ANCA-associated pulmonary-renal syndrome treated with cyclophosphamide, rituximab, repeated methyl-prednisolone pulses and a reduced oral glucocorticoid regime: an observational study

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Abstract

Objective

To describe the clinical outcome of patients with pulmonary-renal syndrome (PRS) due to ANCA-associated vasculitis (AAV) from a single centre.

Methods

Observational study of routine clinical care data of patients diagnosed with PRS due to AAV from 2010 to 2020 at the Autoimmune Diseases Unit, Hospital Universitario Cruces. Mortality due to any cause within 24 months was defined as the primary outcome. Secondary outcomes included end-stage kidney disease and the need for oxygen therapy at 24 months.

Results

Fourteen patients were identified with a mean age at diagnosis of 62.71 years. At diagnosis, the median serum creatinine was 2.46 mg/dl and the median Birmingham Vasculitis Activity Score (BVAS) was 24. All patients were treated with repeated methyl-prednisolone pulses, 13 patients received iv cyclophosphamide 500 mg every two weeks and 12 patients received rituximab. The mean (SD) initial dose of oral prednisone was 25 (7) mg/d. A rapid tapering of oral prednisone was achieved in all patients as per protocol, with a mean (SD) dose of 10.6 (1.9) mg/d received within the first three months. No cases of death, end-stage kidney disease or with need for long-term oxygen therapy were seen. Three patients suffered a relapse and five patients had major infections, none of them opportunistic. The median creatinine and BVAS at 24 months were 1.30 mg/dl and 0, respectively.

Conclusion

Combination therapy with iv cyclophosphamide and rituximab, with repeated methyl-prednisolone pulses and a rapid prednisone taper, results in early disease control, with low mortality, chronic organ damage and infections.

Key words

alveolar haemorrhage, granulomatosis with polyangiitis, microscopic polyangiitis, prednisone, methyl-prednisolone, immunosuppressives

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Introduction

The pulmonary-renal syndrome (PRS) is a condition defined by the concomitant occurrence of diffuse alveolar haemorrhage (DAH) and rapidly progressive glomerulonephritis (GN). The most common causes of PRS are anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV), anti-glomerular basement membrane (anti-GBM) disease and systemic lupus erythematosus (SLE), the three of them accounting for more than 80% of cases (1). PRS is often a presenting feature in AAV, thus a high index of suspicion is crucial in order to reach an early diagnosis, since PRS is a life-threatening condition requiring a rapid and aggressive therapy. Unfortunately, haemoptysis, the main clinical manifestation of this syndrome, may be absent in up to 40% of patients (1), in whom the presenting features can be cough, dyspnoea and fatigue with an associated drop of haemoglobin levels. Treatment is usually based on high-dose glucocorticoids (GC), cyclophosphamide (CYC), rituximab (RTX) and often plasma exchange (PEX) (2). Despite such intensive therapy, high mortality rates have been reported in most series, ranging from 20–40% (1).

Following our published experience in patients with severe forms of SLE treated with reduced-GC dose regimes (3, 4), we have adopted similar therapeutic approaches for other systemic autoimmune diseases, including AAV. Our aim in this study is to describe the therapeutic approach and clinical outcome of patients with PRS secondary to AAV primarily diagnosed and treated in our Unit during the last 10 years.

Patients and methods

Study design and patients

This is an observational study of routine clinical care data from all patients diagnosed with PRS due to AAV treated at the Autoimmune Diseases Unit, Hospital Universitario Cruces between 2010 and 2020. Data were collected from the computerised medical records of the patients. The follow-up included 24 months after the diagnosis of PRS.

All patients fulfilled Chapel Hill criteria for AAV (5). The diagnosis of AAV was based on the presence of circulating ANCA detected by indirect immunofluorescence plus antigen-specific assay along with biopsy-proven small vessel vasculitis or typical clinical features in cases where biopsy was not obtained. The diagnosis of GN included kidney biopsy in 12 patients, all of them with findings consistent with pauci-immune necrotising GN with negative direct immunofluorescence; in two patients the biopsy was not performed due to a previous diagnosis of AAV-associated GN. The diagnosis of DAH was made on the combination of suggestive pulmonary infiltrates plus haemoptysis, or, in the absence of the latter, macroscopic blood or haemosiderin-containing macrophages in the bronchoalveolar lavage and/or dropping haemoglobin levels (1). Anti-glomerular basement membrane antibodies were not routinely tested in our group, given the lack of lineal deposits of IgG in the glomerular basal membrane in all the kidney biopsies.

Patients were enrolled in the longitudinal systemic vasculitis cohort study approved by the Ethics and Clinical Research Committee of Hospital Universitario Cruces (code E18/31). All participants provided a signed informed consent.

Treatment scheme

All patients were managed by a combined team comprising internists with focus on autoimmune diseases and nephrologists. After discharge, all patients were seen every two weeks during the induction phase in a clinic located at day hospital by one internist and one nephrologist. The general treatment scheme is shown on Table I. In our protocol, all patients receive 3 initial methyl-prednisolone pulses (MP) of 250–500 mg/d as soon as the diagnosis is suspected. The usual dose of MP is 250 mg, the dose of 500 mg being reserved for those patients with life-threatening presentations. Then, oral prednisone at doses 20–30 mg/d is started, with a rapid tapering aiming to reach a dose of 5 mg/d at 12-14 weeks. Intravenous CYC is started at doses of 500 mg fortnightly, with dose reduction to 250–300 mg in patients

Table I. The Cruces' therapeutic protocol.

1st week	
Day 1	250-500 mg MP + 500 mg CYC *
Day 2	250-500 mg MP
Day 3	250-500 mg MP
Days 4-7	Prednisone 30 mg/d
2nd week	
Day 8	125 mg MP + 1 g RTX **
Day 9-14	Prednisone 20 mg/d
3rd week	
Day 15	125 mg MP + 500 mg CYC *
Day 16-21	Prednisone 15 mg/d
4th week	
Day 22	125 mg MP + 1 g RTX**
Day 23-28	Prednisone 10 mg/d
5th - 6th week	
Day 29	125 mg MP + 500 mg CYC *
Day 30-42	Prednisone 10 mg/d
7th week	
Day 43	125 mg MP + 500 mg CYC *
Day 44-49	Prednisone 10 mg/d
8th week	
Day 50-56	Prednisone 7.5 mg/d
9th – 10th week	
Day 57	125 mg MP + 500 mg CYC *
Day 58-70	Prednisone 7.5 mg/d
11th week	
Day 71	125 mg MP + 500 mg CYC *
Day 72-77	Prednisone 7.5 mg/d
12th week and beyond	
Day 78 and beyond	Prednisone 5 mg/d with subsequent reduction to 2.5 mg/d depending on clinical status
Maintenance therapy	
	Azathioprine 2-2.5 mg/kg/d or MMF 500-1000 mg/12h + Prednisone 2.5-5 mg/d ± RTX 500 mg/6 months
Adjuvant therapy	
Bone prophylaxis	Vitamin D and calcium supplementation
Antiproteinuric treatment	

CYC: iv cyclophosphamide; MP: methylprednisolone pulse; MMF: mycophenolate mofetil; RTX: rituximab.
*In case of estimated glomerular filtration rate <30 ml/min, cyclophosphamide dose must be reduced accordingly.
**In situations of vital compromise, rituximab ± plasma exchange can be given within the first week and the second dose two weeks later.

with an estimated glomerular filtration rate (eGFR) <30 ml/min. The first CYC dose is given in combination with one of the initial MP. Mirroring our scheme for lupus nephritis (6), subsequent 125 mg MP are given with each dose of CYC. RTX, also preceded by 125 mg MP, is given at weeks 2 and 4 (Table I), although it can be omitted in those patients with a rapid improvement within the first week after receiving the initial doses of MP and CYC. Additional induction therapy can include PEX in case of haemodialysis or mechanical ventilation and/ or iv immunoglobulins (IVIG), the latter when a concomitant infection is suspected. Maintenance immunosuppressive therapy is given with either azathioprine (AZA) or mycophenolate (MMF) after 6 doses of iv CYC. Additionally, and according to the initial severity and/or clinical evolution, maintenance therapy can be reinforced with RTX 500 mg, which can be repeated every 6 months. After the rapid tapering of prednisone to 2.5 mg/d, such doses are maintained until immunosuppressive therapy has been stopped, as is our protocol for lupus nephritis (6). In addition, taking into account such reduced and rapidly tapered doses of prednisone, we do not add cotrimoxazole as *Pneumocystis jirovecii* prophylaxis to the therapeutic scheme.

Study variables

Data collected for the analysis included the following variables: gender; race; age at the diagnosis of PRS; concurrent medical diseases; PRS as the presenting feature of AAV; PRS presenting symptoms; Birmingham Vascular Activity Score (BVAS), version 3 (7), and laboratory values (type and titres of ANCA, urine protein/creatinine ratio [uPr/Cr], serum creatinine, serum albumin, haemoglobin and ANCA levels) at baseline, 3, 6, 12, 18 and 24 months; need for haemodialysis and mechanical ventilation; and treatments received, with special attention to GC.

Outcome measures

Mortality due to any cause within 24 months after the diagnosis of PRS was defined as the primary outcome.

Secondary outcomes included the need for oxygen therapy and chronic haemodialysis at 24 months, as well as the presence of relapses during the follow-up. In addition, the evolution of BVAS and laboratory parameters (uPr/Cr, serum creatinine, serum albumin, haemoglobin and ANCA titres) from baseline at 3, 6, 12, 18 y 24 months was analysed. Major infections needing hospital admission were deemed as a complication of treatment.

Statistical analysis

Descriptive data were generated, using percentages for qualitative variables and mean and standard deviation (SD) or median and interquartile range (IQR) for quantitative variables with normal and non-normal distribution, respectively. Normality was tested using the Shapiro-Wilk W test for normal data.

The variation from baseline values of BVAS, uPr/Cr, serum creatinine, serum albumin, haemoglobin and ANCA titers at 3, 6, 12, 18 and 24 month was analysed using the Wilcoxon matched pairs signed rank test. This non-parametric test was chosen given the non-normal distribution of most of the analysed variables and the reduced sample

size, which precluded the use of paired student t-test.

The statistical analysis was performed using STATA/MP 14.2 for Mac (StataCorp LP, TX, USA).

Results

Demographic and clinical variables

Fourteen patients were diagnosed with PRS secondary to AAV at our Unit between 2010 and 2020. The main clinical and immunological characteristics of the cohort are shown on Table II. Seven patients (50%) were men. All patients were white. The mean (SD) age at diagnosis was 63 (17) years. Arterial hypertension was the most frequent comorbidity, which was present in 35% of patients. Only one patient suffered from previous chronic renal failure, resulting from AAV-GN 9 years before PRS. The current episode of PRS was the first manifestation of AAV in 10 patients (71%). Haemoptysis was the presenting symptom in 8 patients (57%). The median (IQR) BVAS score at presentation was 24 (21-33).

Treatments received

All patients received 3 initial 250-500 mg MP. They were followed by iv CYC in 13 patients (93%). CYC was not given to a 68-year-old woman with a previous diagnosis of AAV and a high cumulative CYC dose. The median (IQR) cumulative CYC dose during the induction phase was 3 g (1-4.5). Three patients (21%) needed temporary haemodialysis and three (21%) required orotracheal intubation with mechanical ventilation.

Repeated 125 mg MP every two weeks were given to all patients, including the one who did not receive CYC. The mean (SD) number of additional MP was 7 (3). Twelve patients (86%) received RTX, 4 patients (29%) received PEX and 4 patients (29%) received IVIG. The mean (SD) initial dose of oral prednisone was 25 (7) mg/d. A rapid tapering of oral prednisone was achieved in all patients as per protocol, with a mean (SD) dose of 10.6 (1.9) mg/d received within the first three months and a mean (SD) dose of 5.29 (0.95) mg/d received between 3 and 6 months after the diagnosis. A detailed description of the doses of GC received during the follow-up is provided in Table III.

As maintenance therapy, 6 patients (43%) received AZA, 6 patients (43%) received MMF and one patient (7%) received methotrexate, due to intolerance to both AZA and MMF. Seven patients (50%) were treated with RTX

Table II. Baseline features (n=14).

Men	7 (50%)
Age	
mean (SD)	63 (17)
White race	13 (92%)
Diabetes mellitus	1 (7%)
Arterial hypertension	5 (35%)
Lung disease*	3 (21%)
Heart disease**	3 (21%)
Chronic kidney disease	1 (7%)
First diagnosis of AAV	10 (71%)
GPA	9 (64%)
MPA	5 (36%)
C-ANCA	6 (43%)
P-ANCA	8 (57%)
PR3 specificity	6 (43%)
MPO specificity	8 (57%)
ANCA (PR3·or MPO) titers Median (IQR)	52.5 (32-88)
Haemoptysis	8 (57%)
Respiratory insufficiency	8 (57%)
Renal biopsy	12 (86%)
BVAS Median (IQR)	24 (21-33)
Serum creatinine (mg/dL) Median (IQR)	2.46 (1.79-4.3)
Haemoglobin (g/dl) Median (IQR)	9.25 (8.5-10.6)
uPr/Cr (mg/g) Median (IQR)	1170 (890-2000)
Serum albumin (mg/dL) Median (IQR)	2.95 (2.6-3.6)
Treatment received	
MP	14 (100%)
CYC	13 (93%)
RTX	12 (86%)
PEX	4 (29%)
IVIG	4 (29%)
AZA	6 (43%)
MMF	6 (43%)
Methotrexate	1 (7%)

*Lung disease: chronic obstructive pulmonary disease, asthma, sleep obstructive apnoea.
**Heart disease: chronic ischaemic heart disease, arrhythmia.
AAV: ANCA-associated vasculitis; ANCA: anti-neutrophil cytoplasm antibody; AZA: azathioprine; CRP: C-reactive protein; CYC: iv cyclophosphamide; ESR: erythrocyte sedimentation rate; GPA: granulomatosis with polyangiitis; IQR: interquartile range; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; MP: methylprednisolone pulses; MPA: micropolyangiitis; MPO: myeloperoxidase; PEX: plasma exchange; PR3: proteinase 3; RTX: rituximab; SD: standard deviation; uPr/Cr: urine protein/creatinine ratio.

Table III. Glucocorticoid load.

	Mean (SD)
Total number of MP	6.9 (3.3)
Maximum initial prednisone dose (mg/d)	25 (7)
Daily prednisone dose 0 - 3rd month (mg/d)	10.6 (1.9)
Cumulative prednisone dose 3rd month (mg)	957 (167)
Daily prednisone dose 3rd - 6th month (mg/d)	5.29 (0.95)
Cumulative prednisone dose 6th month (mg)	1433 (217)
Daily prednisone dose 6th - 12th month (mg/d)	4.7 (3.1)
Cumulative prednisone dose 12th month (mg)	2291 (715)
Daily prednisone dose 12th - 18th month (mg/d)	3.52 (1.13)
Cumulative prednisone dose 18th month (mg)	2957 (880)
Daily prednisone dose 18th - 24th month (mg/d)	3.52 (1.13)
Cumulative prednisone dose 24th month (mg)	3531 (990)

MP: methylprednisolone pulses.

Table IV. Evolution of activity variables.

Parameter median (IQR)	Diagnosis	3rd month	6th month	12th month	18th month	24th month
BVAS	24 (21-33)	0** (0-0)	0 ** (0-0)	0** (0-0)	0** (0-0)	0** (0-0)
uPr/Cr (mg/g)	1170 (890-2000)	395** (190-1260)	310** (160-800)	208** (130-410)	154** (110-500)	118** (79-260)
Creatinine (mg/dL)	2.46 (1.79-4.3)	1.41** (1.1-1.74)	1.46** (1.25-2.05)	1.32** (1.18-1.844)	1.32** (1.15-1.79)	1.30* (1.11-1.73)
Albumin (mg/dL)	2.95 (2.6-3.6)	4.05** (3.5-4.3)	4.15** (3.9-4.5)	4.30** (4.2-4.6)	4.50** (4.3-4.7)	4.30** (4.2-4.7)
ANCA titers (U/mL)	52.5 (32-88)	5.4** (4.4-13)	2.15** (0.65-17.5)	1.15** (0-9)	2.4** (0-11)	3.9** (0-16)
MPO titers (U/mL) (n=8)	32.5 (12-67)	4.9** (3.3-9.3)	2.3** (1.3-16)	1.6** (0.5-8.4)	6.15** (0.8-11.5)	4.65** (1.3-8)
PR3 titers (U/mL) (n=6)	70 (55-177)	8.5* (5.2-30)	2* (0-21)	0* (0-9)	0* (0-5)	0* (0-16)
Haemoglobin (g/L)	9.25 (8.5-10.6)	11.30 (10.1-12)	11.65** (11.4-12.4)	13.15** (11.7-14.3)	13.2** (12.3-14.8)	13.6** (12.6-14.9)

BVAS: Birmingham Vasculitis Activity Score; IQR: interquartile range; uPr/Cr: urinary protein/creatinine ratio.
*p<0.05; **p<0.01.

as maintenance treatment, 6 of them in combination with AZA (n=4) or MMF (n=2). One patient received maintenance RTX without combination with oral immunosuppressive drugs due to intolerance to the latter. None of our patients received cotrimoxazole (see the Methods section).

Primary and secondary outcomes

No patients died by any cause during the 24-month follow-up. Likewise, no patients needed chronic haemodialysis or long-term oxygen therapy.

The BVAS decreased significantly from the diagnosis (median 24, IQR 21–33) to the 3rd month of follow-up (median 0, IQR 0–0) and remained within these values during the whole follow-up period (Table IV). At diagnosis, the lowest BVAS was 19; at 3 months, only one patient had a BVAS of 13, the remaining having scores of 0. At 6 months, only one patient had a BVAS of 14 (after a relapse), with all the remaining 13 patients having scores of 0. All patients had a BVAS of 0 at 12, 18 and 24 months.

Clinical and statistically significant improvements were achieved in all the laboratory parameters (uPr/Cr, serum creatinine, serum albumin, ANCA titers and haemoglobin) by 3 months, and kept improving during the remaining follow-up period (Table IV).

Three patients (21%) patients suffered relapses, all achieving rapid remission. Five patients (36%) had infections, mostly respiratory (n=4) and without major associated morbidity, except for an 85-year-old man who suffered from chronic bronchiectasis previous to the diagnosis of AAV and who became chronically infected by *Pseudomonas aeruginosa*, needing repeated courses of antibiotics. No patients needed admission in the intensive care unit for infections. No opportunistic infections, more specifically *Pneumocystis jirovecii* pneumonias, were observed.

Discussion

PRS constitutes the most severe form of presentation of AAV. The simultaneous occurrence of DAH and GN in patients with AAV worsens the prognosis substantially; in a recent multicentric study of the French Vasculitis Study Group comprising 80 patients with DAH secondary to AAV, the global mortality was 20%; however, 87.5% of non-surviving patients had developed PRS (8). In fact, mortality in patients with AAV-PRS is between 20–40% in most series (1).

In our study, no patients with well-documented PRS secondary to AAV died within the first two years after the diagnosis. Moreover, no patients developed end-stage renal failure requiring permanent dialysis/renal transplantation or chronic respiratory insufficiency with need of oxygen therapy. These results deeply contrast with recent series of similar size, in which mortality rates were between 29% and 69%, as shown in table 5. Most, although not all patients included in these series had AAV as the cause of PRS.

Infections and direct complications of vasculitis are the leading causes of death among patients with PRS (Table V). Therefore, it is crucial to early start a combination therapy, both potent enough to achieve a rapid control of the disease and to minimise the risk for severe infections. How to use GC is therefore a main issue in these patients. The latest EULAR guidelines on the treatment of AAV published in 2016, recommend GC doses of 1 mg/kg/day up to a maximum of 80 mg/day for induction therapy (2). In case of life-threatening disease with vital organ involvement, CYC or RTX should be added to the induction regimen. For maintenance treatment, a rapid taper

Table V. Cohort studies of pulmonary-renal syndrome.

Author/year (ref)	Study design	Treatment	Outcomes
Gallagher/2002 (9)	14 patients: -13 MPA (5 c-ANCA, 7 p-ANCA, 1 ANCA negative), -1 SLE.	14/14 (100%) Prednisolone mean starting dose 54 mg/d, 8 /14 (57%) MP (1.5 to 3 g total dose), 13/14 (93%) CYC (9 patients 2mg/kg/d, 4 patients 1mg/kg/d), 12/14 PEX (86%), 4 of them followed by IVIG.	7/14 (50%) patients died during the first year: -Sepsis 6/7 (86%), -Progressive pulmonary fibrosis 1/7 (14%). 1/14 (7%) chronic haemodialysis.
Córdoba/2015 (10)	14 patients: -8 AAV (3 c-ANCA, 5 p-ANCA), -4 SLE, -1 cryoglobulinaemia, -1 thrombotic microangiopathy	13/14 (93%) MP, followed by Prednisolone 1mg/kg/day 8/14 (57%) CYC (500 mg iv, only 2 patients AAV completed 6 doses), 10/14 (71%) PEX.	8/14 (57%) died: -5 (36%) infections, -1 (7%) retroperitoneal haemorrhage, -1 (7%) brain haemorrhage, -1 (7%) refractory PRS. 1/14 (7%) chronic haemodialysis.
Rajagopala/2015 (11)	27 patients admitted to an ICU. 13/27 immunologic aetiology: -7 SLE, -3 AAV, -2 IGAN, -1 anti-GBM disease.	11/13 (85%) MP, 7/13 (54%) CYC, 6/13 (46%) PEX.	9/13 (69%) died (main cause of death, infections). 3/13 (23%) CKD.
Burgos/2019 (12)	12 patients: -7 AAV (6 p-ANCA, 1 c-ANCA), -4 anti-GBM disease, -1 SLE.	12/12 (100%) immunosuppressive treatment*, 6/12 (50%) PEX.	5/12 (42%) died due to infections. 4/12 (33%) chronic haemodialysis.
Khan/2019 (13)	17 patients: -13 AAV (10 GPA, 3 PAM), -2 SLE, 2 anti-GBM disease.	15/17 (88%) MP, 2/17 (12%) Prednisolone 1 mg/kg/day, 12/17 (71%) CYC (8 oral, 4 intravenous), 2/17 (12%) RTX, 10/17 (59%) PEX. Maintenance therapy: Prednisolone 1 mg/kg/day with tapering, 7/17 (41%) AZA, 4/17 (23.5%) MMF.	5/17 (29%) died (main cause of death severe respiratory distress, followed by nosocomial infection). 1/17 (6%) chronic haemodialysis.

*Treatment not detailed.
AAV: ANCA-associated vasculitis; anti-GBM disease: anti-glomerular basement membrane disease; AZA: azathioprine. CKD: chronic kidney disease; GPA: granulomatosis with polyangiitis; ICU: intensive care unit; IGAN: IgA nephropathy; IVIG: intravenous immunoglobulin; MP: methylprednisolone pulse; PAM: microscopic polyangiitis; PEX: plasma exchange; PRS: pulmonary-renal syndrome. RTX: rituximab. SLE: systemic lupus erythematosus.

of GC with a goal of 7.5–10 mg/d of oral prednisone at 12 weeks is recommended, although it is described that in routine clinical practice this goal may not be achieved until 20 weeks. No specific mention of MP is made across the text (2).

More recently, the American College of Rheumatology (ACR) has published the 2021 update of the guidelines for the management of AAV (14). In case of vital organ involvement, it is recommended to start induction therapy with either iv MP or high-dose oral GC (*i.e.* prednisone 1 mg/kg/d up to 80 mg/d in adults). Based on the results of a RCT published in 2020 (15), they conditionally recommend a reduced-dose GC regimen over a standard-dose GC regimen for remission induction (14). Such reduced-dose regime starts with three MP (500–1000 mg/d) followed by 50–75 mg/d (depending on patient's weight) of oral prednisone for one week, then reducing the dose by one half and tapering down to 5 mg/d by week 15 to 19, also depending on patient's weight (15). In case of severe involvement in granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), RTX is preferred over CYC for induction (14). Also based on Walsh *et al*. study (15), PEX is not routinely recommended (14).

While high-dose GC regimes have been the rule in patients with PRS (Table V), our therapeutic scheme differs in some aspects from those proposed in the EULAR and ACR guidelines. This was based on our studies on patients with SLE (3, 6) and giant cell arteritis (16), showing the efficacy and safety of combining MP with reduced-dose oral GC regimes. The rationale for this combination is maximising the activation of the non-genomic way and minimising the toxicity intrinsic to the genomic way of action of GC: this is achieved by reducing starting doses to 20-30 mg/d and by rapidly tapering over a period of few weeks to 5 mg/d (4, 17), whilst MP are given not only at the beginning of the induction therapy, but also with each dose of CYC (4, 6). This combination (500 mg of CYC + 125 mg of MP) given every two weeks has resulted in complete remission rates over 85% in

our cohort of patients with lupus nephritis (6); in addition, the use of the reduced dose-prednisone with a rapid tapering scheme has minimised the rate of infections in our patients, including a virtual absence of opportunistic agents despite the lack of prophylaxis (18). Once the dose of prednisone is 2.5 mg/d, it can be maintained long-term as a background therapy without a significant risk for major complications (17).

As many as 85.7% of our patients received RTX as an induction regime in addition to iv CYC, in contrast with the studies summarised in Table V, in which RTX was used in a minority of patients and in only one series (13). Although current guidelines put CYC and RTX as two different options for induction therapy (2, 14), the combination of both has obtained very good results in patients with severe AAV, including those with GN and/or DAH (19-21), with survival and renal remission rates over 80%. In these studies, however, the cumulative doses of oral GC and the number of patients with unfavourable outcomes were both higher than in our group. In the most recent one, among 64 patients with severe AAV (52% with DAH), the survival rate at 24 months was 89%, with 19% of the surviving patients being on end stage kidney disease (21). Moreover, the cumulative dose of prednisone during the first 6 months was 2.6 g (21), compared with 1.433 g in our series (Table III). This group put all patients on PEX, however only 50% were given MP. We believe that the repeated MP used in our therapeutic scheme with each dose of CYC played a main role to explain these differences, both in clinical response and oral GC load. This was an effect similar to that seen in patients with lupus nephritis, in whom this scheme resulted in complete remission rates at one year over 85% (6). However, it must be also noted that patients in the study by Gulati *et al*. had on average a worse renal function at diagnosis than our patients (21). This fact must also call for an early diagnosis and initiation of treatment in order to obtain better long-term outcomes.

Our study has a number of limitations. The most obvious is the lack of a control group with which to compare our therapeutic protocol. However, the scheme of repeated MP combined with CYC and RTX has not been used elsewhere, with our results being superior in terms of outcome and oral GC sparing to those of other well-characterised series. Our data come from routine clinical care, thus although patients' therapy was attached to a common protocol, some variability could be seen, like the fact that one patient did not receive CYC and two were not treated with RTX. On the other hand, we used repeated MP and a rapid tapering scheme of prednisone in all patients, which resulted in a low oral GC load in all of them. The number of patients was relatively small, although similar to other previously published cohorts of PRS (Table V). Due to the lack of adverse outcomes, we could not analyse the potential differences between patients with different types of AAV or different ANCA specificity, or between those receiving different doses of MP or different maintenance immunosuppressive therapy. Finally, all patients were white, all with full access to public health system, which makes some difference with other cohorts. Moreover, we offered a multidisciplinary approach with the same combined team of internists and nephrologists taking care of all patents, which has also shown to improve the outcome of patients with autoimmune diseases involving the kidneys (22).

In summary, we present our real-life experience with the management of PRS due to AAV, showing that a combination regime including, iv CYC and RTX plus repeated MP results in very favourable outcomes in terms of survival, end-stage organ dysfunction, infections and oral GC sparing in this life-threatening form of presentation of AAV. Our results open the door to further research exploring this approach.

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