)	15 (20)	13 (28)		8 (30)	16 (25)	4 (14)	
Year diagnosed	<2008	4 (44)	15 (20)	8 (17)	0.100	6 (22)	14 (22)	6 (21)	0.656
	2008-2012	2 (22)	28 (37)	26 (55)		14 (52)	28 (44)	10 (34)	
	2013-2017	3 (33)	32 (43)	13 (28)		7 (26)	22 (34)	13 (45)	
Country of residence	CAN	3 (33)	32 (43)	13 (28)	0.524	12 (52)	16 (25)	13 (45)	0.007*
	USA	5 (56)	31 (41)	25 (53)		7 (26)	41 (64)	11 (38)	
	Other	1 (11)	12 (16)	9 (19)		8 (30)	7 (11)	5 (17)	
eGFR (ml/min/1.73m^2)	≥60	4 (44)	26 (38)	16 (40)	0.857	17 (63)	20 (38)	7 (25)	0.022*
	15-59	3 (33)	21 (30)	9 (23)		5 (19)	16 (30)	7 (25)	
	<15	2 (22)	22 (32)	15 (38)		4 (15)	17 (32)	14 (50)	
Dialysis	Yes	2 (22)	15 (20)	12 (26)	0.750	3 (11)	14 (22)	9 (32)	0.144
Plasmapheresis	Yes	2 (22)	27 (36)	15 (32)	0.732	4 (15)	16 (25)	18 (62)	0.0001*
Alveolar haemorrhage	Yes	2 (22)	23 (31)	15 (32)	0.916	3 (11)	20 (32)	18 (62)	0.0001*
Time to diagnosis (months)	Median (IQR)	2 (1,5)	1 (1,4)	1 (1,3)	0.524	3 (2,6)	1 (1-3)	1 (0,2)	0.004*
PVAS	Median (IQR)	19 (14,20)	20 (18,24)	20 (18,24)	0.891	20 (19,24)	19 (18,24)	22 (19,27)	0.177
Primary remitting agent	CYC	7 (78)	56 (75)	39 (82)	0.674	21 (78)	51 (80)	22 (76)	0.280
	RTX	2 (22)	8 (11)	5 (11)		1 (4)	10 (16)	2 (7)	
ANCA	PR3	3 (33)	37 (50)	24 (51)	-	14 (48)	26 (41)	20 (69)	-
	MPO	5 (56)	29 (39)	22 (47)		11 (38)	32 (50)	7 (24)	
Organ system	General	7 (78)	63 (85)	40 (85)	-	19 (70)	55 (86)	28 (97)	-
	Pulmonary	5 (56)	46 (62)	32 (68)		17 (63)	37 (58)	24 (83)	
	MSK	6 (67)	43 (58)	27 (57)		19 (70)	32 (50)	18 (62)	
	ENT	2 (22)	33 (45)	20 (43)		12 (44)	27 (42)	11 (38)	

PVAS: paediatric vasculitis activity score; CYC: cyclophosphamide; RTX: rituximab.
*p-value deemed significant <0.05.

Table IV. Renal outcomes and glucocorticoid-related adverse effects at 12-months after diagnosis for 131 patients with pAAV-related renal disease. Percentages denote the proportion within each glucocorticoid dosing category. Improved or worsened eGFR change refers to change in eGFR of at least 10ml/min/1.73m^2 between time of diagnosis and 12-months. Glucocorticoid-related (GC) adverse effects (n) include: avascular necrosis (2), osteoporosis (0), cataract (10), new onset obesity (11), growth delay (1), diabetes (2). Hospitalisations are expressed in number of patients who were hospitalised at least once in 1 year of follow up, and in total number of hospitalisations per 100 years of patient follow-up.

Outcomes		Oral Glucocorticoid (mg/kg/d) (n=131)				Cumulative IV Glucocorticoid (mg/kg) (n=120)			
n (%)		Low <0.5 (n=9)	Moderate 0.5-1.5 (n=75)	High >1.5 (n=47)	*p*-value	None 0 (n=27)	Low-moderate ≤90 (n=64)	High >90 (n=29)	*p*-value
eGFR(ml/min/1.73m^2)	≥60	6 (67)	48 (66)	25 (57)	0.484	21 (84)	40 (63)	14 (48)	0.095
	15-59	3 (33)	13 (18)	9 (21)		2 (8)	13 (21)	7 (24)	
	<15	0	12 (16)	10 (23)		2 (8)	10 (16)	8 (28)	
eGFR change	Improved	2 (29)	24 (42)	12 (39)	0.280	8 (40)	19 (48)	10 (39)	0.950
	Stable	4 (57)	21 (37)	17 (55)		8 (40)	15 (37)	11 (42)	
	Worsened	1 (14)	12 (21)	2 (6)		4 (20)	6 (15)	5 (19)	
GC related adverse effects	Yes	2 (22)	17 (23)	11 (23)	0.994	4 (15)	14 (22)	9 (31)	0.259
Hospitalisation (all causes)	Rate	3 (33)	29 (39)	17 (36)	0.958	10 (37)	21 (33)	14 (48)	0.373
	Per 100pt f/u yrs	3.7	37.6	26.5		13.7	30.7	26.6	
Hospitalisation due to infection	Rate	0	12 (16)	9 (19)	0.461	3 (11)	8 (13)	8 (28)	0.175
	Per 100pt f/u yrs	0	9.6	10.3		2.4	8.1	10.5	

Rates of glucocorticoid-related adverse effects were high across all 3 IVMP dose categories (15–31%), with rates rising with greater cumulative IV glucocorticoid dose, without reaching statistical significance. Similarly, hospitalisation rates secondary to infection were highest in the high dose oral and IVMP glucocorticoid categories (19% and 28%). Adult studies have demonstrated higher rates of infection with even one dose of IVMP compared to none, and traditional slow tapering of oral glucocorticoid compared to new rapid tapering schedules (8-10). These rates of glucocorticoid-related adverse effects argue for evaluating standardised glucocorticoid dosing regimens in pAAV that result in reduced cumulative glucocorticoid exposure.

The greatest strength of this ambispective study is that it reports on the largest cohort of pAAV-associated glomerulonephritis published to date. Limitations to the study include inability to calculate total cumulative dose of glucocorticoids as this data was not collected. Associations of glucocorticoid use with presenting manifestations was an exploratory exercise to determine if there was an overtly identifiable theme or bias to explain treatment choice; this was not intended to determine treatment consensus or guidance but could inform future prospective study design. Given the small sample size in some of the glucocorticoid dosing groups, this study may not have been powered to detect differences in outcomes at 12 months. Due to the observational nature of the study, there may be confounding by indication as we cannot rule out the possibility that patients with severe disease had outcomes similar to patients with less severe disease because they were treated with higher doses of glucocorticoid.

Because of the rarity of pAAV, future studies examining optimal glucocorticoid dosing may require a pragmatic registry-based design. Such a study would require detailed records of IV and oral glucocorticoid doses at disease onset, and the tapering schedule. Additional glucocorticoid-specific side effects, other than those identified through the pVDI, should be captured, including infection frequency and severity.

Until better evidence is available, our preliminary findings and the experience in recent adult studies suggest glucocorticoid use for moderate to severe pAAV should be within the dose constraints described by SHARE guidelines, *i.e.* 1 to 3 pulses of 10–30 mg/kg of IV methylprednisolone (to a maximum of 1 g) followed by 1–2 mg/kg day of oral prednisone (to a maximum of 60 mg). Within these dosing constraints, it may be feasible to evaluate some specific glucocorticoid treatment regimens derived by consensus. For IVMP, that might include comparisons between none, one or 3 doses. For oral glucocorticoids, it might include evaluation of 1 mg/kg *versus* 2 mg/kg of prednisone as starting doses, and comparison of current weaning practices against an accelerated weaning schedule modelled on the PEXIVAS study.

In conclusion, there were substantial variations in the use of oral and IV glucocorticoids in pAAV-related renal disease in this observational study. High doses of oral and IV glucocorticoids were common, and more frequent in patients with greater renal impairment and more severe disease at presentation. No significant associations emerged between oral or IV glucocorticoid doses and 12-month renal disease outcomes. The results of this study support calls to limit the use of oral and IV glucocorticoids within certain dosing ranges. Limiting the variation in glucocorticoid dosing is essential for evaluation of optimal dosing schedules for the treatment of pAAV.

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