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Vasculitis (C Pagnoux and M Walsh, Section Editors)

Therapeutic Management of Pediatric Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

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Opinion statement

Purpose of the Review To provide an overview of recent advances in the treatment of pediatric antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).
Recent Findings With advances in research, use of standardized clinical assessment tools, advent of biologic therapies, and use of patient registries, concepts relating to the optimal management of pediatric patients with chronic primary systemic vasculitis have evolved and newer treatments strategies and treatment guidelines continue to emerge.
Conclusion Although most of what we have learned about pediatric AAV has come from adult data, the quality and breadth of pediatric data is accumulating because of multicenter, international collaborations. These efforts are critical given that optimal treatment strategies likely differ in the context of a developing immune system, and in a physically and emotionally developing child. Pragmatic clinical trials linked with international patient registries could help close the pediatric AAV evidence gap.

Introduction

The primary systemic vasculitides (PSV) are a group of disorders characterized by the presence of inflammation in the blood vessel wall. The vasculitic syndromes are variably classified according to their clinical manifestations, the size and type of the involved blood vessels, and the pathologic changes found within the involved vessels. The two most common pediatric vasculitic syndromes, Kawasaki disease and immunoglobulin A (IgA) vasculitis (previously Henoch-Schonlein purpura), are acute and generally self-limited albeit damaging in some cases. Although rare in children, chronic PSV are potentially organ or life-threatening; hence, early diagnosis and treatment are critical in order to minimize morbidity and improve outcomes. Disease rarity has limited pediatric-specific data, and therefore, evidence-based guidelines for management of chronic childhood PSV have been largely adapted from adult literature. Because children are still developing physically and psychologically, and also have less mature immune systems, the effects of disease and treatment likely differ. The known long-term risks for any of the therapies (malignancy, osteoporosis, infertility, and cardiovascular risk) should be weighed differently to adults who usually develop disease in their 50s; the short-term pediatric-specific considerations include effects on growth, puberty, and educational attainment. Thus, it is important that children with AAV are managed at specialized pediatric centers, usually by a team of clinicians (e.g., pediatric rheumatologists, nephrologists, and other specialists) with expertise in the management of these rare diseases. Fortunately, through increased international collaboration, registry development, and multicentered research initiatives, the quality and extent of pediatric-specific data continues to increase.

The purpose of this review is to provide an overview of recent advances in the treatment of pediatric antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) which encompasses granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), and renal limited pauci-immune glomerulonephritis.

Treatment

General principles

The treatment of AAV depends upon the nature and severity of the disorder. Defining how active the disease is, which organs are involved, and how severe the disease is are key considerations in determining optimal treatment. Treatment risk must always be balanced against the consequences of ongoing inflammation. Similar to other primary systemic vasculitides, the treatment strategy is to use the model of remission induction followed by remission maintenance. Glucocorticoids remain the cornerstone of therapy for remission induction in children with AAV. However, given the chronic and relapsing nature of AAV, steroid-sparing immunesuppressing or immune-modulating agents are generally required in addition to glucocorticoids to improve chance of sustained remission and to reduce the toxic burden of long-term glucocorticoid use. Traditional treatments like cyclophosphamide and glucocorticoids have predominated as mainstay therapy for severe life- or organ-threatening disease; however, newer treatment strategies have focused on minimizing treatment when possible or utilizing less aggressive treatment regimens for less severe or less extensive disease. In addition, evidence supporting the effectiveness of newer treatments such as rituximab and other biologic agents is increasing.

Defining disease activity

Determining whether a patient's disease is active or inactive is critical for deciding what type of treatment, if necessary, is appropriate. The disease is active when there are objective signs of an ongoing inflammatory process that are distinguished from other processes such as concurrent infection, medication effects, or sequelae from previous inflammation. Ascertaining whether the disease is active often requires assessment of a number of different clinical parameters—symptoms, signs, trends in laboratory tests such as urinalyses or inflammatory markers like C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), and results of other investigations like imaging studies or biopsies. When there are no signs of ongoing inflammation, the disease is considered inactive. When there is persisting inactivity, then the disease is considered to be in *remission*. Remission can be further qualified according to the duration of inactive disease, and whether the patient is on or off immunosuppressive medications.

In adult AAV, the Birmingham Vasculitis Activity Score (BVAS) is a validated and widely accepted tool for monitoring disease activity and response to treatment [1]. A pediatric tool, the Pediatric Vasculitis Activity Score (PVAS), was developed based on modifications to the BVAS and was preliminarily validated in 2013 [2•]. The utility of PVAS in assessing and monitoring disease activity in pediatric AAV will be determined over time; however, it is being increasingly used in pediatric studies [3••, 4•, 5].

Balancing the risks and benefits of treatment

Decisions about optimal treatment for a patient with AAV require balancing the risks of treatments against the risks of damage from ongoing untreated active inflammation. There are risks to under-treating aggressive disease and risks to over-treating milder disease. In an effort to standardize treatment that employs these principles, criteria have been developed in adult vasculitis for classifying or "staging" patients by disease severity according to two main systems: The Wegener's Granulomatosis Etanercept Trial (WGET) group's system which classifies patients into "limited" or "severe" [6], and the European Vasculitis (EUVAS) group's system which classifies patients as "localized," "early systemic," "generalized," "severe," and "refractory" [7]. Although both tools may be applicable to childhood vasculitis [8], neither has been formally validated and their relevance to pediatric patients (versus adults) is relatively limited in that a large majority of patients have more generalized and more severe disease [9•].

Remission induction

Treatment of pediatric AAV should be based on a *remission induction* followed by *remission maintenance* model (Table 1).

Severe disease

Severe disease should be considered that which has life or major organ-threatening manifestations, for example, severe and progressive kidney involvement, massive alveolar hemorrhage, severe gastrointestinal, cardiac, central nervous system, and/or eye involvement. A combination of high-dose

Table 1. Treatment of pediatric AAV adapted from EULAR [10••] and EULAR/ERA-EDTA [11••] recommendations

Induction: severe disease	Induction: non-severe disease	Refractory or relapsing disease	Remission maintenance
Glucocorticoids •30 mg/kg (max 1 gram) intravenous methylprednisolone 3 days •oral prednisone 1–2 mg/kg/day (max 60 mg) for 4 weeks then taper plus Cyclophosphamide intravenous pulses •15 mg/kg (max 1.2 g) every 2 weeks for 3 doses then every 3 weeks for 3–6 doses •alternative dosing 500–1000 mg/m^2 monthly or Cyclophosphamide oral •2 mg/kg/day (max 200 mg/day) plus Therapeutic plasma exchange •consider if rapidly progressive glomerulonephritis or pulmonary hemorrhage is present	Glucocorticoids •oral prednisone 1–2 mg/kg/day (max 60 mg) for 4 weeks then taper plus Methotrexate 0.5–1 mg/kg (max 25 mg) weekly oral or subcutaneous injection or Mycophenolate mofetil 600 mg/m^2 (max 1 g) twice daily **Localized disease** *Systemic disease-modifying therapy as above may not be required* Trimethoprim-sulfamethoxazole and/or Prednisone oral	Glucocorticoids •as per severe disease induction plus Cyclophosphamide-pulsed therapy •if rituximab given at first induction or Rituximab •if cyclophosphamide given at first induction 375 mg/m^2 weekly for 4 doses or 500 mg/m^2 every 2 weeks for 2 doses (max 1 g) Consider •Adjunctive intravenous immunoglobulin 2 g/kg monthly	Glucocorticoids •oral prednisone •wean by 0.1–0.2 mg/kg/day per month to less than 0.2 mg/kg/day by month 6 *Continue maintenance disease-modifying therapy for at least 24 months* Azathioprine 2 mg/kg/day or Methotrexate 0.5–1 mg/kg (max 25 mg) weekly oral or subcutaneous injection or Mycophenolate mofetil 600 mg/m^2 (max 1 g) twice daily or Leflunomide 10–20 mg daily (if intolerant to above options) consider Rituximab (see text)

glucocorticoids and cyclophosphamide (CYC) for 3–6 months (oral or intravenous) should be used for remission induction in children with severe disease. This is consistent with published recommendations by the European League Against Rheumatism (EULAR) for the management of small and medium vessel vasculitis in adults [10••]. From adult studies, the use of intermittent pulse intravenous CYC for remission induction uses 30–50% less CYC than oral daily CYC and is not inferior at inducing remission; however, intravenous treatment is associated with a higher rate of relapse in the long term [12•] but lower rates of leukopenia and infection [13•]. Given the longer-term toxicity concerns related to cumulative CYC exposure, we prefer pulse intravenous CYC over oral CYC at our center and follow the EULAR recommendations [10••]. Children with severe disease should receive high-dose glucocorticoids concurrently with CYC.

Glucocorticoids can be administered as high-dose intravenous methylprednisolone pulses (30 mg/kg, up to a maximum of 1 g daily) for 3 days in critically ill children, followed by oral prednisone 1–2 mg/kg/day (maximum 60 mg daily) for a minimum of 4 weeks before tapering [10••].

For select patients with rapidly progressive glomerulonephritis or severe pulmonary hemorrhage, plasma exchange may be considered. In adult studies, plasma exchange may reduce dialysis dependence and end-stage renal disease, but has not been shown to improve survival [14, 15]. Studies are ongoing to clarify the role of plasma exchange in AAV [16].

As an alternative to CYC, there is now strong evidence for the use of rituximab (RTX) in the treatment of AAV. Two randomized trials in adult patients have demonstrated that RTX is non-inferior to CYC for remission induction [17•, 18•] and may be more effective for relapsing disease [18•, 19•]. In 2016, EULAR updated their recommendations for the management of AAV (EULAR/European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) Recommendations) and the current recommendations state that CYC or RTX can be used for remission induction of new-onset organ-threatening or life-threatening AAV [11••]. There is accumulating information in both children and adults about the risks for prolonged immunodeficiency following use of RTX [20–22]. Lifetime risks for RTX (and other therapies) should be weighed differently in a child compared to the usual adult patient aged over 50. Given the limited pediatric-specific data related to RTX use in AAV or other diseases, RTX is currently only recommended for consideration in the treatment of children who fail to respond to conventional induction therapy with glucocorticoids and CYC or for patients with relapsing disease where there is particular concern regarding cumulative glucocorticoid and/or CYC toxicity [23•].

Non-life-threatening or non-organ-threatening disease

There is strong evidence for the use of combination glucocorticoids and methotrexate (MTX) for remission induction in patients with less severe AAV [24–26]. Patients with renal disease should not be treated with MTX for induction as the trials using MTX excluded patients with renal involvement. Mycophenolate mofetil (MMF) is now included in the EULAR/ERA-EDTA recommendations as an alternative to MTX for remission induction in non-organ-threatening disease [11••] as it has been shown in two randomized controlled trials to be an

effective remission induction agent [27, 28]. The MMF trials included patients with renal disease so it may be considered in patients with non-life-threatening disease but who have renal involvement. In the absence of pediatric-specific recommendations, we use MTX preferentially over MMF for remission induction in non-life- or non-organ-threatening disease; however, MMF is a consideration in cases where mild renal disease is present and more aggressive options such as CYC or RTX may not be warranted.

Localized disease

For patients with localized disease, such as GPA patients with isolated nasal disease or isolated subglottic stenosis, systemic immunosuppression may not always be warranted or may not be effective. Trimethoprim-sulfamethoxazole (TMP-SMX) alone or in combination with glucocorticoids may be considered for remission induction for select cases of localized GPA, especially when limited to the upper respiratory tract [29–32]. In addition, when added to standard treatment, TMP-SMX may have a role in limiting rates of relapse and reducing rates of respiratory infections [33, 34].

The apparent increased frequency of subglottic stenosis in children versus adults (respectively 48 versus 12% in one study from 1992) [35] has led to its inclusion as one of the six pediatric classification criteria for GPA [36]. Although its frequency at diagnosis among pediatric patients from a more recent larger cohort is less than 15% [9•], subglottic stenosis (or tracheal stenosis) may be difficult to treat and can develop or persist in the presence of optimal systemic immunosuppression. Pediatric-specific data about the optimal management approach is lacking. Limited response of laryngotracheobronchial GPA to CYC has been demonstrated in small retrospective studies, and RTX may be promising although prospective data is required [37–39]. Intralesional glucocorticoid injections, tracheostomy, stent placement, and endoscopic dilatation [37, 38, 40] can be used as adjunctive treatments and likely require the expertise of a highly specialized center [41••].

Remission maintenance

Relapse rates following remission induction are high; therefore, treatment should be maintained for at least 24 months following induction of sustained remission [11••]. Azathioprine (AZA) following remission induction was shown to be not inferior to CYC for remission maintenance in a large randomized trial [42] and is the most common treatment choice for maintenance in pediatric AAV with renal disease [3••]. MTX may be considered as an alternative to AZA in patients without significant renal impairment [9•, 43]. MMF appears to be less effective than AZA for remission maintenance in adults [44], but is an alternative if there is intolerance to AZA or MTX. There is increasing evidence for the use of RTX for remission maintenance. When RTX was compared to AZA as maintenance therapy in the adult MAINRITSAN trial, relapse rates at 28 months were 29% in the AZA group compared to 5% in the RTX group [45••]. Leflunomide is effective in remission maintenance in GPA but may be associated with more adverse effects than methotrexate [46]. Although the current consensus is to continue maintenance treatment for 24 months after remission has been achieved [11••], results from a recently published randomized controlled trial suggest that a longer duration of maintenance with conventional

agents like AZA is associated with lower relapse rates [47•]. The study compared 24 months of AZA versus 48 months of AZA following remission after induction with CYC and glucocorticoids and found that 63% of patients in the 24-month group compared to 22% in the 48-month group relapsed during the 48-month follow-up period [47•]. A majority of pediatric rheumatologists continue a disease-modifying agent for at least 24 months [48•]. In the absence of pediatric studies, we have followed the adult recommendation to continue maintenance treatment with a disease-modifying agent for at least 24 months following remission off prednisone.

During remission maintenance, tapering of prednisone should continue. The EULAR/ERA-EDTA guidelines consider 7.5–10 mg of prednisone to be an appropriate target after 3 months; however, a review of tapering practices suggested that these doses are often not reached for at least 5 months [11••]. A large majority of pediatric practitioners aim to discontinue prednisone within 12 months [48•], and in the absence of specific pediatric recommendations, a reasonable approach is to reduce the prednisone dose by 0.1–0.2 mg/kg/day monthly aiming for a dose of less than 0.2 mg/kg after 6 to 12 months of treatment.

Refractory disease

A recent pragmatic definition of refractory disease is that which is unchanged or worsened despite 6 weeks of appropriate remission induction therapy, or the presence of persistent disease activity after 3 months of appropriate remission induction therapy [41••]. Strategies for management of refractory disease provided by EULAR/ERA-EDTA suggest to first reevaluate as follows: consider an alternative diagnosis, investigate for a complication or comorbidity (e.g., infection or malignancy), ensure disease activity is distinguished from disease damage, and ensure that doses and administration of standard therapy are optimized [11••]. After these considerations, recommendations are to retreat as per induction with the alternative agent; RTX if CYC was used initially and vice versa [23•]. If RTX is unavailable, oral CYC may be helpful in patients who received pulsed therapy initially [49]. Adult data suggest that the addition of intravenous immunoglobulin may be of benefit in patients with persistent low-grade disease or in the case of refractory disease when other immunosuppressive medications are contraindicated [50, 51]. The use of IVIG as an adjunctive medication in pediatric AAV has not been reported. Anti-TNF therapies have been trialed in refractory disease; however, etanercept should specifically be avoided due to a known increase in the incidence of solid tumors [52]. Other therapies that have been used include antithymocyte globulin [53], alemtuzumab [54], stem cell transplant [55], or deoxyspergualine [56]. In general, patients with refractory disease should be managed by subspecialists who work regularly in close collaboration with a referral center for vasculitis.

Relapsing disease

For relapse (worsening of disease activity or new-onset disease features), an approach as described above for treating refractory disease is appropriate [11••]. RTX, if not already used for primary remission induction, is recommended for children to prevent cumulative CYC toxicity [23•]. For non-life-threatening relapses, MMF has recently been shown to be a viable alternative to

CYC [57]. Additionally, there may be a need to escalate prednisone therapy while compliance is being ensured.

General management considerations

Patients with a diagnosis of AAV should be managed in a center of expertise, or in settings where collaboration with an expert center is possible [11••]; for pediatric AAV, this should be a pediatric center [58]. Antibiotic prophylaxis for *Pneumocystis jiroveci pneumonia* (PJP) with TMP-SMX, or aerosolized pentamidine where contraindications exist, is recommended particularly in the induction phase of treatment [59]. Children with PSV are at risk of low bone mineral density; hence, routine screening for bone health, and ensuring adequate intake of vitamin D and calcium should be standard of care [60]. Linear growth should be monitored as it may be compromised in both pre- and peri-pubertal children from factors including elevated pro-inflammatory cytokines and significant glucocorticoid exposure [61, 62]. Vaccinations should be completed according to the local policy; however, live vaccinations should be avoided where possible [63]. Patients should be counseled about the potential risk of reduced fertility after CYC; this risk is influenced by the patients' age, stage of sexual maturation, and cumulative CYC dose [64]. The estimated risk of 0–11% for patients less than 25 years is low compared to older patients [65, 66]. Children with PSV will require ongoing medical care in adulthood, and transition to adult services should occur as a planned, coordinated process, at a time of developmental readiness [67, 68].

Emerging therapies

Given the success of B cell-directed therapies in AAV, BLyS (B lymphocyte stimulator) and BAFF (B cell-activating factor)—both of which have been shown to be elevated in GPA [69, 70]—have become potential therapeutic targets. Belimumab, a humanized monoclonal antibody directed at soluble BAFF, approved for use in systemic lupus erythematosus [71], may have a role in reducing relapse frequency as part of remission maintenance therapy for AAV [72]. The BREVAS phase III trial which included adult patients with GPA and MPA comparing AZA maintenance monotherapy with the addition of belimumab for relapse prevention was completed in February 2017 and results are awaited (NCT01663623).

Complement has an increasingly recognized role in the pathogenesis of AAV, and particularly C5a, a chemoattractant and neutrophil activator, is being evaluated as another potential therapeutic target [73]. CCX168 (avacopan), a C5a receptor inhibitor, in an exploratory trial with small numbers of adult patients only with follow-up limited to 12 weeks, was shown to have a possible role in replacing high-dose glucocorticoids [74]. The ADVOCATE study, a phase III randomized controlled trial comparing AZA plus CCX168 inhibitor or prednisone for maintenance therapy following standard induction therapy with CYC or RTX, is currently recruiting (NCT02994927).

Higher levels of IL-6 are thought to be associated with more severe organ damage and higher rates of relapse in GPA and MPA [75] and this has provided a rationale for use of tocilizumab [76], but evidence for its use remains limited to case reports [77].

The pathogenic role of helper T cells type 2 in EGPA has prompted development of therapies targeting IL-5. Mepolizumab (anti-IL-5) was shown to be

safe in small open-label studies in EGPA [78], but the benefits in an initial trial showed that although patients treated with mepolizumab had more weeks in remission, allowing for reduced glucocorticoid use, only half reached remission [79].

Conclusions

Progress in the management and outcome for children with AAV in recent years is largely because of research involving adult patients. Almost all children require cytotoxic, biologic, or other immunosuppressive therapy [9•] and generally they have more severe disease presentation than adults [9•, 80]. With current therapies, children usually do not die within a year of presentation as previously, but the ongoing challenge in children and adults is to limit both disease relapses and accumulating disease and treatment damage.

CYC remains the remission induction treatment of choice for most children at presentation; however, there are other less toxic alternatives for patients with less severe or localized disease, and for long-term "maintenance" treatment. RTX has an emerging role for relapsing disease or as an induction remission alternative to CYC in selected patients; however, we should remain circumspect about the potential long-term risk of sustained immunosuppression. There are no studies in children to inform treatment choice and the effects of both the disease and its treatments probably differ as they are still developing physically, educationally, emotionally, and in their immune system. Weighing the risks of potential lifetime damage of treatments or disease is different in children compared to adults. There remains a need to study children separately and determine optimal type and duration of therapy.

Even though there are an increasing number of pediatric-specific clinical assessment tools for classifying and assessing pediatric patients, and emerging guidelines for treatment, uptake and implementation by rheumatologists and other physicians is limited [48•]. Pragmatic clinical trials linked with international patient registries could help close the pediatric evidence gap but will require strategies to improve uptake.

Compliance with Ethical Standards

Conflict of Interest

KM, GT, and DC declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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