The changing role of glucocorticoids in the treatment of ANCA-associated vasculitis

The changing role of glucocorticoids in the treatment of anti–neutrophil cytoplasmic antibody–associated vasculitis

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Glucocorticoids (GCs) have been a cornerstone of treatment for patients with anti–neutrophil cytoplasm antibody–associated vasculitis (AAV) for decades. They were first used as monotherapy for "polyarteritis" in the 1950s,[1,2] and then successfully combined with cyclophosphamide in the 1970s.[3] Since then, there have been major efforts to refine the non-GC components of AAV treatment—through the evolution of antimetabolite and biologic immunosuppressive agents—whilst GC regimens have remained largely unchanged and based on historic practice or consensus opinion. This may account, at least in part, for the persistence of adverse outcomes related to treatment in patients with AAV. The toxicity associated with GC was well recognized in the early studies.[4] This was also apparent in the subsequent controlled trials of non-GC agents, and is still a feature of recent meta-analyses and registry-based studies, including patients from around the world treated in current health care settings using modern immunosuppressive regimens. Despite, then, being a potentially modifiable risk factor for adverse outcomes, it is only in the last few years that GC regimens (and GC alternatives) have been tested in randomized control trials.

GC reduction during remission-induction

Plasma Exchange and Glucocorticoids for Treatment of ANCA-Associated Vasculitis (PEXIVAS) was the first study to compare oral GC regimens in a controlled manner, and the largest randomized control trial in AAV to date.[5] It recruited >700 patients with moderate to severe kidney impairment (estimated glomerular filtration rate [eGFR] <50 ml/min per 1.73 m^2; no lower limit) who were randomized in a 2 × 2 factorial design to receive (i) either plasma exchange or no plasma exchange, and (ii) a standard *versus* a reduced dose GC taper (~3.2 g vs. ~1.8 g oral GC in the first 3 months) following induction therapy with i.v. methylprednisolone (1–3 g) and either cyclophosphamide (followed by azathioprine maintenance) or rituximab. During a median follow-up of 2.9 years, the reduced-dose regimen was noninferior with respect to the primary outcome of kidney failure or death, with fewer serious infections in the first year. There were no other differences in secondary end points, there was no interaction with plasma exchange allocation, and the results were broadly similar across the predefined subgroups. Of note, there was a trend toward higher rates of kidney failure or death in patients who received low-dose GC alongside rituximab, which may warrant further investigation.

The last 12 months have seen the publication of 2 further randomized control trials that have examined modified GC regimens for remission-induction. The Low-Dose Glucocorticoid Vasculitis Induction Study (LoVAS)[6] recruited 140 older Japanese patients (median age, 73 vs. 63 years in PEXIVAS) with predominantly myeloperoxidase (MPO)-AAV (85%), who underwent open-label randomization to a standard (initially 1 mg/kg per day; median actual total dose, 4.2 g) *versus* low-dose (0.5 mg/kg per day; 1.3 g) GC induction regimen alongside rituximab for mild disease (median eGFR, 52–55 ml/min per 1.73 m^2 with a significant proportion having no kidney involvement). There was no difference in the primary end point of remission at 6 months. Adverse events appeared to be less frequent in patients treated with the low-dose regimen, and this included serious infections (7% vs. 30%). These findings are broadly consistent with those of PEXIVAS—that a reduced GC regimen alongside rituximab is noninferior for remission-induction in patients with mild disease. Interestingly, an analysis of the induction phase of the Rituximab Versus Azathioprine as Therapy for Maintenance of Remission for ANCA-Associated Vasculitis (RITAZAREM) study (which primarily compared maintenance treatment with fixed-interval rituximab to azathioprine) also showed that both a standard

dose (initially 1.0 mg/kg per day; cumulative dose 3.0 g at month 4) and a reduced-dose GC regimen (0.5 mg/kg per day; 2.0 g) alongside rituximab were effective for remission-induction in patients with relapsing disease who were predominantly proteinase-3–anti–neutrophil cytoplasm antibody–positive.[7] It must be highlighted that GC dosing in RITAZAREM was physician determined and not a primary study outcome. It remains unclear if patients with more severe disease may be successfully managed using a combination of low-dose GC and rituximab, without cyclophosphamide and/or plasma exchange.

Although the CCX168 (Avacopan) in Patients With ANCA-Associated Vasculitis (ADVOCATE) trial did not compare GC regimens *per se*, it investigated complement blockade as a substitution for GC treatment.[8] It recruited patients with active AAV (median age, 61 years) receiving rituximab (65%) or cyclophosphamide/azathioprine (35%) for remission-induction and randomized them to a "standard" 6-month GC taper (initially, 60 mg/d; median actual total dose, 3.7 g) or a 12-month period of treatment with the selective C5aR1 antagonist, avacopan. The avacopan-based regimen was noninferior to GC for the attainment of disease remission at 6 months (72% vs. 70%), and superior to GC for sustained remission at 12 months (66% vs. 55%). The latter was driven by a higher rate of relapse in the standard GC arm of the study. Avacopan treatment was associated with fewer adverse events and greater improvements in quality-of-life assessments. Noteworthy are the data relating to kidney function. Of recruited patients, 80% had kidney involvement (median eGFR, 45 ml/min per 1.73 m^2); avacopan-treated patients displayed more rapid improvements in albuminuria and better recovery of eGFR over the study period, with the greatest benefit achieved in those with more severe renal dysfunction at enrollment. These differences were apparent within the first 6 months of the study, when patients in the control group were still receiving GC, suggesting that avacopan may not only allow GC avoidance, but also provide better kidney recovery than a GC-based treatment alone.

The ADVOCATE findings are a major step forward in AAV management, providing evidence for an entirely new class of drug that may limit GC exposure. However, the study has limitations, including the lack of per-protocol maintenance therapy in patients treated with rituximab, that months 6 to 12 of the study compared *no* GC to avacopan rather than to GC treatment, and that avacopan was associated with reduced, but not no, GC use (1.3 g vs. 3.7 g overall). Nevertheless, the US Food and Drug Administration has recently approved the use of avacopan as "adjunctive treatment… alongside standard therapy" in patients with AAV.

GC minimization during remission-induction

Although the PEXIVAS, LoVAS, and ADVOCATE studies demonstrate that GC dose may be successfully reduced during remission-induction, overall GC burden in these studies was not insignificant. This is important when considering recent uncontrolled studies that suggest a rapid GC taper may be feasible without the use of avacopan or other adjunctive therapies, and instead using a regimen combining cyclophosphamide and rituximab. The use of this combination was first tested, alongside a "standard" GC regimen, in patients with severe disease in the RITUXVAS study.[9] Since then, we and others have shown that this approach may provide rapid and prolonged disease control, whilst permitting a rapid taper of oral GC and avoidance of high-dose i.v. methylprednisolone, without increasing infection risk.

This combination approach formed the basis of an open-label cohort study that implemented a rapid GC taper.[10] Forty-nine patients with active AAV were treated with a combination of low-dose i.v. cyclophosphamide ($\sim$3 g), rituximab (2 g), and a 1- to 2-week course of GC (total dose, $\sim$1.2 g; i.e., equivalent to the dose of GC received by avacopan-treated patients in ADVOCATE). Two patients required reintroduction of GC for treatment of active disease during the first 6 months, although all remaining patients had achieved disease remission by this time. At 12 months, 90% of patients were in sustained remission. A case-control analysis of matched patients enrolled in previous European Vasculitis Society (EUVAS) trials using standard GC dosing showed comparable remission rates and improvements in eGFR during the first year, but a lower incidence of new-onset diabetes (0% vs. 8%) and severe infections (12% vs. 30%). These promising preliminary results in patients with significant kidney disease (eGFR, 29 ml/min per 1.73 m^2), of whom the majority were MPO–anti–neutrophil cytoplasm antibody–positive and so at lower risk of relapse, should be examined further in controlled studies.

GCs during remission-maintenance

There are no controlled studies directly comparing maintenance GC dose and duration in AAV. A 2010 meta-analysis (including 13 trials and observational studies) found that GC regimen was the most significant variable associated with disease relapse, and that targeting complete GC withdrawal linked to an increased risk of relapse.[11] These findings are broadly consistent with those of the Prolonged REmission-MAINtenance therapy in systemic vasculitis (REMAIN) study, which found that prolonged maintenance treatment with azathioprine *and* prednisolone resulted in a lower risk of relapse in patients who were in remission following cyclophosphamide-based induction.[12] These observations may not hold true in the era of rituximab-based treatment. However, in those studies investigating rituximab as a maintenance therapy, most patients continued to receive GC—albeit at a low dose—and their contributing effects cannot be excluded. The Assessment of Prednisolone in Remission study is ongoing and will prospectively evaluate GC withdrawal in patients with granulomatosis with polyangiitis (www.clinicaltrials.gov/ NCT01933724 and NCT01940094).

Looking to the future

Studies to date consistently show that reduced-dose GC regimens are as effective for early disease control as standard (i.e., historic) practice, but benefit from fewer adverse events, particularly infection. Encouragingly, these data have already informed recent consensus guidelines for AAV treatment from both the American College of Rheumatology[13] and Kidney Disease: Improving Global Outcomes (KDIGO).[14] However, although these studies have helped define the "upper limit" of GC dose needed to control disease in most patients, the minimum required dose (especially when combined with modern immunosuppressive treatment) remains unclear. This should be the focus of future studies in this space. Indeed, complete GC avoidance may be possible,[15] although at present may risk inadequate disease control (and the accrual of organ damage related to this and future treatment escalation), an increased risk of future relapse, and the potential for unchecked smouldering, subclinical inflammation to increase the longer-term risks of cardiovascular and thrombotic complications.

These considerations highlight the need for more sensitive and specific biomarkers of disease activity and flare, and for more accurate means to quantify disease-related damage and treatment toxicities. The GC Toxicity Index was recently developed to enable evaluation of GC-related adverse effects over time. Of note, cumulative GC Toxicity Index was lower after 6 months in patients treated with avacopan compared with GC in the ADVOCATE study. Unfortunately, many GC-related adverse events occur after many years of follow-up, and capturing these will be a challenge for future clinical trials in this field. The identification of biomarkers that predict cardiovascular, endocrine, and other GC toxicities, perhaps incorporating pharmacogenomic or metabolomic approaches, offers a potential way forward.

The development of more targeted drug therapies, particularly those directed against components of the innate immune system, may make complete GC avoidance a reality. Several inhibitors of the complement system are in clinical development, including an anti-C5a monoclonal antibody under investigation in AAV (www.clinicaltrials.gov/ NCT03895801 and NCT03712345). Therapeutic inhibition of MPO and of neutrophil extracellular trap formation shows promise in experimental studies, and both are desirable approaches given their broad beneficial effects on vascular inflammation. In parallel, the use of adjunctive treatments, such as endothelin antagonists and sodium-glucose cotransporter 2 inhibitors, that address the longer-term cardiovascular morbidity of AAV, which is increased further by GC use, should be investigated in this patient group.

For now, we are assured that high-dose i.v. GC, particularly methylprednisolone, can be avoided in most patients with AAV, and that "reduced" dose oral GC regimens should become standard care. With careful and expert monitoring, more radical GC minimization (or avoidance) may be attempted in many. More important, GC treatment should be tailored to an individual's disease phenotype and risk of adverse events. For example, indolent presentations, in the absence of rapidly evolving organ damage or significant systemic upset, are unlikely to require high-dose GC treatment. Similarly, preexisting comorbidities (e.g., diabetes and mental health disorders) may also favor GC minimization. Finally, elderly patients, who are particularly vulnerable to GC-related adverse events, potentially more so than to the toxicities of cytotoxic or biologic immunosuppression, would likely benefit from more radical GC avoidance, especially given the competing longer-term risks of disease relapse and impaired kidney function may be less important.

DISCLOSURE

ND has consulted for Travere Therapeutics; and SPM has consulted for GSK and Vifor Pharmaceuticals and received honoraria from Celltrion and Vifor Pharmaceuticals.

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