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Glucocorticoid-free treatment of severe anti-neutrophil cytoplasm antibody-associated vasculitis

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Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a rare, small-vessel vasculitis with a peak in incidence in the seventh and eighth decades [1]. Previous studies have shown that older age and poorer performance status are associated with worse outcomes likely as a consequence of the disease and its treatment [2, 3]. Also, best practice for elderly patients is unclear, as they are underrepresented in randomized controlled trials of induction immunosuppression in AAV; mean participant ages in the CYCLOPS, RAVE, MYCYC and PEXIVAS trials were 57, 53, 60 and 63 years, respectively [4–7].

Glucocorticoids form the mainstay of treatment for AAV. However, glucocorticoid use may be complicated by numerous side effects. In the short term, infection is the main treatment-related complication [8]. In the longer term, cardiovascular disease and osteoporosis are important morbidities [9]. Recent data suggest that glucocorticoid-sparing regimens may treat AAV effectively while reducing complications [7, 10]. Here we present a series of predominantly elderly patients with active AAV treated without any glucocorticoids during both remission induction and maintenance. Glucocorticoids were avoided due to patient- or disease-related factors that rendered their use either high-risk or unnecessary. We demonstrate that in select patients with AAV, effective disease control can be achieved without glucocorticoids.

Eleven patients with active, organ-threatening AAV were treated without any oral or intravenous glucocorticoids (Table 1); six patients presented with *de novo* disease and five with relapse. The median age was 82 years and seven patients were female. Six patients had granulomatosis with polyangiitis (GPA) and five patients had microscopic polyangiitis. Four patients were proteinase 3 (PR3)-ANCA positive, five were myeloperoxidase (MPO)-ANCA positive, one was positive for both PR3- and MPO-ANCA and one was ANCA negative. The median circulating C-reactive protein (CRP) was 72 mg/L (normal range 0–5).

The majority of patients (8/11) had kidney involvement, with 6 patients undergoing kidney biopsy to confirm this (Figure 1A). The median serum creatinine in those patients with kidney involvement was 178 µmol/L (normal range 60–120) with a urine protein:creatinine ratio of 195 mg/mmol (normal range 0–30). Four patients had lung involvement with radiologic features of lung nodules with or without cavitation (Figure 1C).

All 11 patients received rituximab treatment (1–2 g) for remission induction. Five patients received additional intravenous cyclophosphamide (0.5–2 g). No patient received oral or intravenous glucocorticoid throughout the treatment period.

All 11 patients achieved disease remission by 6 months. Over this period the median CRP fell to 8 mg/L and all ANCA-positive patients demonstrated a decrease in ANCA titre. Renal excretory function improved in all patients with renal involvement (decrease in median serum creatinine to 100 µmol/L and urine protein:creatinine ratio to 95 mg/mmol). Two patients underwent an interval kidney biopsy to confirm histologic disease remission (Figure 1B). Those patients with lung involvement had interval imaging to demonstrate improvement in disease (Figure 1D).

Nine of 11 patients received maintenance immunosuppression comprising rituximab alone in 7 patients, azathioprine alone in 1 patient and methotrexate alone in 1 patient. One patient experienced a major disease relapse; this patient presented with relapsing PR3-ANCA-positive GPA with kidney disease alone and relapsed with kidney disease at 12 months. One patient experienced an adverse event of a community-acquired respiratory tract infection that was treated successfully in the community.

Our experience builds on recent data from the PEXIVAS study that compared 'standard' (~3.2 g in the first 3 months) and 'low'-dose (~1.8 g) oral glucocorticoid regimens in severe AAV. Low-dose glucocorticoids were as effective at preventing

Table 1. **Demographic, clinical and pathologic features, treatments and outcomes**

Demographics											
Patient	1	2	3	4	5	6	7	8	9	10	11
Age (years)/gender	85/M	85/F	84/F	84/F	83/F	82/F	74/F	61/M	53/M	44/F	84/M
Diagnosis	MPA	MPA	GPA	GPA	GPA	GPA	MPA	GPA	GPA	MPA	MPA
ANCA serotype	MPO	MPO	Negative	PR3	PR3	MPO	MPO and PR3	PR3	PR3	MPO	MPO
Comorbidities	None	Rectal cancer Breast cancer Atrial fibrillation Severe LVD	Colorectal angiodysplasia	Aortic stenosis	Bipolar disorder Recurrent UTI	Hypertension Recurrent UTI Cerebrovascular disease Hyperlipidaemia	Bipolar disorder	Type 2 diabetes	ESRD (anti-GBM) HCV positive COPD Previous psychosis	Trisomy 21 Epilepsy Congenital heart disease Hypothyroid	Hypertension
Factors contributing to glucocorticoid avoidance	Age Disease tempo	Age Frailty	Age Frailty	Age Disease tempo	Age and frailty Psychiatric illness	Age Disease tempo	Frailty Psychiatric history	Type 2 diabetes	ESRD Psychiatric history	Disease tempo Comorbidities	Age Disease tempo
Disease status at baseline											
Stage	New	Relapse	Relapse	New	Relapse	New	New	Relapse	Relapse	New	New
CRP (mg/L)	56	78	18	12	87	23	134	67	77	79	72
ANCA titre (IU/mL)	47	115	Negative	25	>200	17	MPO >134 PR3 7	>177	59	61	37
Organ involvement	Kidney	Kidney	Lung cavitation	Lung nodules	Kidney	Kidney Lung cavitation	Kidney	Kidney	Lung cavitation	Kidney	Kidney
Creatinine (μmol/L)	188	297	101	128	171	191	202	133	ESRD	103	146
uPCR (mg/mmol)	136	1265	NA	NA	202	123	284	952	ESRD	77	183
Renal histology											
Class	Mixed	Not done	NA	NA	Focal	Focal	Focal	Not done	NA	Focal	Mixed
Glomeruli: total/ normal/necrotizing/crescentic/sclerotic	21/8/3/2/6				18/12/1/1/5	18/12/5/2/1	22/13/9/4/0			14/7/3/3/3	18/8/4/4/2
IFTA (%)	40				15	0	0			5	30
Treatment											
Induction	RTX 1 g CYC nil Glucocorticoid nil	RTX 1 g CYC nil Glucocorticoid nil	RTX 1 g CYC nil Glucocorticoid nil	RTX 1 g CYC nil Glucocorticoid nil	RTX 1 g CYC nil Glucocorticoid nil	RTX 2 g CYC 0.5 g Glucocorticoid nil	RTX 2 g CYC 0.5 g Glucocorticoid nil	RTX 2 g CYC nil Glucocorticoid nil	RTX 2 g CYC 2 g Glucocorticoid nil	RTX 2 g CYC 3 g Glucocorticoid nil	RTX 1 g CYC 0.5 g
Maintenance	RTX 500 mg 6 months	None	RTX 500 mg 18 months	RTX 500 mg 12 months	RTX 500 mg 6 months	RTX 500 mg 6 months	RTX 1 g 6 months	MTX	RTX 1 g 6 months	AZA	None
Outcomes											
Status at 6 months	Remission	Remission	Remission	Remission	Remission	Remission	Remission	Remission	Remission	Remission	Remission
Status at 12 months	N/A	Remission	Remission	Remission	Remission	NA	NA	Relapse	Remission	Remission	NA
CRP 0, 6, 12 months (mg/L)	56, 13	78, 8, 12	18, 8, 10	12, 12, 18	87, 0, 0	23, 12	134, 0	67, 3, 55	77, 5, 1	79, 22, 0	72, 8
ANCA titre 0, 6, 12 months (IU/mL)	47, 19	115, 86, 26	Negative	25, 8.3,	>200, 125, 102	17, negative	MPO >134, >134 PR3 7, negative	>177, 43, 96	59, 14, negative	61, 15, negative	37, 17
Creatinine 0, 6, 12 months (μmol/L)	188, 145	297, 232, 243	101, 121, 101	128, 139, 139	171, 72, 78	191, 112	202, 77	133, 105, 160	ESRD	103, 78, 80	146, 91
uPCR 0, 6, 12 months (mg/mmol)	136, 65	1265, 170, 50	NA	NA	202, 145, 98	123, 167	284, 97	952, 105, 344	ESRD	77, 12, 33	183, 81
Adverse events	No	No	No	Community LRTI	No	No	No	No	No	No	No

AZA: azathioprine; COPD: chronic obstructive pulmonary disease; CYC: cyclophosphamide; F: female; GBM: glomerular basement membrane; HCV: hepatitis C virus; IFTA: interstitial fibrosis and tubular atrophy; LRTI: lower respiratory tract infection; LVD: left ventricular dysfunction; M: male; MTX: methotrexate; MPA: microscopic polyangiiits; RTX: rituximab; NA: not applicable; uPCR: urinary protein:creatinine ratio; UTI: urinary tract infection.

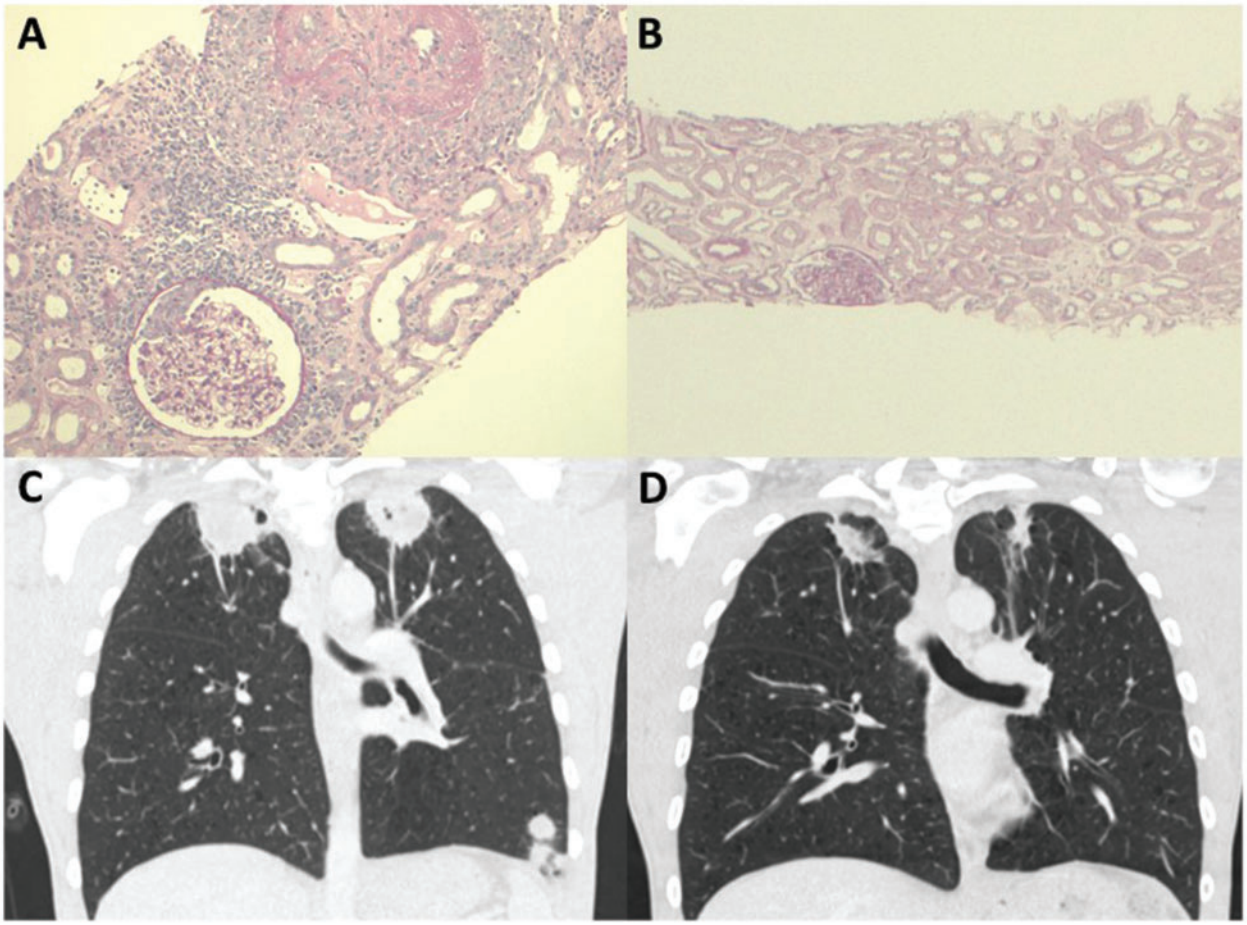

FIGURE 1: Renal histopathology (Patient 7) and imaging findings (Patient 9) before and after treatment. (**A**) Area of perivascular granulomatous inflammation and early cellular crescent formation in a glomerulus with periglomerular interstitial inflammatory cell infiltrate (×100). (**B**) Post-treatment biopsy demonstrating resolution of interstitial and vascular inflammation (×40). (**C** and **D**) Computed tomographs of the thorax. (**C**) Pretreatment findings of bi-apical cavities and left lower lobe nodules. (**D**) There was a significant reduction in nodule size after treatment, so only a small area of residual scarring was evident on the follow-up scans obtained after 3 months.

end-stage renal disease or death but caused fewer infections [7]. These data, as well as our own, might explain why several randomized controlled trials in AAV have failed to demonstrate a reduction in adverse events despite reducing (or entirely eliminating) cyclophosphamide exposure (thought to be a major driver of toxicity) with drugs such as mycophenolate mofetil or rituximab. High-dose glucocorticoids may actually be the major contributor to adverse events in these patients [11]. Indeed, a recent study found that initial high-dose glucocorticoid exposure (and not the use of cyclophosphamide or rituximab) was a major risk factor for severe infection in elderly patients (defined in this study as >65 years old) with AAV [12].

Advanced age and frailty are two key factors that drove our decision to completely avoid glucocorticoid treatment. The nature and tempo of the presenting disease were also important in our decision making. Of the 11 patients described here, 5 were MPO-ANCA positive. MPO-AAV-related glomerulonephritis in particular may present with advanced renal impairment, features of glomerular and interstitial scarring and only low-grade active inflammation on kidney biopsy, suggesting a smouldering disease process. This type of disease is often associated with limited systemic upset. Here, the treatment goal should be control of the underlying autoimmune response, and this may not require glucocorticoids in the absence of clinically rapid disease progression. This is particularly relevant for the elderly, who are at the greatest risk of glucocorticoid-related adverse events and in whom an acceptable loss of glomerular filtration rate is unlikely to affect quality or quantity of life. Critical to the approach described here is the need for frequent patient follow-up to monitor disease progression and treatment response, and, if necessary, treatment escalation.

We recognize our study is small, retrospective and uncontrolled. In addition, follow-up was limited to 12 months, so longer-term effects on disease activity, relapse and adverse events could not be assessed. We do not suggest that complete glucocorticoid avoidance should be adopted in all patients. Rather, we highlight our observation that in select patients, with careful and frequent follow-up, treatment of severe AAV with complete glucocorticoid avoidance is possible. In the cases described, this was a complex and multifaceted decision made by experienced physicians with expertise in AAV.

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DATA AVAILABILITY STATEMENT

Requests for original and additional data should be directed to the corresponding author.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest related to the submitted work.

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