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Management and Outcomes of ANCA Associated Vasculitis at a Tertiary Healthcare Facility

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Introduction

AAV is a rare disorder with annual incidence estimated to be around 1.3 per 100,000 population[1,2]

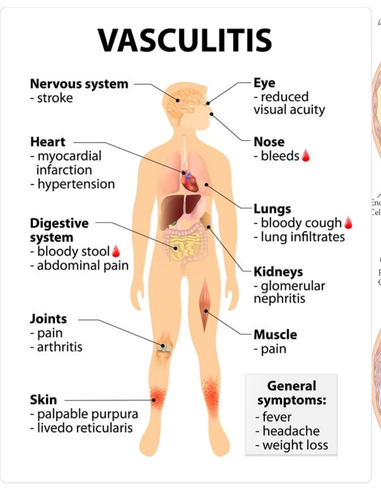
Renal involvement is one of the main predictors of mortality and morbidity[1]

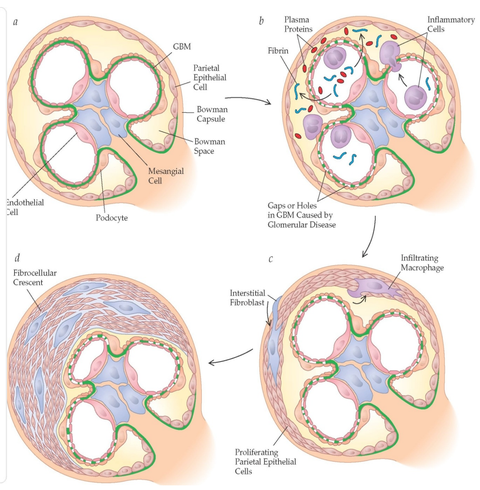
Approximately 30% of patients with renal involvement progressing to ESRD after 5 years[1]

Renal biopsy can provide a definite diagnosis, and may predict the renal prognosis in AAV[3]

Aims/Background

Limited data is available on its management and outcomes, thus we aim to assess this at our tertiary care renal facility





Methods

This was a retrospective cohort study

Inclusion criteria:
ANCA positive vasculitis
Documented between: 1st January 2012-31st December 2017
Follow up period until: 31st December 2019

Standardized data collection form included:
The number of patients who had a renal biopsy
Induction and maintenance therapies used
Relapse induction and maintenance therapies
Outcomes at the end of the follow up period

Outcomes:
Progression to end-stage renal disease(ESRD) or death
Established chronic kidney disease(CKD)
Preservation of renal function

Summary following inclusion and exclusion criteria	N=36
Age (years)[a]	63.5 (54.5-71.5)
Gender (male %)	23 (66.7)
Hypertension (%)	26 (72)
Hyperlipidaemia (%)	8 (22.2)
Ischaemic Heart Disease (%)	4 (11.1)
Gout (%)	3 (8.3)
Diabetes Mellitus (%)	2 (5.6)
BVAS[b]	15
Creatinine[a] (ml/min/1.73m^2)	301.5 (169-718.5)
Anti-PR3/Anti-MPO titre[a] (IU/ml)	28 (12.5-87.5)

[a]Median (interquartile range)
[b]Mean

Table 1: Patient baseline characteristics

Results

Data of thirty-six patients were included in the final study

Thirty-two patients(94.1%) had a documented renal biopsy

Induction and Maintenance Treatment
The majority of patients(66.7%) had cyclophosphamide for induction, followed by rituximab(19.4%)

Four patients(11.1%) had azathioprine as an induction; this was due to mild symptoms and/or comorbidities

Seven patients(19.4%) had a documented relapse during the study period, 4 MPO+ and 3 PR3+

Six patients(85.7%) had rituximab as an induction therapy for relapse

The majority of patients were on azathioprine(61.1%) as maintenance therapy after induction. This was similar to the maintenance therapy used after relapse(57.1%)

Therapy	Induction % (n=36)	Maintenance % (n=36)	Relapse induction % (n=7)	Relapse maintenance % (n=7)
Cyclophosphamide	66.7 (24)	0 (0)	0 (0)	0 (0)
Rituximab	19.4 (7)	16.7 (6)	85.7 (6)	28.6 (2)
Cyclophosphamide and rituximab	2.8 (1)	0 (0)	0 (0)	0 (0)
Azathioprine	11.1 (4)	61.1 (22)	0 (0)	57.1 (4)
Corticosteroids alone	0 (0)	16.7 (6)[a]	14.3 (1)	14.3 (1)
Plasmapheresis	27.8 (10)	0 (0)	0 (0)	0 (0)
Mycophenolate mofetil	0 (0)	2.8 (1)	0 (0)	0 (0)
No treatment	0 (0)	2.8 (1)[b]	0 (0)	0 (0)

[a] Due to commencement of HD or death in 4 (66.7%) of patients, no information available on 2 (33.3%) patients
[b] Not given further immunosuppression due to bowel perforation following cyclophosphamide. However remained clinically stable, no worsening renal function.

Table 2 Summary of induction and maintenance treatment

Patient Outcomes

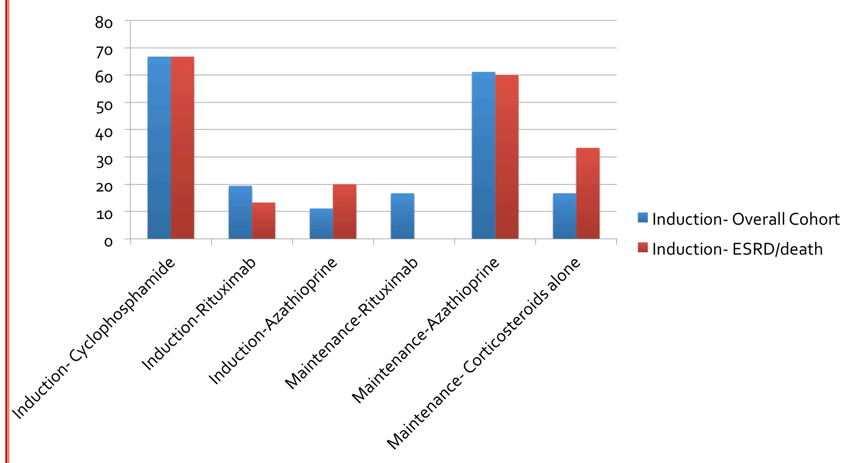


Figure 1. Summary of induction and maintenance treatment: Overall cohort vs ESRD or Death cohort

Progression to ESRD occurred in eleven(30.6%), death in four(11.1%), established CKD in fifteen(41.7%), and preservation of renal function in six(16.7%) patients by the end of the follow up period

Ten patients(66.7%) with ESRD/death had induction therapy with cyclophosphamide, two(13.3%) were induced with rituximab, and continued on steroids. Three(20%) were started on azathioprine due to comorbidities

Of those induced with cyclophosphamide, the majority (six patients) were commenced on azathioprine for maintenance, one was commenced on mycophenolate mofetil (MMF), and corticosteroids alone were used in three patients

Discussion

While cyclophosphamide remains the choice of induction immunosuppresion therapy, we favour rituximab as an induction agent in relapse of AAV

Cumulative exposure to cyclophosphamide is associated with increased incidence of malignancy and recent studies with rituximab have shown high efficacy in reinduction of remission in AAV[4]

In some patients who had significant comorbidities, and/or were commenced on haemodialysis, azathioprine or steroids alone were used

The treatment used in the ESRD/death group was reflective of the overall group

Feature	Overall	PR3-ANCA+	MPO-ANCA+
Age at diagnosis	45-70 years	45-60 years	60-70 years
Sex	♂=♀	♂>♀	♀>♂
Incidence	3.3/100 000	0.8-1.3/100 000 (GPA)	Not reported
Racial/geographic characteristics	White and Asian > > > African-American or Hispanic	↑ Northern Europe and Americas	↑ Asia and Southern Europe
Genetics	20% of risk due to genetic factors	■ HLA-DPA1 and DPB1 ■ SERPINA1 ■ PRTN3 ■ PTPN22	■ HLA-DQA2 and DQB1 ■ PTPN22
Pathogenesis	■ PR3-ANCA and MPO-ANCA are thought to be pathogenic ■ Spontaneous NET formation ■ Complement activation	■ Normally expressed on PMN cell surface ■ Granulomatous manifestations ■ ↑ IL-6, IL-15, IL-18, IL-18 binding protein, sIL-2 receptor a, gCSF, and mCSF	■ Not normally expressed on PMN cell surface ■ ↑ sIL-6 receptor, sTNF-receptor type II, neutrophil gelatinase associated lipocalin, and soluble intercellular adhesion molecule
Risk factors	Silica exposure	±Staphylococcus aureus	Drugs (eg, hydralazine, levamisole, propylthiouracil)
Clinical phenotype	GPA more common than MPA	> >GPA (~90%)	> > >MPA (~100%)
Organ involvement	Vasculitic manifestations ■ Glomerulonephritis ■ Diffuse alveolar hemorrhage ■ Mononeuritis multiplex ■ Cutaneous vasculitis	Granulomatous manifestations ■ Ear, nose, and sinus disease ■ Upper airway involvement ■ Pulmonary nodules/cavitary lesions	■ Pulmonary fibrosis ■ Bronchiectasis ■ Increased severity and chronicity of renal disease
Response to treatment	■ Most patients reach remission ■ RTX is non-inferior to CYC ■ Two to threefold ↑ risk of death	RTX may be superior to CYC for remission induction	RTX likely equivalent to CYC for remission induction
Outcomes	■ ↑ risk of CVD and DVT ■ Decreasing risk of ESRD ■ ↓ quality of life	↑ relapse and treatment failure	↑ non-fatal CVD events

Table 3 Features of AAV[1]

The five year survival for AAV is estimated to be around 75%[5,6]

Early mortality is attributed to active vasculitis or infection, and late mortality being due to infection, cardiovascular disease and malignancy[5,6]

This reflects the rate of morbidity and mortality associated with AAV, and highlights the need for continued early aggressive immunosuppresion therapy despite it's complications

Conclusion

The current management and outcomes in our study are comparable to present international guidelines and cohorts, despite aggressive immunosuppresion therapy the incidence of ESRD and death remains high in these patients

We look forward to new updates and therapies to improve outcomes in AAV

References

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