

Treatment of Granulomatosis with Polyangiitis and Microscopic Polyangiitis Should Type of ANCA Guide the Treatment?

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CJASN 15: 1519–1521, 2020. doi: <https://doi.org/10.2215/CJN.15861219>

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are two major clinical entities recognized among ANCA-associated vasculitides. GPA and MPA differ in the presence or absence of granuloma, organ involvement, and risk of relapses. GPA is more often, but not exclusively, associated with proteinase 3 (PR3)-ANCA, and MPA is more often, but not exclusively, associated with myeloperoxidase (MPO)-ANCA.

A recent genome-wide association study demonstrated that genetic polymorphisms predisposing to ANCA-associated vasculitis are more closely associated with the subtype of autoantibody (*i.e.*, PR3-ANCA and MPO-ANCA) than with GPA and MPA, respectively, and differ between PR3-ANCA-associated vasculitis and MPO-ANCA-associated vasculitis, suggesting different pathogenesis associated with each individual autoantibody. PR3-ANCA-associated vasculitis and MPO-ANCA-associated vasculitis also have different geographic distribution, pathology (granulomatous lesions are more often linked with PR3-ANCA), kidney histology (more active lesions—necroses and crescents in PR3-ANCA-associated vasculitis—and more chronic lesions—glomerulosclerosis and tubulointerstitial fibrosis in MPO-ANCA-associated vasculitis), and clinical phenotype (with ENT or eye involvement and lung nodules and cavities more common [but not exclusively present] in PR3-ANCA-associated vasculitis and isolated ANCA GN more common in MPO-ANCA-associated vasculitis) (1). Patients with PR3-associated GN are (compared with those with MPO-associated GN) more often men, are of younger age, and have higher GFR at presentation.

Importantly, relapses are significantly more frequent in PR3-ANCA compared with MPO-ANCA (1,2), and they are also positively associated with upper respiratory tract and lung involvement and negatively associated with serum creatinine (2). Relapses contribute to the progressive organ damage and require repeated courses of induction immunosuppressive treatment associated with potential adverse events, including, for example, higher risk of secondary malignancy. Despite the differences described above, both patients with PR3-ANCA and patients with MPO-ANCA were recruited to (almost all) large randomized controlled trials in patients with ANCA-associated vasculitis and

treated with the same induction and maintenance treatment. In most of these trials (NORAM, CYCAZAREM, CYCLOPS, and WEGENT), there was not only (at least a trend to) a higher relapse rate in patients treated in the induction phase with lower cumulative dose of cyclophosphamide, but also a higher relapse rate in patients who remained ANCA positive at the end of the induction treatment and in both treatment limbs in PR3-ANCA-associated vasculitis compared with MPO-ANCA-associated vasculitis.

In the CYCAZAREM trial comparing early and late switch from oral cyclophosphamide to azathioprine, relapses were more frequent during the long-term follow-up (median of 8.5 years) in PR3-ANCA-associated vasculitis compared with MPO-ANCA-associated vasculitis both in the limb with early switch (after 3 months, 61% versus 37%) and in the limb with later switch (after 12 months, 41% versus 26%) from cyclophosphamide to azathioprine (3). Similarly, in the CYCLOPS trial comparing induction treatment with oral continuous versus pulsed cyclophosphamide, the risk of relapse during long-term follow-up (median of 4.3 years) was significantly (hazard ratio, 2.47; $P=0.04$) higher in PR3-ANCA-associated vasculitis compared with MPO-ANCA-associated vasculitis in both treatment limbs (4).

These data suggest that in patients with PR3-ANCA-associated vasculitis treated with conventional immunosuppression, the relapse rate remains high. Although we may quite safely decrease the cumulative dose of cyclophosphamide, this approach may be associated with further increase of an already high relapse rate in patients with PR3-ANCA-associated vasculitis. It should be, however, stressed that in the clinical trials (*e.g.*, CYCLOPS), higher relapse rate was not directly associated with higher mortality and morbidity and that regular monitoring and increased vigilance may at least partly limit the negative effect of relapses.

Could the high relapse rate in PR3-ANCA-associated vasculitis be decreased by the prolongation of the maintenance treatment? In the REMAIN trial (5), prolonged maintenance treatment with azathioprine/prednisone (48 versus 24 months) and ANCA negativity at randomization but not ANCA specificity (despite the trend to higher relapse rate in anti-PR3 patients) were associated with a significantly lower relapse rate.

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However, a *post hoc* analysis of pooled data from six European randomized controlled trials (6) including 380 patients with newly diagnosed ANCA-associated vasculitis demonstrated that the length of maintenance treatment had no significant effect on the risk of relapse, which was associated with ANCA specificity (higher in PR3-ANCA) and type of induction treatment (oral continuous versus pulsed cyclophosphamide), suggesting that to prevent relapses in PR3-ANCA-associated vasculitis, we need both more effective induction and maintenance treatment.

In the RAVE trial, a single course of rituximab without any maintenance treatment compared with cyclophosphamide followed by azathioprine achieved more effectively ANCA negativity at 6 months in patients with PR3-ANCA-associated vasculitis (50% versus 17%; $P < 0.001$) but not in patients with MPO-ANCA (40% versus 41%). At 6 months, complete remission was also achieved more frequently in rituximab-treated compared with cyclophosphamide-treated PR3-ANCA (65% versus 48%; $P = 0.04$), and the higher rate of complete remission persisted in PR3-ANCA-associated vasculitis in the rituximab limb (without any maintenance treatment) compared with the cyclophosphamide limb (followed by azathioprine) even after 18 months (7). No such association between treatment limb and complete remission was observed in patients with MPO-ANCA-associated vasculitis.

After exclusion of patients with uncontrolled disease, rituximab-treated patients with PR3-ANCA-associated vasculitis also experienced fewer early flares (within 6 months from the initiation of the induction treatment) than patients treated with cyclophosphamide/azathioprine (14% versus 32%; $P = 0.02$ [8]). In MPO-ANCA-associated vasculitis, the rate of early flares was low, with no difference between rituximab- and cyclophosphamide/azathioprine-treated patients (18% versus 9%, respectively [8]).

Rituximab could thus be the treatment of choice for PR3-ANCA-associated vasculitis, especially for those with non-renal disease because no association between rituximab treatment and complete remission in PR3-ANCA-associated vasculitis was demonstrated in a subgroup of patients in the RAVE trial with kidney involvement.

Rituximab was also more effective than azathioprine as a maintenance treatment in preventing relapses in patients with ANCA-associated vasculitis induced into remission with conventional treatment with cyclophosphamide (MAINRITSAN trial [9]). In this trial, the risk of relapses was also more than two times higher in patients with PR3-ANCA-associated vasculitis compared with patients with MPO-ANCA-associated vasculitis, suggesting that (possibly longer) rituximab maintenance should be the preferred treatment especially in patients who are PR3-ANCA positive.

Recent data from the PEXIVAS trial do not suggest any effect of ANCA specificity on the response to both standard or reduced doses of corticosteroids and the response to plasma exchange.

Although ANCA specificity may be more associated with relapses than clinical diagnosis of GPA or MPA (10), clinical characteristics, including, for example, severity of kidney involvement or ENT and lung involvement, can be associated with not only the risk of relapses but also mortality and the risk of ESKD. On the basis of the previous cluster analysis, three major clinical phenotypes of ANCA-associated vasculitis ([1] kidney PR3-ANCA-associated vasculitis, [2]

kidney non-PR3-ANCA-associated vasculitis, and [3] non-renal, nonsevere ANCA-associated vasculitis) were recently proposed. Nonsevere ANCA-associated vasculitis (usually PR3+, sometimes negative, predominantly granulomatous features, and no kidney involvement or other prominent vasculitic features) has a low risk of life-/organ-threatening disease and high relapse rate. Severe PR3-ANCA-associated vasculitis (mixed granulomatous-vasculitic lesions, kidney involvement, and/or other prominent vasculitic features) has an intermediate risk of life-/organ-threatening disease and intermediate risk of relapses, and severe MPO-ANCA-associated vasculitis (predominantly vasculitic lesions, kidney involvement, and/or other prominent vasculitic features) has a high risk of life-/organ-threatening disease and low risk of relapses.

In conclusion, not only ANCA specificity but also especially kidney function (and the type of extrarenal involvement) should be considered to assess the risk of relapses and select the optimal type of induction and maintenance treatment. In patients with severe PR3-ANCA-associated vasculitis and severe MPO-ANCA-associated vasculitis, rituximab and cyclophosphamide are similarly effective as induction treatment, but we have limited data for rituximab in patients with severe kidney involvement (serum creatinine > 5.7 mg/dl). In PR3-ANCA-associated vasculitis with a higher risk of relapses because of better preserved kidney function (with serum creatinine < 2.3 mg/dl) and with extrarenal involvement, rituximab maintenance may be the best option. Because the risk of relapses progressively declines with increasing serum creatinine in patients with severe MPO-ANCA-associated vasculitis, the length of maintenance treatment can be individually tailored on the basis of the presence, type, and extent of extrarenal involvement.

Despite still limited evidence, prolongation of the maintenance treatment with azathioprine or newly with rituximab beyond 18 months (up to 4 years or even more) should be considered in patients with persistent ANCA positivity, especially those with PR3-ANCA and those with repeated relapses of the disease. On the other hand, maintenance treatment may be shorter in MPO-ANCA, especially when they become ANCA negative, and may be even completely avoided in some (closely watched) rituximab-treated patients with MPO-ANCA (7,8).

Future randomized controlled trials in ANCA-associated vasculitis should at least stratify the patients on the basis of the ANCA specificity and/or newly defined clinical phenotype. On the basis of the data coming from these studies (and accumulating observational data), it will be possible to personalize the expanding armamentarium used in the treatment of ANCA-associated vasculitis.

Disclosures

V. Tesar reports receiving personal fees from Abbvie, Alexion, Amgen, Boehringer-Ingelheim, Chemocentryx, and Fresenius Medical Care. The remaining author has nothing to disclose.

Funding

Funding was provided by PROGRES Q25, Ministry of Education, Czech Republic.

Acknowledgments

The content of this article does not reflect the views or opinions of the American Society of Nephrology (ASN) or CJASN. Responsibility

for the information and views expressed herein lies entirely with the author(s).

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Published online ahead of print. Publication date available at www.cjasn.org.