



EDITORIAL COMMENT

Slo-Mo anti-neutrophil cytoplasmic antibody-associated renal vasculitis

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ABSTRACT

Nephrologists are familiar with severe cases of anti-neutrophil cytoplasmic antibodies-associated vasculitis (AAV) presenting as rapidly progressive glomerulonephritis. However, less is known about AAV with slowly progressive renal involvement. While its existence is acknowledged in textbooks, much remains unknown regarding its relative frequency versus more aggressive cases as well as about the optimal therapeutic approach and response to therapy. Moreover, this uncommon presentation may be underdiagnosed, given the scarce familiarity of physicians. In this issue of *Clinical Kidney Journal*, Trivioli *et al.* report the largest series to date and first systematic assessment of patients with AAV and slowly progressive renal involvement, defined as a reduction in estimated glomerular filtration rate (eGFR) of 25–50% in the 6 months prior to diagnosis after excluding secondary causes. Key findings are that slowly progressive AAV may be less common than previously thought, although it still represents the second most common presentation of renal AAV, it usually has a microscopic polyangiitis, anti-myeloperoxidase, mainly renal phenotype in elderly individuals, diagnosis may be late (over one-third of patients had end-stage kidney disease at diagnosis), clearly identifying an unmet need for physician awareness about this presentation, but those not needing renal replacement therapy at diagnosis still responded to immunosuppression.

Keywords: ANCA, MPO, mycophenolate, outcomes, rapidly progressive glomerulonephritis, rituximab, therapy, vasculitis

In this issue of *Clinical Kidney Journal*, Trivioli *et al.* report a retrospective European case series of 41 patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) with slowly progressive renal involvement not attributable to other causes, defined as a reduction in estimated glomerular filtration rate (eGFR) of 25–50% in the 6 months prior to

diagnosis since rapidly progressive glomerulonephritis usually implies a eGFR reduction >50% in up to 3 months (Figure 1) [1]. Given the few published studies, mostly consisting of case reports or small case series and mainly from Asia [2–5], the present report, the largest and first systematic assessment to date in slowly progressive renal AAV, provides several key insights.

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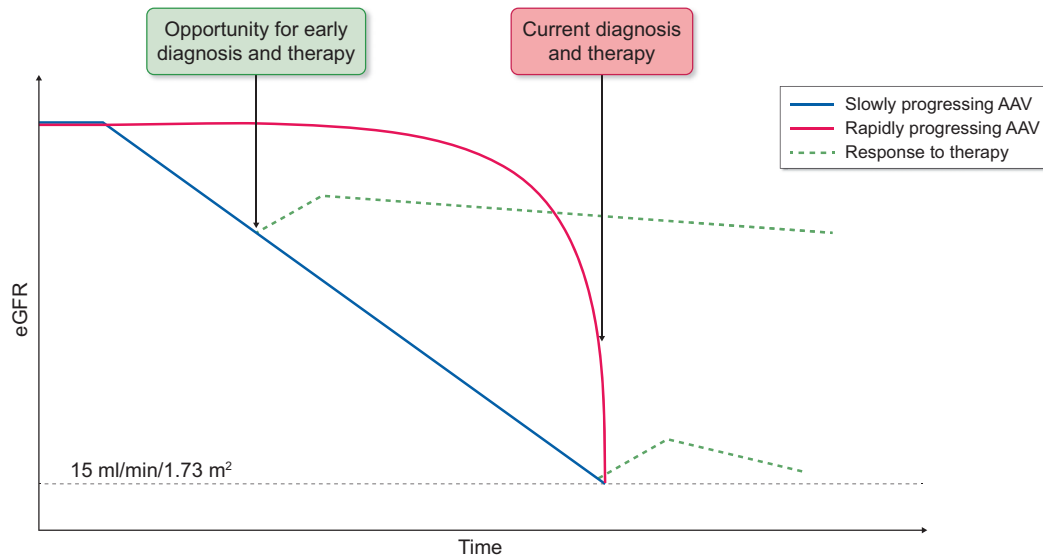
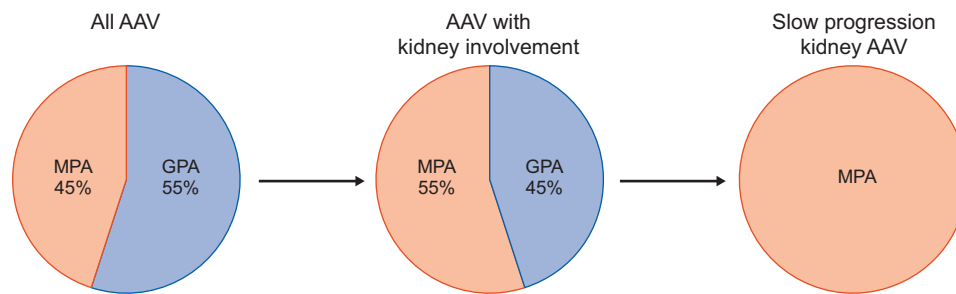
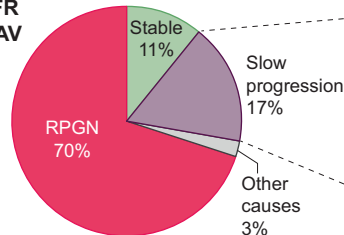


FIGURE 1: Slow motion AAV: an opportunity to improve outcomes. The graph represents the current situation: AAV with a rapidly progressive glomerulonephritis pattern is usually diagnosed late from a kidney function point of view, given the rapid loss of renal function. Surprisingly, this late diagnosis is also the case for slowly progressive AAV, probably because the disease was not suspected earlier in its course. An increased awareness of this presentation may lead to earlier diagnosis and therapy, thus improving outcomes.

A Relative frequency of different forms of AAV



B Timelines of eGFR loss in kidney AAV



C Kidney biopsy pattern

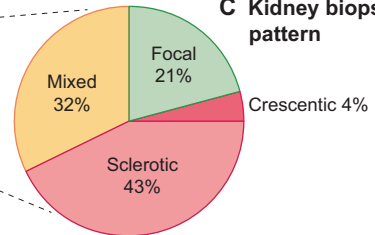


FIGURE 2: Slowly progressive AAV in the general context of AAV: frequency, clinical presentation and kidney biopsy patterns [1]. (A) Relative frequency of different forms of AAV. Notice that while in the whole series, granulomatosis with polyangiitis was more common than MPA, MPA was more common among patients with renal involvement and was the only AAV phenotype found among patients with slowly progressive AAV. (B) Timelines of eGFR loss in kidney AAV. Although uncommon, slowly progressive AAV was the second most common presentation of AAV with kidney involvement. (C) Kidney biopsy pattern. In patients with slowly progressive AAV in whom a kidney biopsy was available, the most common pattern in the Berden classification was sclerotic (>50% globally sclerotic glomeruli), followed by mixed, in which up to 50% of glomeruli may be globally sclerotic, representing a predominance of late diagnoses [24]. Numbers represent percentage of patients. Data from Trivioli et al. [1].

SLOW MOTION RENAL AAV: AT LAST INSIGHTS INTO REAL FREQUENCY

Trivioli et al. report that 5% of a large multicentre series of 856 patients with AAV had slowly progressive renal AAV, corresponding to 11% of the microscopic polyangiitis (MPA) cases and 17% of AAV cases whose pre-diagnostic kidney function course could be ascertained (Figure 2) [1]. Although it has been claimed that up to 30% of AAV patients with renal involvement present slow progression, we did not find full reports as sources for this claim which was present in abstracts, book chapters or review manuscripts without detailed patient characterization [2]. In Trivioli's data, the slowly progressive presentation was almost exclusive of MPA patients with anti-myeloperoxidase (MPO) antibodies/pANCA (all but one), usually elderly (mean age 70 years, 39% >75yearsold) with mostly renal-limited AAV (the most common extrarenal manifestation was subclinical interstitial lung lesions). These findings are aligned with the literature since we only found one report of slowly progressive ANCA-PR3 AAV in a 65-year-old woman with granulomatous polyangiitis kidney disease [5]. In this regard, the mean age for MPA patients with anti-MPO antibodies in the literature is around 60 years [6].

A LATE DIAGNOSIS DESPITE MULTIPLE KIDNEY FUNCTION ASSESSMENTS

In the report by Trivioli et al., eGFR at diagnosis was low [23 mL/min/1.73 m², interquartile range (IQR) 15–35] and 37% of patients were considered to have end-stage kidney disease (ESKD), including some requiring renal replacement therapy (RRT), implying that diagnosis was late [1]. Indeed, renal abnormalities had been present and observed for a median (IQR) of 13 months (6–35) before diagnosis and this was longer among patients with end stage renal disease (ESRD) at diagnosis (38 months, IQR 13–52). During this time, patients have lost a median of 53% of renal function, equivalent to 25 mL/min/1.73 m². As most (93%) patients had three or more renal function assessments during this time, the delay in diagnosis appeared to be related to physician non-acquaintance with this presentation, precluding earlier ANCA testing. Besides decreasing eGFR, at diagnosis all patients had evidence of glomerular inflammation (proteinuria around 1 g/day, microhaematuria), which should have triggered earlier testing for ANCA if present at earlier stages. Kidney biopsy was available for 28 patients and besides the characteristic presence of glomerular crescents (90% of cases), the main feature was the high frequency of chronic, irreversible damage: in patients with crescents, 90% were purely fibrous, and global glomerulosclerosis was found in a median of 38% glomeruli per biopsy (Figure 2).

DESPITE LATE DIAGNOSIS AND LONG-STANDING DISEASE, TREATMENT MAY STILL BE EFFECTIVE

Fear of immunosuppression-related complications in elderly patients with chronic features in the kidney biopsy may be the main reason why patients with slowly progressive AAV often receive only supportive therapy and/or low-level immunosuppression. In the report by Trivioli et al., however, 56% of patients received steroids without (12%) or with immunosuppressants (44%: cyclophosphamide, mycophenolate or azathioprine) and 34% received a rituximab-based regimen, while only 10%

were not treated with immune suppressants as renal recovery was considered unlikely [1]. Within 6 months, 73% of treated patients had an improved eGFR. Improvement was even observed in some patients with 'sclerotic' kidney biopsies. At 24 months, microhaematuria had improved in all patients and proteinuria had decreased, evidencing improvement in glomerular inflammation. At the last follow-up (32 months, IQR 12–52), eGFR had increased $\geq 25\%$ in almost 60% of treated patients and was stable in another 9%, without differences between therapeutic regimens. However, given the low eGFR at diagnosis, the absolute improvement in eGFR may be estimated at around 6 mL/min/1.73 m² which cannot be considered a huge success and should be clearly improved. While the most severe patients at diagnosis (ESKD, RRT and non-treatment) progressed or remained on ESRD at the end of follow-up, treatment was considered safe, as none of the nine deaths (22%) was considered vasculitis- or treatment-related.

WHAT IS THE OPTIMAL THERAPEUTIC APPROACH FOR SLOWLY PROGRESSIVE AAV?

Kidney Disease: Improving Global Outcomes (KDIGO) 2012 glomerulonephritis guidelines do not have a specific section for slowly progressive AAV and KDIGO 2020 may also lack this section [7]. They do mention that a minority of patients present an indolent course, but no specific therapeutic recommendations are made for these patients. In the early stages, slowly progressive AAV may be considered 'not severe disease'. For not severe disease, there are recommendations: induction therapy is rituximab plus corticosteroids followed by azathioprine, alternatives being mofetil mycophenolate (MMF) or methotrexate, the latter only if eGFR > 60 mL/min/1.73 m². The European League Against Rheumatism (EULAR) 2015 update on AAV recommends induction of non-organ-threatening AAV with corticosteroids and either methotrexate or MMF and maintenance with low-dose corticosteroids and either azathioprine, rituximab, methotrexate or MMF [8]. The KDIGO not severe disease and EULAR non-organ threatening AAV definitions for the kidney are based on the slope of declining renal function but they do not provide specific thresholds. The concept does not appear to be better defined in the draft for public review of the KDIGO 2020 glomerulonephritis guidelines. Thus, corticoids plus rituximab or methotrexate or MMF are recommended for induction by different guideline bodies for what may encompass the clinical presentation of slowly progressive AAV. Since kidney function is frequently reduced at diagnosis, MMF and rituximab are the key induction options. Cyclophosphamide is conspicuously absent from guidelines when disease is not severe. However, despite the slow progression, Trivioli et al. remind us that by the time the disease is diagnosed, mean eGFR was already sufficiently low to consider the disease as organ-threatening and emphasizing again the need for efforts at early diagnosis that allow milder immunosuppressive regimens.

Recent studies support the efficacy of MMF as induction treatment for AAV [9–14]. MMF plus corticosteroids can be used in elderly patients with low risk of relapse [10] and a lower MMF dose (1 g/24 h) achieved 100% of remissions at Month 18 [11]. A further report achieved 14 remissions in 17 MPO-AAV patients with MMF and corticosteroids [9]. Nonetheless, is MMF the best option for remission maintenance? While an randomized controlled trial (RCT) observed higher relapse rates for MMF than for azathioprine, a majority (70%) of patients were PR3-positive, which are known to have higher relapse rates [15]. In this

regard, two meta-analyses of the same four studies found no differences regarding remission and relapses between MMF and cyclophosphamide [13, 14] and a meta-regression analysis indicated an association between 6-month remission rates and MPO-ANCA positivity [14]. This is relevant given that almost all patients with slowly progressive AAV have MPO-ANCA.

Therefore, starting MMF at 2 g/day plus corticosteroids at 1 mg/kg/day and tapering to 10 mg/day between Months 3 and 6 for induction followed by MMF 1 g/day or switch to azathioprine 2 mg/kg/day in MPO-ANCA AAV patients to complete 18–24 months could be an option. Rituximab could be also used as induction and maintenance therapy [16–20]. The advantage of rituximab over MMF would be that rituximab is effective independently of ANCA type [18]. However, in the absence of specific clinical trials, it remains unknown whether this represents the optimal immunosuppressive regimen for slowly progressive AAV.

UNMET CLINICAL NEEDS

This manuscript identifies several unmet needs.

The first relates to an insufficient familiarity of physicians with slowly progressive AAV, leading to delayed ANCA testing. Thus, despite several sequential renal function assessment over a few months, in which kidney function progressively deteriorated, ANCA testing was only performed late in the course of disease, when mean eGFR category was already G4. This may represent a lack of suspicion of the disease in the absence of features of RPGN.

The second unmet need relates to the optimal therapeutic approach. Being a less aggressive form of AAV, it is likely that the optimal balance between efficacy and safety of immunosuppression can be reached by a milder immunosuppression regimen than for RPGN. However, there are no prospective studies in this regard, related to the *post hoc* diagnosis of this entity.

A subanalysis of patients enrolled in randomized controlled trials having relatively preserved renal function (eGFR > 50–60 mL/min/1.73 m²) may provide some clues. However, it is likely that earlier in the course of disease, most slowly progressing AAV patients would not have met entry criteria for AAV therapeutic trials [16, 21–23].

The third unmet need would be understanding what would be the early kidney biopsy pattern of slowly progressive AAV and whether the sclerotic glomeruli found in the current report at diagnosis represent the consequence of a single or repeated bouts of AAV with non-immune, haemodynamic loss of eGFR in between, or the consequence of developing AAV over a pre-existent condition, that may just be kidney ageing or a low-level autoimmune disease causing mostly non-specific kidney injury or accelerating pre-existent kidney tissue loss (Figure 3). In this regard, among patients with initial eGFR improvement, a subsequent decline of >25% was observed in 37% by Trivioli et al., potentially representing haemodynamic loss of kidney function related to reduced renal mass [1]. Regarding potential pre-existent kidney injury, at start of data availability, baseline eGFR was around 50 mL/min/1.73 m² and other potential causes of or contributors to kidney injury were present in a large proportion of patients, including age >75 years (39%), hypertension (63%) and diabetes (22%).

In conclusion, despite the retrospective nature and arbitrary definition of slowly progressive AAV, this case series shows that a relatively low percentage of AAV patients have a slow progression of renal involvement. Clinical presentation at diagnosis is characterized by low eGFR and chronic and severe kidney lesions, implying a late diagnosis. Despite these findings, a non-negligible and higher than expected percentage of patients with slowly progressing AAV appeared to benefit from immunosuppressive treatment to slow down kidney disease progression. This study has identified unmet clinical needs regarding earlier

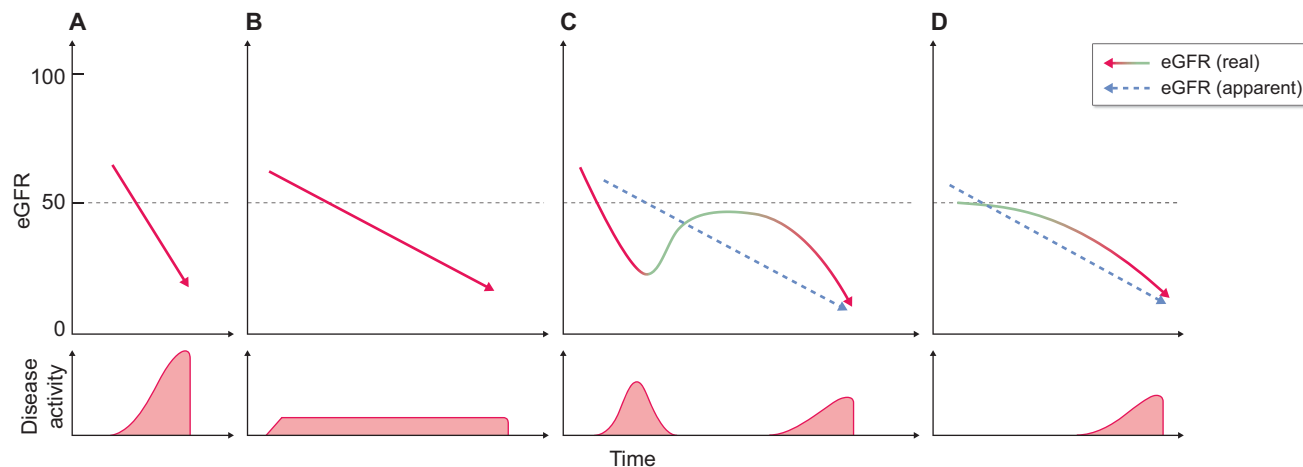


FIGURE 3: Potential trajectories of eGFR loss and relationship to immune disease activity in slowly progressive AAV natural history. Based on the definition of slowly progressive AAV and the clinical and histologic features at diagnosis, several potential trajectories of the eGFR could be envisioned, as compared to the classical pattern of rapidly progressive glomerulonephritis (A). (B) The slow loss of eGFR could be sustained in time as a consequence of sustained low level AAV autoimmune disease activity. (C) As an alternative, separate bouts of autoimmune disease activity could be responsible for an earlier decrease in eGFR and functioning nephron numbers that may explain the abundance of fibrous crescents. This may be followed by partial recovery of renal function and posterior accelerated haemodynamically mediated eGFR loss as a consequence of reduced renal mass and eventually, this may be followed by the episode of autoimmune disease activity detected at diagnosis. (D) Finally, slowly progressive AAV may be the consequence of developing AAV over a previously injured kidney (notice that the eGFR trajectory in D starts below the chronic kidney disease (CKD) definition threshold for eGFR) and this prior injury may contribute to this very characteristic phenotype. The fact that relapses following therapy are less common in MPO-ANCA than in PR3-ANCA would argue against relapsing disease as a driver of slow progression. However, potential natural history (in the absence of immunosuppression) trajectories are represented here. Green parts of the eGFR trajectory represent absence of autoimmune disease activity.

diagnosis and personalized immunosuppressive regimens in AAV patients with slowly progressive kidney disease.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest.

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