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Vasculitis (C Pagnoux and M Walsh, Section Editors)

IgA Vasculitis in Adults

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Abstract

Purpose of review Immunoglobulin A vasculitis (IgAV) is a small vessel vasculitis with skin, joint, gastrointestinal and renal manifestations. Our understanding of the natural history of this disease is limited due to the overall low incidence of IgAV in adults and a lack of consensus regarding diagnostic criteria. In this review, we describe IgAV in the adult population, focusing on diagnostic and classification systems, and treatments strategies.
Recent findings Recent data from larger longitudinal adult cohorts demonstrate that IgAV is associated with significant morbidity and mortality. Treatment regimen remains controversial but emerging retrospective observational data support potential benefit of immunosuppression. As illustrated in trials of IgA nephropathy, immunosuppression carries significant risks of toxicity.
Summary Treatment regimen and selection of patients who will benefit from treatment remains challenging. Prospective treatment trials are needed to elucidate both the patient populations that will derive benefit and what treatment is most efficacious.

Introduction

The small vessel vasculitides affect capillaries, venules or arterioles with particular predilection for certain organs; IgAV (IgA vasculitis), is an immune complex small vessel vasculitis characterized by skin, joint, gastrointestinal and renal manifestations [1]. The initial clinical description was made by Heberden in 1806, with Sch nlein first describing the association between arthralgia and purpura in 1837 and Henoch describing the gastrointestinal and renal manifestations in 1897 and 1899, respectively [2]. Thus, IgAV was previously known by the eponym *Henoch-Sch nlein purpura.* The term "IgA vasculitis" is now used to describe this clinical syndrome, to better reflect the immunopathogenesis of this disease.

Heterogeneity in diagnostic criteria across studies of IgAV poses challenges when identifying classical clinical and pathologic presentations of this disease and outcomes. This is particularly relevant in the adult population where the incidence of IgAV is low, and renal outcomes in patients with IgAV and rapidly progressive

renal failure are relatively poor compared to pediatric patients where the disease has been most intensely studied. While our review is focused on treatment strategies, we also discuss the limits of our knowledge regarding the diagnosis and natural history of IgAV as this is essential to balance the risks and benefits of treatment in this disease, and to interpret the available literature describing treatment outcomes.

Epidemiology

Understanding the frequency IgAV is challenging due to the lack of clear validated diagnostic criteria and varied methods of case ascertainment (ex. discharge summary vs biopsy registry) [3]. The disease primarily affects children with an incidence of approximately 15/100,000 children per year [4]. A recent review of available literature suggests an incidence of 16–20-fold higher in children compared to adults [5].

Classification and diagnostic criteria

There are no current widely accepted clinical diagnostic criteria for adult IgAV. The main classification guidelines for IgA vasculitis are the 1990 American College of Rheumatology (ACR) criteria [6] and the European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/ Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) [7] 2010 classification criteria (Table 1). These classification systems were not designed as diagnostic criteria per se, but to guide classification of patients with these rare diseases, particularly for research purposes.

The 1990 ACR criteria were derived in a sample of 807 patients with vasculitis, of which 85 were diagnosed as having IgAV. The diagnosis of IgAV requires two of the following criteria to be present: age ≤ 20 years, palpable purpura, acute abdominal pain and biopsy showing granulocytes in the walls of the small arterioles or venules [6]. The 2010 EULAR 2010 classification criteria were derived primarily for diagnosis of pediatric IgA vasculitis. Based upon an analysis of 827 children with IgAV, these criteria require the presence of purpura

Table 1. ACR 1990 Classification Criteria

Features included in the ACR 1990 classification criteria	EULAR/PRINTO/PRES 2010 classification criteria
Two of the following: • *Age ≤ 20 years* • Palpable purpura • Acute abdominal pain • Biopsy: leucocyte in the walls of small arterioles or venules	Purpura or petechiae *(required)* with lower limb predominance, in absence of thrombocytopenia and one of the following: • New abdominal pain • Arthritis/arthralgia • Renal: proteinuria, and/or hematuria • Leucocytoclastic vasculitis with dominant IgA immune deposits OR kidney biopsy with proliferative glomerulonephritis with dominant IgA immune deposits

ACR American College of Rheumatology, *EULAR/PRINTO/PRES* European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society. Differences are indicated with italics

or petechiae in addition to one of the following: abdominal pain, arthritis or arthralgia, renal involvement, leucocytoclastic vasculitis with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits. These criteria had a higher diagnostic sensitivity in pediatric IgAV, without loss of diagnostic specificity [7].

The performance of the EULAR and ACR classification systems were compared in the adult population in a review of 350 adults with vasculitis including 129 with IgAV. The diagnostic sensitivity and specificity of the EULAR/PRINTO/PRES vs the ACR IgAV criteria were 99.2% (95% CI 95.4–99.9%) vs 86.8% (95% CI 79.7–92.1%) ($p = 0.02$) and 86.0% (95% CI 80.7–90.3%) vs 81.0% (95% CI 75.2–85.9%) ($p < 0.01$), respectively [8••].

The Chapel Hill vasculitis classification scheme is a nomenclature system (nosology), and is not used for diagnostic purposes [1]. It is a classification scheme focusing on immuno-pathologic findings without requisite clinical organ-specific criteria for diagnosis. The scheme describes IgAV as a "vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur".

A validated, clinically relevant diagnostic and prognostic scheme is needed for adult IgAV in order to identify patients most likely to benefit from early immunotherapy. The ongoing Diagnostic and Classification of Vasculitis (DCVAS) study aims to develop validated diagnostic criteria [9]. As of March 2016 978 adults with IgAV have been recruited. Description and longitudinal follow-up of this cohort will likely inform future diagnostic and classification schema. The CureGN cohort includes both children and adults with IgAV, and will provide guidance regarding the natural history and prognosis of patients with IgAV with biopsy-proven renal involvement (www.curegn.org).

Clinical presentation

The largest cohort of adult patients with biopsy-confirmed IgAV includes 260 patients with long-term follow-up (median 14.8 years) [10••]. The median age at disease onset is 50 years (± 18 years) with a male: female ratio of 1:7. The commonest clinical manifestation is purpura (96–100%) primarily of the lower limbs but rarely the facial/mucosal surfaces (3%). Symmetrical arthralgias usually of the knees or ankles are observed in nearly all patients, with frank arthritis in 16%. Renal involvement is present in 70% with leg edema in 27%, macroscopic hematuria in 10% and hypertension in 22%. Renal function is often preserved with median creatinine of 77 μmol/l (IQR 65–99) but 30% have a GFR of < 60 ml/min/1.73m^2. Median proteinuria at presentation is 1.5 g/day (IQR 0.6–3), with microscopic hematuria observed in 88%. Gastrointestinal tract (GI) involvement is present in half and is classically characterized by colicky abdominal pain, with GI bleeding in 31%. Constitutional symptoms are present in one third of patients. Other laboratory tests anomalies include elevated inflammatory markers (median C-reactive protein of 27 mg/l) and elevated serum IgA levels in half of subjects. Occasional ANCA positivity is observed (4% of those tested).

The overall incidence of renal involvement in adults varies from 45 to 85% depending upon the method and circumstances of case ascertainment (ex. dermatology vs nephrology cohort). A cohort of 57 adults presenting with purpuric skin manifestations proven by biopsy to be IgA positive leukocytoclastic vasculitis were evaluated for renal involvement [11]. One quarter had biopsy-proven glomerulonephritis, and another quarter had abnormal urinary sediment. Renal function is often normal (67.6%) at time of renal biopsy despite active glomerulonephritis [5] though 14% have a creatinine clearance of less than 30 ml/min.

Age affects the clinical presentation with those under 30 years more commonly presenting with recent infection (54.7% compared to 23.5% of over 60 year olds) and arthritis (71.7% compared to 48.2% over 60 year olds). In contrast, in those aged greater than 60 years purpura was more frequently necrotic (44.7 vs 16.7%), and initial creatinine clearance is lower (99 vs 46 ml/min).

Pulmonary involvement is rarely observed in patients with IgAV. Age appears to be associated with the risk of pulmonary involvement, which can include alveolar hemorrhage and interstitial pneumonia [12]. A literature review suggests that over half of reported cases of pulmonary hemorrhage occured in patients over 20 years old, typically in the setting of multi-organ involvement [13].

Systemic illnesses and malignancy associations

IgAV can be associated with and possibly caused by other diseases, such as liver disease, inflammatory bowel disease, and ankylosing spondylitis. Underlying malignancy should be considered in adult patients with IgAV. The disease has been associated with underlying cancer including hematologic malignancies and solid tumours, and the prevalence of neoplasia in adults with cutaneous or systemic vasculitis has been estimated at 2.5 to 5% [14, 15]. Malignancy has been an exclusion criterion for many IgAV studies thus potentially leading underestimate of risk [11, 16, 17]. In older adults, a causal link between the two conditions is compelling but is difficult to establish given the baseline risk of cancer in patients of similar age and overall increased risk of cancer associated with nearly all forms of vasculitis [18]. Given the elevated risk of cancer in older age groups, a timely age, risk and symptom-appropriate cancer screen is prudent particularly when contemplating immunotherapy.

Renal pathology in IgA vasculitis

Primary IgA nephropathy (IgAN) is an immune complex-mediated glomerulonephritis defined immunohistologically by the IgA-dominant or co-dominant mesangial immune deposits, accompanied by varied histopathologic lesions reflecting the clinical diversity of IgA nephropathy. Biopsy appearances may range from virtually normal histology by light microscopy to severe necrotizing, crescentic glomerulonephritis or advanced glomerulosclerosis, and tubular atrophy. The Oxford classification scheme is used to describe the histologic lesions of primary IgAN and consists of parameters that are reproducible, and correlate independently with patient outcomes [19]. The Oxford

criteria, however, have not been validated in IgAV. While it is now understood that the presence of crescents is associated with adverse prognosis in IgAN [20], the presence of crescents does not define IgAV. Indeed the kidney biopsy of patients with IgAN can be histologically identical to IgAV.

A classification scheme was proposed for IgAV biopsies in a retrospective analysis of determinants of prognosis in IgAV (Table 2) [5]. In this series, 61% were found to have proliferative endocapillary glomerulonephritis (class 3). Fibrinoid necrosis of the glomerular tuft, often associated with ANCA-type vasculitides, was present in 48% of biopsies. Inflammatory infiltrates and interstitial fibrosis were common, present in 50 and 54% of the biopsies, respectively. Some pathologic features were correlated with poor renal prognosis by multivariable analysis, including the degree of interstitial fibrosis, percentage of sclerotic glomeruli and presence of glomeruli with fibrinoid necrosis. This schema requires validation in larger population.

Disease activity and monitoring

A validated tool for monitoring disease activity in IgAV is needed to follow patient treatment response and define remission endpoints for clinical research. Differentiating active disease from chronic damage is also essential to avoid the excess use and toxicity of immunosuppressants [21]. In the absence of quantitative IgAV-specific activity measures, activity indices employed in other vasculitides, in particular ANCA-associated vasculitis (AAV), have been extrapolated to IgAV. For the assessment of disease activity, the European League Against Rheumatism (EULAR) has recommended use of the Birmingham Vasculitis Activity Score (BVAS) and the Disease Extent Index (DEI) [22].

The role of BVAS in IgAV is not well described and a minority of cases of IgAV was included in the initial 1994 criteria. The role of BVAS in pediatric IgAV was examined a retrospective review which used physician global assessment as the standard against which disease activity was measured. A moderate

Table 2. Proposed pathologic classification of IgA vasculitis [5]

Class	Description	Light microscopy findings
1	Mesangiopathic glomerulonephritis	Normal
2	Focal and segmental glomerulonephritis	Segmental endo- and extracapillary proliferation involving less than 50% of the glomeruli. The remaining involved and uninvolved glomeruli were either normal or exhibited minimal mesangial prominence.
3a	Endocapillary proliferative glomerulonephritis	Moderately pure endocapillary proliferative lesions
3b	Endocapillary proliferative glomerulonephritis	Severe endocapillary proliferation, possibly with extracapillary proliferation involving less than 50% of the glomeruli
4	Endocapillary and extracapillary glomerulonephritis	As 3b with with crescents involving more than 50% of the glomeruli
5	Fibrotic kidney	Global glomerular sclerosis involving more than 50% of glomeruli

correlation of BVAS with physician global assessment was observed, and consistent with other vasculitides, CRP and ESR correlated poorly with BVAS [23].

Pathogenesis of IgAV

Our understanding of the immunopathogenesis of IgAN has expanded substantially, and this knowledge has been extended to IgAV. Both IgAV and IgAN are immune complex-mediated diseases characterized by the presence of tissue and circulating IgA1-containing immune complexes [24–26]. The pathognomonic granular IgA-dominant deposits in the mesangium are indistinguishable from those seen in isolated primary IgAN.

Circulating and tissue immune complexes are comprised of aberrantly glycosylated IgA1 and specific IgG autoantibodies targeting the underglycosylated hinge region. Components of the complement cascade (particularly C3) are also identified within immune complexes [27]. The stimulus and primary site for production of IgA in IgAN and IgAV are unknown, but the fact that polymeric IgA1 dominates immune complexes supports mucosal origin. The presence of a high proportion of underglycosylated IgA1 is an important contributor to development of the disease, but is not sufficient on its own to cause the disease phenotype. Indeed parents of children with IgAV also have elevated levels of underglycosylated IgA1 [28].

Ultimately deposition of immune complexes in the mesangium leads to mesangial cell activation and proliferation and stimulation of a cascade of glomerular injury pathways. It remains to be determined why these immune complexes have a predilection for deposition in the mesangium and in small vessels of target affected organs. Based upon the pathobiology of the disease, potential therapeutic pathways that could be targeted include plasma cell IgA production, inflammatory mediators and the alternative pathway of complement activation.

Clinical outcomes

It is essential to understand the outcome of IgAV in order to assess risks and benefits of immunotherapy for the individual patient. Renal outcome tends to be relatively poor in adults with RPGN, and patient survival is significantly affected by this disease. In one series of 219 cases—136 adults—13% of adults reached ESRD needing dialysis (1–20 months) [14]. Ten-year renal survival was 90.2% in children and 75.8% in adults. Baseline clinical characteristics at the time of diagnosis were not predictive of renal outcome in this series; however, persistent proteinuria was closely associated with adverse kidney outcome. In the retrospective study of 250 patients over 15 years of age, 11% of patients reached ESRD, 13% had “severe” renal failure with an eGFR of < 30 ml/min/1.73 m2 and 14% had “moderate renal failure”—eGFR < 50 ml/min/1.73 m^2 [5]. In this retrospective study, multivariable analysis suggested that at the time of biopsy, creatinine > 120 μmol/l and proteinuria > 1 g/24 were independently associated with “severe” renal failure. Pathologic features of interstitial fibrosis, glomerular sclerosis and necrosis were also predictive of “severe” renal failure (discussed below).

Prediction of prognosis has been a source of intense discussion in IgAN, with the development of pathologic and clinical risk models. One such model developed in a large cohort of patients with primary IgAN was derived to estimate the "Absolute Renal Risk" score to identify patients at the time of presentation who are at risk of the primary combined endpoint of the need for dialysis with an eGFR < 15 ml/mn/1.73 m^2 S (stage 5D) or death [29]. The risk factors evaluated include hypertension, quantitative proteinuria and severe histologic lesions. These variables are assigned points, and the summative score correlates with risk of the primary renal risk outcome. This risk score was subsequently validated in a cohort of 74 adult patients with IgAV [30]. Similar to primary IgAN, IgAV recurrence post-transplantation will not typically cause graft loss, although can be observed in up to 11% at 15 years [31].

A retrospective single-centre study of 184 adults with IgAV devised a scoring system to identify those at risk in the short term of "severe disease". Severe renal disease was defined as nephrotic or nephritic syndrome with acute renal failure. Severe gastrointestinal (GI) disease was defined by bloody diarrhoea, ileus or bowel perforation. The presence of new onset abdominal pain, generalized purpura (above the waist) at presentation and smoking history identified over 75% of patients with severe IgAV [32].

Mortality in the largest reported series is 26% with a median survival time of 15 years (IQR 13–21 years); death occurred at 67.3 years. The commonest cause of death was cancer (27%) followed by infection (16%) and active vasculitis (11%), in particular GI involvement [10••].

Treatment

The treatment of IgAV remains controversial. Challenges to designing clinical trials for this disease include the low incidence of IgAV, as well as the lack of validated diagnostic criteria activity indices, remission end points and the heterogeneity of disease presentation from isolated benign skin IgAV to rapidly progressive kidney decline or life threatening gastrointestinal involvement. The high rate of spontaneous remission of IgAN in children further complicates evaluation of treatment efficacy in observational studies. Current regimens are based on the treatment of other systemic vasculitides and include oral corticosteroids, pulsed methylprednisone, cyclophosphamide, plasma exchange and novel therapies including rituximab and anecdotal reports of eculizumab. The KDIGO (Kidney Disease Improving Global Outcomes) guidelines suggest that IgAV with nephritis in adults be treated the same as in children with a 2D level of evidence—supporting steroid monotherapy (level 2 defined as "we suggest" with level D referring to the quality of evidence for this recommendation as "very low") [33]. Yet the guidelines also suggest treating crescentic (> 50% glomeruli) IgA nephropathy with rapidly progressive loss of function with dual therapy including corticosteroid and cyclophosphamide. Clearly there is a gap in knowledge in this realm. The high level of kidney failure observed in adult IgAV cohorts highlight the lack of highly effective treatments. Clinical renal remission, defined as the absence of proteinuria, hematuria and a normal renal function, is achieved in only 20% [5, 10••].

While significant GI and refractory skin involvement would be reasonable criteria to treat patients with IgAV with immunosuppressive therapy, selection

of the drug of choice is based primarily upon observational data. Rapidly progressive loss of kidney function is generally considered an indication for immunosuppressive treatment in adults.

Corticosteroids

In adults with IgAV corticosteroids given at onset of purpura do not prevent the development of glomerulonephritis [34].The KDIGO guidelines (largely expert opinion) suggest that in the absence of a rapidly progressive course, those with persistent proteinuria (> 1 g/day per $1.73m^2$, after a trial of ACE-I or ARBs, and GFR > 50 ml/min per $1.73m^2$), should be treated similarly to IgAN with a 6-month course of corticosteroids. In the context of adults with rapid loss of kidney function, corticosteroids are the cornerstone of therapy.

Less is known about the role of corticosteroids in patients with IgAV with persistent proteinuria or stable renal function. It should be noted that there is currently significant clinical equipoise regarding the use of corticosteroids in primary IgAN (in the absence of rapid disease progression). A recent randomized clinical trial demonstrated significant benefit of corticosteroids for proteinuria reduction and loss of kidney function [35]. However, this therapy was associated with significant toxicity, including death from opportunistic infection, necessitating halting enrolment and protocol amendment. This is in contrast with the STOP-IgAN trial, which showed little additional benefit of corticosteroids above conservative therapy in patients with relatively mild IgAN [36]. Whether data from trials of primary IgAN can be extrapolated to patients with IgAV and persistent urinary abnormalities is not known. Patients with rapid loss of kidney function were excluded from these studies.

Plasma exchange

The rationale for PLEX in IgAV is removal of putative IgA1-containing immune complexes and the galactose-deficient IgA1-targeted IgG autoantibodies. The effects of PLEX are temporary; therefore, it may be considered a bridge to halting immune complex deposit formation with immunotherapy. One of the largest case series of adult patients treated with plasma exchange included 11 consecutive patients with severe renal or GI IgAV treated with concomitant corticosteroids and 10–15 plasma exchanges [37]. The median GFR pre-PLEX was 67 ml/min and at month 12 was 85 ml/min. One out of 11 patients developed ESRD at 2-week post-diagnosis and subsequently died of sepsis at 2.1 years, another patient died from a pneumothorax at 1 year post dx. Ten out of 11 patients responded to plasma exchange in this retrospective case series; however, there are clear limitations to the interpretation of this small series.

A review of 67 pediatric and adult case series by the American Society of Apheresis led to a category III recommendation for PLEX in patients with IgAV (optimum role not established, individualized decision) based upon grade 2C evidence(level 2 defined as “we suggest” with level C referring to the quality of evidence for this recommendation as “low”).

This was restricted to patients with "severe crescentic renal disease" or refractory GI involvement [38].

Cyclophosphamide

The CESAR study [39] was a randomized open label trial comparing steroid alone vs steroids plus cyclophosphamide with a primary end point of no active vasculitis at 6 months. Eligible patients had severe IgAV as defined by renal biopsy with diffuse endocapillary proliferation alone or with extracapillary proliferation, severe GI involvement, pulmonary hemorrhage, CNS involvement or episcleritis. While patients with a wide spectrum of renal function were included, median renal function was relatively well preserved and patients with rapidly progressive GN were not included. A total of 54 patients were recruited and followed for a median of 5 years. The primary end point was a Birmingham Vasculitis Activity Score of 0- at 6-month post-diagnosis. Intervention included six doses of intravenous cyclophosphamide. Both arms received IV methylprednisolone for 3 days followed by prednisone initially 1 mg/kg/day for 1 week tapering to stop by the end of month six. At 6 months 10% in the steroid-alone group compared to 12% in steroids + cyclophosphamide group achieved the primary end point of BVAS of 0 (ns $p = 1.00$). One patient in each group developed ESRD (at 8- and 12-week post-diagnosis, respectively). Notably, there were seven deaths, six in steroids alone, one in steroid + cyclophosphamide (ns, HR 3.0, 95% CI 0.8–11.3). The conclusion of the authors was that in "severe" IgAV there is no benefit to the addition of cyclophosphamide to steroid therapy in adults, although the small size of the study precluded definitive conclusions. Certainly, the toxicity of immunotherapy in this population was highlighted by this study.

Rituximab

Rituximab is a murine/human chimeric monoclonal antibody directed against and depleting CD20+ B cells. In ANCA vasculitis, circulating levels of B cells correlate with disease activity [40], but the same is not established in IgAV. Children with IgAV do have an increased percentage of B lymphocytes (CD19/20+), supporting a potential role for rituximab in IgAV. However, an open-label randomized, controlled multi-centre study of rituximab in IgAN (2 with IgAV) with proteinuria > 1 g/day and eGFR < 90 ml/min per 1.73 m^2 failed to show efficacy in proteinuria reduction or reduction in serum levels of galactose-deficient IgA1 and anti-galactose-deficient IgA1 antibodies despite B cell depletion [41••]. This has led to speculation that lack of efficacy relates to the fact that pathogenic antibody-producing plasma cells in IgAN are mucosal in origin and CD20 negative, unlike humoral plasma cell precursors, which are effectively depleted by the rituximab [42].

Case series suggest clinical response to rituximab therapy in both IgAV [43] and IgAN with crescents [44]. A single-centre case series of five patients with refractory IgAV (immunosuppressive failure or intolerance) described complete clinical resolution of IgAV with rituximab. No serious adverse events were noted [45]. The largest series included 22 patients with relapsing/refractory IgAV (16/22) or contraindications to conventional therapy (6/22) and severe organ

involvement [46••]. The median BVAS pre-treatment was 16.5. Following rituximab, cumulative remission was 90.9% during the first 12 months and 35% subsequently relapsed. Remission was defined as a BVAS score of 0 (or < 5 if due to persistent hematuria, proteinuria with stable or improving renal function). Relapses occurred at a median of 12-month post-treatment and one patient ultimately progressed to ESRD. There was one death from cirrhosis and pneumonia 60-month post-rituximab therapy.

The lack of efficacy of rituximab in a prospective study of IgAN is at odds with observational case series of IgAV. Only a prospective controlled clinical trial can adequately inform clinicians regarding the utility of rituximab in IgAV.

Azathioprine and mycophenylate mofetil

While azathioprine is commonly prescribed in IgAV, there are relatively little data to support efficacy beyond non-controlled observational pediatric studies. It is typically described in cases of severe or steroid-resistant disease [47, 48]. Based upon a rigorous randomized trial mycophenolate mofetil (MMF) is regarded as a less effective maintenance agent compared with azathioprine in ANCA-associated vasculitis [49] but data regarding IgAV are more limited. Ren et al. compared combination of mycophenylate mofetil (1.0–1.5 g/day) with low dose prednisone (0.4–0.5 mg/kg/day) to high-dose prednisone (0.8–1.0 mg/kg/day) in a cohort of IgAV with biopsy-proven renal involvement and urine protein > 2 g/day [50]. Remission rates at 1 year were 77.8 and 80.8%, respectively. The authors concluded that MMF could safely be used as a steroid sparing agent for induction of remission.

In the pediatric literature, Du et al. [9] treated 12 pediatric HSPN patients with MMF who failed steroid treatment. At the end of the median 46.8-month follow-up, all patients achieved remission with no relapses [51].

Colchicine

Colchicine is an alkaloid derived from *Colchicum autumnale* (autumn crocus), which prevents polymorphonuclear leucocyte chemotaxis by inhibiting microtubule formation [52]. The suppressive effect of colchicine on the inflammatory pathway may explain its effect on the skin lesions in IgAV [53]. Case series suggest that low doses of colchicine (0.5–1 mg once daily) are effective in treating leucocytoclastic vasculitis and that up to 80% of patients treated respond, usually within the first 4–7 days [49]. It has been reported as a successful treatment for cutaneous limited and severe cutaneous IgAV [54].

Future approaches: novel complement inhibitors

The classical, and alternative, and lectin pathways of complement activation are implicated in the pathogenesis of IgAN following observation of products including C3, C4d, C5b-9, properdin, factor H, C4BP and MBL deposition within the glomerulus [55–57]. In addition, genome-wide association studies identify a protective allelic variant at 1q32, encoding regulators of alternative pathway activation.

Case reports detailing the use of eculizumab in the management of refractory IgAV are beginning to emerge, although the drug is prohibitively expensive. A small open label phase 2 study of Avacopan, an inhibitor of the C5aR, in primary IgAN has been completed and results area awaited (NCT02384317).

Conclusions

Several gaps remain in our knowledge regarding the pathogenesis and treatment of IgAV in adults. The relatively low disease incidence and lack of consensus diagnostic criteria challenge our ability to evaluate treatment strategies. Fortunately, multi-centre collaborative intiatives are underway to prospectively refine diagnostic criteria and serve as clinical trial networks. Given the significant morbidity and mortality associated with IgAV and its treatment in adults, clinical trials of novel therapeutics are desperately needed.

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Compliance with Ethical Standards

Conflict of Interest
Sarah Moran declares that she has no conflict of interest.
Heather N. Reich declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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