of the inflammatory cellular infiltration in the kidney or in the lungs, but the adjunction of an immunosuppressive drug such as cyclophosphamide – intravenous or oral – is mandatory to control the necrotizing vasculitis and allow tapering of steroids. Although rituximab is probably as effective as cyclophosphamide for induction of remission in MPA or GPA, the recently published studies [12] had excluded patients with severe kidney failure (serum creatinine > 4 mg/dl) or DAH requiring mechanical ventilation. Until future studies demonstrate that the use of rituximab can also be beneficial in this group of patients, cyclophosphamide must remain the immunosuppressive drug of choice for life-threatening AAV.

The use of plasma exchange has also been proposed, in addition to the immunosuppressive medication, in AAV patients with acute renal failure or severe DAH. The possible direct pathogenic role of ANCA supports the hypothesis that early removal of preformed circulating auto-antibodies can contribute to the control of the AAV, during the first days of immunosuppressive therapy. The MEPEX study has shown that addition of seven plasma exchanges within the two first weeks of treatment increases the rate of renal recovery, without affecting the short-term mortality [13]. Furthermore, although no controlled trial has been performed, some series suggest that plasma exchange may improve pulmonary outcome in severe DAH [14].

Conclusion

Severe and rapidly progressive, single or multi-organ failure can reveal or complicate AAV. Early detection of vasculitis during an acute kidney, lung, heart or gut dysfunction is not always easy, especially in critically ill patients entering the intensive care unit and requiring supportive mechanical ventilation, hemodialysis or treatment of congestive heart failure. Presence of general signs preceding the admission of the patient or identification of a pulmonary-renal syndrome, which remains the most frequent clinical presentation of fulminant vasculitis, must lead to detection of ANCA and urgent initiation of specific AAV treatment, with corticosteroids, cyclophosphamide and sometimes plasmapheresis.

Disclosure of interest: the authors have not supplied their declaration of conflict of interest.

References


L41. Perspectives on the treatment of giant cell arteritis

Giant cell arteritis (GCA) is a vasculitic disease that predominantly affects the large – to medium-sized arteries. It occurs in people over the age of 50 and is the most common primary systemic vasculitis that affects humans. Since the 1950s,
Glucocorticoids have been known to provide benefit in the treatment of GCA. Many excellent articles and chapters have been written that review the efficacy and safety data of glucocorticoids and the trials that have explored therapeutic alternatives [1]. Rather than duplicate these thorough publications, this perspective will seek to examine some of the challenges that currently face physicians and investigators in the treatment of GCA in looking towards the future.

**Goals of treatment**

For the past 60 years, GCA has been a disease for which effective treatment exists in the form of glucocorticoids [2]. For every disease, however, the decision to use a specific intervention is based upon how that approach addresses therapeutic goals. In the case of GCA, these goals include:

- prevent disease-related morbidity and mortality;
- reduce disease-related symptoms that affect quality of life;
- stop disease relapse;
- avoid treatment-induced morbidity and mortality.

Glucocorticoids have been the standard of care because of their ability to reduce disease-related morbidity, mortality, and symptoms that negatively impact quality of life but they are not curative, they do not prevent relapse, and they are associated with significant toxicity. For this reason, there remains a great need to identify better treatment options in GCA. While the evaluation of novel therapies will appropriately be based on their ability to achieve specific outcome measures, their utility will be ultimately gauged by how they meet these goals in relationship to glucocorticoids.

**Impact of disease phenotype on treatment**

GCA is most readily associated with cranial disease manifestations related to vasculitis involving the carotid and vertebral arteries. However, GCA is now well recognized to possess a diverse range of phenotypes that include not only cranial arteritis but also polymyalgia rheumatica (PMR), systemic inflammatory disease, and large vessel vasculitis (LVV) [3–6]. These phenotypes can occur in isolation, in combination, or sequentially. In considering treatment, it is important to recognize that the published therapeutic data is almost exclusively based on cranial arteritis or isolated PMR. Although the initial treatment of LVV typically consists of prednisone 40 to 60 mg daily, similar to what is used in cranial arteritis, the optimal glucocorticoid dose for LVV has not been established. It is also unclear whether the use of other immunosuppressive agents may have a differing degree of effectiveness in LVV than has been observed with cranial disease. In Takayasu arteritis, a systemic vasculitis involving the aorta, its major branches and the pulmonary arteries, methotrexate and tumor necrosis factor inhibitory agents have been used in combination with glucocorticoids based on promising data from open-label studies. An intriguing question raised by a number of authors is whether GCA and TAK represent differing phenotypes along the LVV continuum [7,8]. As we gain a greater understanding of GCA, phenotypic disease expression and the pathophysiologic underpinnings of that expression, may play a significant role in therapeutic management.

**Assessing disease activity**

Accurate assessment of disease activity represents one of the most significant challenges faced both in the clinical management of patients with GCA and in clinical trials. To date, there remains no biomarker that can conclusively determine disease remission and relapse. The current assessment of disease activity is based upon patient symptoms, physical examination, laboratories, and imaging, each of which has individual limitations. Determining whether a symptom/sign is due to active disease, disease or treatment-related damage, acute treatment-related toxicity, or glucocorticoid withdrawal can be difficult. Acute phase reactants such as erythrocyte sedimentation rate and C reactive protein are commonly used in disease activity assessment but they can be elevated for other causes and can also be normal in the setting of active disease. Imaging plays an important role in LVV. While new lesions in new vascular territories are considered to be indicative of active disease, worsening of previous lesions can occur as a result of scarring. Ultrasound and arteriography via computed tomography (CTA) or magnetic resonance (MRA) provide information not only on luminal dimensions but also on the vessel wall. To date, however, vessel thickness and signal intensity have not been found to correlate well with disease activity. Identification of an effective laboratory – or imaging-based biomarker would represent a major advancement in GCA that would benefit both clinical patient care and trial endpoint assessment.

**Reducing disease-related morbidity**

Disease-related morbidity in GCA largely results from cranial ischemic complications (CIC) or LVV. Visual loss due to ischemic optic neuropathy occurs in about 14 to 20% of patients with GCA. While no treatment to date has been found to completely reverse blindness once it has occurred, there is strong data to support that once glucocorticoids have been started the risk of visual loss is low [9]. It is for this reason that glucocorticoids should be started in patients suspected to have GCA while the diagnostic evaluation is in progress. Retrospective studies have also found that patients who are on aspirin have a lower risk of CIC [10,11]. A challenge in further reducing visual loss beyond these measures, however, has been that the majority of CIC occur at the time of diagnosis prior to the opportunity to initiate interventions. In several series, patients who had a strong inflammatory response were found to have a lower rate of CIC [12–15]. While it is possible that a stronger inflammatory response leads to diagnosis, initiation of glucocorticoids, and the prevention of ischemic events, this may also suggest that certain patients could be predisposed to CIC. Other risk factors for CIC include transient ischemic events, in particular amaurosis.
fugax, as well as a prior CIC [12–14]. These associations emphasize the importance of seeking evidence of transient or permanent CIC as this may identify patients at greater risk of further disease-related morbidity and the need for more aggressive treatment. It is unclear whether intravenous methylprednisolone 1000 mg daily for 3 days provides additional benefit beyond prednisone 1 mg/kg/day, although this is often used in patients with an acute fixed or transient CIC with the goal of preventing additional CIC [16]. LVV also represents an important cause of disease-related morbidity and potentially mortality. Large artery stenosis occurs in 13% and commonly involves the subclavian/axillary/brachial arteries with resultant upper extremity claudication [3]. Patients with GCA are 17.3 times more likely to develop thoracic aortic aneurysms, which occur in 1 out of every five patients [3,4]. While having a diagnosis of GCA is not associated with increased mortality, survival is decreased in patients with an aortic aneurysm or dissection compared to the general population [5]. As thoracic aortic aneurysms can be a late-onset manifestation in patients who have previously had cranial arteritis or PMR, an important question is how to best monitor for aneurysm development in asymptomatic patients with no findings of LVV on physical examination. The safety, effectiveness, and cost-utility of different imaging techniques and risk stratification algorithms to detect thoracic aortic aneurysms remain under active investigation.

Reducing treatment-related morbidity

While glucocorticoids have made GCA a treatable disease, they possess significant toxicities which are particularly problematic for the older patient population who develops GCA. Up to 86% of patients with GCA experience one or more side effects of glucocorticoids [17]. Infection remains the most significant concern with glucocorticoids and includes bacterial pneumonia, urinary tract infections, herpes zoster, and opportunistic infections. Fractures also represent a significant risk due to increased bone loss and an increased risk of falls from steroid myopathy and cataract formation. Glucocorticoids also negatively impact quality of life with weight gain, changes in appearance, and mood changes. While the toxicity of glucocorticoids begins with the high doses used for initial treatment, relapses occur in 70 to 90% of patients, which often result in glucocorticoid treatment for 2 years or longer. It is because of the cumulative glucocorticoid exposure and risk of toxicity that efforts have been made to identify therapeutic adjuncts or alternatives to glucocorticoids in GCA. To date, important randomized trials have been conducted in GCA to examine methotrexate, azathioprine, and initial use of intravenous pulse methylprednisolone [18–22]. While controversies have existed regarding whether these therapies provide benefit, none of these approaches has been found to reduce glucocorticoids toxicity. This leaves open the necessity to identify a therapeutic agent that reduces the risk of relapse and that has the ability to replace glucocorticoids.

Future directions

Despite great efforts made by dedicated investigators and the many important insights that have been gained, how we treat GCA has changed very little over the past 60 years. The fact that glucocorticoids and aspirin remain the foundation of treatment for GCA in 2013 reflects both the efficacy of this regimen and the complexity of the disease itself. Taking the next step beyond glucocorticoids will undoubtedly come from a partnered investigation of the mechanisms involved in disease pathogenesis with the continued exploration of agents that these advancements suggest. As exemplified by the pathophysiologic rationale behind the investigation of infliximab in GCA and PMR, this is by no means a new concept [21]. Two randomized trials in GCA are currently ongoing that are based upon this principal. Abatacept (CTLA4-Ig) is being investigated in GCA based upon the rationale of modulating the costimulation signal required for antigen-specific T cell activation. Case reports and small series have provided encouraging results with the interleukin 6 receptor antagonist tocilizumab prompting the conduct of a comparative trial to determine efficacy [23,24]. As this perspective has hoped to highlight, advances in the treatment of GCA will come not only from clinical trials of new therapeutic agents, but also in understanding more about the nature of the disease itself, how phenotype influences treatment, how to identify those at risk of early and late disease-related morbidities, and recognition of improved laboratory or imaging biomarkers. This is exciting time in GCA in which novel discoveries in GCA are being made on many different fronts [25]. With the research advancements that are occurring in GCA, these challenges and the next wave of questions to follow will ultimately be answered.

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References


L42. Morbidity in patients with ANCA-associated vasculitis

Over the last 30 years, treatment has improved the outcome for patients with ANCA-associated vasculitis (AAV). Patient survival is reported as 45–91% at 5 years and 75–88% at 10 years compared with 80% mortality at 2 years if left untreated [1]. Despite advances in therapy, patients with AAV continue to have a substantially higher mortality than a matched background population [2] with advanced renal failure and increasing age identified as poor prognostic markers in many studies [2-4]. Infection accounts for the majority of deaths in the first year. Malignancy and cardiovascular disease are more common causes of death beyond 1 year but infection remains an important cause of death at this time [2].

Morbidity due to disease

Despite the improved survival, morbidity remains common and may result from damage due to disease or the adverse effects of immunosuppressive treatment. Chronic kidney disease resulting from renal vasculitis is common and occurs in up to 90% of patients with microscopic polyangiitis and 80% with granulomatosis with polyangiitis (GPA). Proteinuria often rises during the recovery phase of renal vasculitis reflecting glomerular damage, especially in those with complement deposition [5]. Patients with reduced renal function are at high risk of end-stage kidney disease (ESKD) if they have a relapse of their glomerulonephritis.

End-stage kidney disease (ESKD) is not uncommon in patients with AAV; approximately 20% of those who have evidence of renal involvement will develop ESKD by 5 years [6,7]. Renal survival is best predicted by presenting serum creatinine and