IgA vasculitis (Henoch–Shönlein purpura) in adults: Diagnostic and therapeutic aspects

Alexandra Audemard-Verger a,⁎, Evangeline Pillebout b, Loïc Guillevin a, Eric Thervet c, Benjamin Terrier a

a Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris Descartes, Paris, France
b Department of Nephrology, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France
c Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris Descartes, Paris, France

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ABSTRACT
Immunoglobulin A (IgA) vasculitis, formerly called Henoch–Schönlein purpura, is an immune complex vasculitis affecting small vessels with dominant IgA deposits. Clinical manifestations mainly involve cutaneous purpura, arthralgias and/or arthritis, acute enteritis and glomerulonephritis. IgA vasculitis is more common among children than adults, with more severe disease in adults. Gastrointestinal and renal involvements represent the principal causes of morbidity and mortality in adults. Factors associated with long-term end-stage renal disease (ESRD) include baseline renal function impairment and baseline proteinuria > 1 or 1.5 g/day, and on renal biopsy degree of interstitial fibrosis, sclerotic glomeruli and fibrinoid necrosis. Management of IgA vasculitis in adults is rendered difficult for clinicians because of the absence of correlation between initial presentation and long-term renal outcome, and the possible occurrence of spontaneous remission in patients with severe presentation or, in contrast, possible evolution to ESRD in patients with mild symptoms. Treatment is often symptomatic because disease course is usually benign. Treatment of severe involvement, including severe gastrointestinal complications or proliferative glomerulonephritis, remains controversial, with no evidence that corticosteroids or immunosuppressive agents improved long-term outcome. Prospective, randomized, controlled trials are thus needed to analyze the benefit–risk ratio of such treatments.

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Contents
1. Introduction .............................................................. 580
2. Epidemiology ........................................................... 580
3. Classification, definition, diagnostic criteria and their limitations .............................................................. 580
3.1. The American College of Rheumatology classification criteria .............................................................. 580
3.2. The 1994 Chapel Hill International Consensus Conference .............................................................. 580
3.3. The 2012 revised Chapel Hill International Consensus Conference for Nomenclature of Vasculitides .............................................................. 580
3.4. Limitations of classification criteria and nomenclatures .............................................................. 580
4. Clinical manifestations ................................................ 581
4.1. Cutaneous involvement ............................................. 581
4.2. Joint involvement ................................................... 581
4.3. Gastrointestinal involvement ..................................... 581
4.4. Renal involvement .................................................. 581
4.5. Others’ involvement ................................................ 581
4.6. Baseline characteristics between childhood and adulthood IgA vasculitis .............................................................. 581
5. Disease course and prognosis ........................................ 581
6. Treatments ................................................................. 581
6.1. Symptomatic measures ............................................. 581

⁎ Corresponding author at: Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, 27, rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France. Tel.: +33 1 58 41 14 61; fax: +33 1 58 41 14 50.
E-mail address: alexandra.audemard@gmail.com (A. Audemard-Verger).

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1. Introduction

Immunoglobulin A (IgA) vasculitis, formerly called Henoch–Schönlein purpura, is an immune complex vasculitis predominantly affecting small vessels. The disease was first described in 1802 by Heberden [1], and recognized as the association of purpura and arthralgias by Schönlein in 1837 [2]. Latter, Henoch added to this syndrome the presence of gastrointestinal symptoms in 1874 and renal involvement in 1899 [3]. Overall, clinical spectrum of the disease mainly includes cutaneous purpura, arthralgias and/or arthritis, acuteenteritis and glomerulonephritis, with gastrointestinal and renal involvements representing the main causes of morbidity and mortality in adults.

Although the cause of the disease remains unknown, it is clear that IgA system plays a central role in the pathophysiology [4]. IgA1 levels are commonly elevated in the serum of patients, resulting from an increase in their production and a defect in their clearance, and recent studies have shown aberrant glycosylation of IgA1 [5]. Increased IgA synthesis could be related to antigen exposure processed by the mucosal-associated immune system. Bacteria, virus or parasitic agents were suspected to trigger the disease in genetically prone individuals, but causative agents and factors remain to be identified [6,7]. The role of genetic background was supported by the identification of susceptibility genes in the human leukocyte antigen (HLA) system, including HLA-DRB1 [8]. Besides “primary” IgA vasculitis, a small subset of IgA vasculitis in adults could also be related to malignancies, in particular lung cancer.

Treatment is often symptomatic because of the frequent benign course with spontaneous remission. However, organ and life-threatening complications may occur and require more aggressive systemic treatments, particularly in adults. Herein, we review the diagnostic aspects, the prognosis and the therapeutic management of IgA vasculitis in adults.

2. Epidemiology

IgA vasculitis is the most common systemic vasculitis in childhood with an annual incidence of 3 to 26 per 100,000 children, occurring most frequently between 4 and 7 years [9]. In adults, the disease remains rare with an annual incidence of 0.1 to 1.8 per 100,000 individuals [10,11]. Disease is more frequent in males, with a male/female ratio of 1.5. While IgA vasculitis most commonly occurred in fall and winter in children, summer and winter are the most common seasons of onset in adults [12]. Finally, IgA vasculitis is represented worldwide and described in all ethnic groups, but Black children had a significantly lower annual incidence than did white or Asian children [9].

3. Classification, definition, diagnostic criteria and their limitations

IgA vasculitis classifications have been exhaustively reviewed elsewhere, the main classifications are [13]:

3.1. The American College of Rheumatology classification criteria

In 1990, the American College of Rheumatology proposed criteria for distinguishing IgA vasculitis from other forms of vasculitis. Four criteria were identified: age ≤20 years at disease onset, palpable purpura, acute abdominal pain, and biopsy showing granulocytes in the walls of small arterioles or venules. The presence of any 2 or more of these criteria distinguished IgA vasculitis from other forms of vasculitis with a sensitivity of 87.1% and a specificity of 87.7% [14].

3.2. The 1994 Chapel Hill International Consensus Conference

In 1994, an International Consensus Conference was convened in Chapell Hill to reach consensus on names of vasculitis and to construct specific definition for each vasculitis. In the this Consensus Conference, IgA vasculitis (formerly called Henoch–Schönlein purpura) was defined as a small vessel vasculitis with IgA-dominant immune deposits, typically involving skin, gut, and glomeruli, and associated with arthralgia/arthritis (15).

3.3. The 2012 revised Chapel Hill International Consensus Conference for Nomenclature of Vasculitides

The revised International Consensus Conference took into account advances in the understanding of vasculitis. In this Consensus Conference, IgA vasculitis was chosen to replace the eponym “Henoch–Schönlein purpura” based on the compelling body of literature indicating that abnormal IgA deposits in vessel walls are the defining pathophysiology feature. IgA vasculitis was thus defined as a vasculitis with IgA1-dominant immune deposits, still affecting small vessels, and often involving the skin, gastrointestinal tract, joints, and kidney with glomerulonephritis indistinguishable from IgA nephropathy (16).

3.4. Limitations of classification criteria and nomenclatures

The ACR classification may be very useful in pediatric population, but not appropriate in adults. In particular, these criteria would be not enough sensitive to distinguish others forms of vasculitis frequent in adults, such as cryoglobulinemia vasculitis or microscopic polyangiitis. New classifications including IgA-dominant immune deposits as main criteria could be interesting. The European League Against Rheumatism, Paediatric Rheumatology International Trials Organization and Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) have proposed new classification criteria in pediatric population. Based on these criteria, a patient was classified as IgA vasculitis in the presence of purpura or petechiae (mandatory) with lower limb predominance plus one of four criteria: (1) abdominal pain; (2) histopathology (IgA); (3) arthritis or arthralgia; (4) renal involvement. Unfortunately, these criteria are not adapted for adults.
4. Clinical manifestations

Purpura, arthralgia, and abdominal pain are known as the “classic triad” of IgA vasculitis.

4.1. Cutaneous involvement

Symmetric palpable purpura is nearly constant in the patients, mainly in the pressure areas, especially around the ankles but can extend to the entire body [17]. In adults, purpura may be necrotic or hemorrhagic in one third of cases. Purpura gradually and spontaneously disappears with resting in roughly 2 weeks, but it can reoccur and become chronic.

4.2. Joint involvement

Arthralgias are very frequent during the course of IgA vasculitis, in approximately two third of cases. Arthralgias mainly involve knees or ankles, while arthritis is very rare [17]. Myalgia have been also reported but without increase of creatine phosphokinase (CPK).

4.3. Gastrointestinal involvement

Gastrointestinal involvement is frequent, occurring in about two third of cases. Abdominal pain is constant and represented by typical colicky pain. In a recent Spanish series, main clinical manifestations were abdominal pain (100%), nausea and vomiting (14.4%), melena and/or rectorrhagia (12.9%), and positive stool guaiac test (10.3%) [18]. Symptoms are caused by bowel ischemia and oedema. Serious complications include intussusception, infarction, and perforation. Descending duodenum and the terminal ileum are frequently involved, with endoscopic features including diffuse mucosal redness, petechiae, hemorrhagic erosions and ulcers [19]. CT scan features are commonly bowel wall thickening with engorgement of mesenteric vessels.

4.4. Renal involvement

Renal involvement occurs with a prevalence ranging from 45 to 85% in the literature [17]. Microscopic hematuria is the most sensitive and earliest symptom suggestive of nephropathy during IgA vasculitis, in association with urine protein excretion of variable range, sometimes nephrotic. Macroscopic hematuria is exceptional. Hypertension is noted in one third of cases. In adults, renal failure at the time of diagnosis is noted in approximately 30% while occurrence of renal failure is rare in children [17]. Conversely, among all causes of glomerulonephritis, IgA vasculitis is responsible for only 0.6 to 2% of adult nephropathy.

The most commonly used classification was established by Pillebout et al., containing 5 histologic classes, as shown in Table 1, defined by the degree and extension of glomerular lesions, and demonstrated strong clinico-pathological correlation [24].

4.5. Others’ involvement

Myocarditis, orchitis, alveolar hemorrhage or episcleritis represent very rare manifestations of IgA vasculitis. Central nervous or peripheral nervous system involvement may also occur, including altered level of consciousness, convulsions, focal neurological deficiency, visual loss and verbal disability [20].

4.6. Baseline characteristics between childhood and adulthood

Previous studies showed that IgA vasculitis is generally benign and self-limited in children and more severe in adults [12]. Adults had a lower frequency of abdominal pain and fever, and a higher frequency of joint symptoms. During the clinical course, adults had more frequent and severe renal involvement [21].

5. Disease course and prognosis

Management of IgA vasculitis in adults is rendered difficult for clinicians because of the absence of correlation between initial presentation and long-term renal outcome, and the possible occurrence of spontaneous remission in patients with severe presentation or, in contrast, possible evolution to end-stage renal disease (ESRD) in patients with mild symptoms [22]. There are no guidelines concerning when to perform renal biopsy, but it seems appropriate to discuss such biopsy in case of acute renal failure related to rapidly progressive glomerulonephritis, nephrotic syndrome, diagnostic uncertainty, or in case of persistent proteinuria (> 1 g/day) at 3–6 months despite angiotensin-converting enzyme inhibitors.

In contrast with children in whom disease flare is usually unique, relapses occur in adults in roughly 20% of cases. Early and acute life-threatening manifestations include gastrointestinal perforation and/or bleeding and pulmonary involvement with intraalveolar hemorrhages [23]. Long-term organ-threatening is in contrast related to the course of renal involvement. In a large study in adults, 11% of patients reached ESRD, 13% exhibited severe renal failure (estimated glomerular filtration rate (eGFR) < 30 mL/min), and 14% moderate renal insufficiency (eGFR < 50 mL/min) [24].

Factors associated with long-term ESRD include baseline renal functional impairment, baseline proteinuria > 1 or 1.5 g/day, macroscopic hematuria, hypertension, and proteinuria ≥ 1 g/day during follow-up [24–26]. On renal biopsy, degree of interstitial fibrosis, sclerotic glomeruli and fibrinoid necrosis are also associated with a poor renal prognosis [24].

Finally, IgA vasculitis may recur after renal transplantation. Meuldners et al. reported a risk of renal recurrence and graft loss due to recurrence in 35 and 11% at 5 years after transplantation, respectively [27].

6. Treatments

Treatment is often symptomatic because the disease course is usually benign. There have been many reports dealing with the use of corticosteroid and immunosuppressive drugs. The mechanism of action, benefit and side effects of these drugs are described below. These specific treatments are still controversial and their efficacy remains to be evaluated. Currently, most available studies were performed in pediatric patients, with results often extrapolated to adults. In case of severe involvement, including severe gastrointestinal complications or proliferative glomerulonephritis, steroids or/and immunosuppressive drugs may be required.

6.1. Symptomatic measures

Benign manifestations as nonnecrotic purpura or arthralgias are usually managed by appropriate symptomatic measures (resting, analgesia, compression stockings). Nonsteroidal antiinflammatory drugs have to be avoided in case of renal or gastrointestinal involvement. In case of kidney involvement with mild to moderate proteinuria, angiotensin-converting enzyme inhibitors are required. Severe
gastrointestinal complications may occasionally require surgical interventions.

6.2. Colchicine

Colchicine is an alkaloid drug derived from Colchicum autumnale used for the treatment of acute gout flares since 1763. It inhibits polymorphonuclear chemotaxis to the site of inflammation by perturbing microtubule function of polymorphonuclear cell cytoskeleton and it also blocks lymhosomal fusion [28]. Side effects mainly include abdominal pain and/or diarrhea. Suppressive effect of colchicine on inflammatory pathway may explain its clinical effects in some autoimmune diseases such as familial Mediterranean fever or Behçet disease [29,30]. Efficacy of colchicine has also been reported in cutaneous leukocytoclastic vasculitis by Callen et al. In their series including 13 adults, low-dose colchicine (1 mg daily) was effective in 80% of patients, usually within the first 7 days [31]. Purpura reappeared after discontinuation of colchicine, and reinstitution of the treatment was associated with disappearance of lesions. Limitation of this study was the absence of control group and difficulties in the evaluation of response, because of frequent spontaneous remisision during cutaneous leukocytoclastic vasculitis. Because skin biopsies from IgA vasculitis demonstrate leukocytoclastic vasculitis of small vessels, colchicine has been used, with few case reports showing efficacy [32,33]. This therapeutic approach could improve symptoms and quality of life in patients with chronic IgA vasculitis with purpura, with a good benefit–risk ratio, but further studies are warranted.

6.3. Dapsone

Dapsone is a bacteriostatic antibacterial sulfonamide drug used for a variety of dermatological conditions associated with accumulation of neutrophils, including leukocytoclastic vasculitis. The exact mechanism of action of dapsone remains unknown. There is evidence that dapsone has an antioxidant scavenger effect, may suppress the generation of toxic oxygen-derived radicals in neutrophils and inhibits chemiotaxis of neutrophils through CD11b/CD18 interactions [34]. Dapsone may also inhibit IgA-neutrophils interactions. Side effects include hemolysis and methemoglobinemia, especially in patients with glucose-6-phosphate dehydrogenase deficiency. No controlled trial using dapsone in IgA vasculitis was done, but some cases in childhood and adulthood population revealed effectiveness in chronic purpuric skin lesions [35–37]. Response to dapsone is often quick, between few days and one week. However, relapses occurred after discontinuation in most cases. Original report shows that abdominal pain and arthritis could respond to dapsone [38]. As previously indicated with colchicine, randomized controlled trials are warranted to demonstrate the efficacy of dapsone in IgA vasculitis.

6.4. Anti-leukotriene agents

Leukotrienes were showed to be involved in the pathogenesis of IgA vasculitis in children [39]. Montelukast, a leukotriene receptor antagonist, inhibits the cysteinyl leukotriene receptor and exhibits potential antiinflammatory effect, modulating IL-6, TNF-α, and MCP-1 through the inhibition of NF-κB pathway [40]. Montelukast was evaluated in children as an add-on therapy on symptomatic treatment [41]. Montelukast alleviated the symptoms of IgA vasculitis including purpura, abdominal pain, stool occult blood, arthritis, proteinuria and hematuria. Montelukast also inhibited relapses during the first three months after treatment, but did not alter the outcome of nephritis at the end of the follow-up. No data are available in adults.

6.5. Corticosteroids

Corticosteroids are effective on arthralgias and abdominal pain, but ineffective on skin purpura, and there is a considerable controversy on the benefit of corticosteroids to treat renal involvement and prevent evolution to end-stage renal disease.

In patients presenting with purpura and mild arthralgias with no clinical renal involvement, or in those with microscopic hematuria, mild proteinuria and normal renal function, corticosteroids does not seem to be indicated, and these forms are usually managed symptomatically. In adults with severe disease, nor data on the efficacy of corticosteroids to prevent progression of nephritis neither prospective randomized controlled trials are available in the literature.

In contrast in children, 3 randomized, placebo-controlled, prospective trials were conducted. In the study by Huber et al., the authors included 40 children to evaluate whether early corticosteroids (2 mg/kg/day during 2 weeks) could reduce the rate of renal or gastrointestinal complications [42]. At one year, there was no difference in the rate of renal involvement and gastrointestinal complications. Ronkainen et al. included 171 children in a double-blinded, placebo-controlled trial in order to evaluate the efficacy of early prednisone therapy in preventing renal and treating extrarenal and renal symptoms [43]. Prednisone (1 mg/kg/day for 4 weeks) was effective to reduce the intensity of abdominal and joint pain. Prednisone did not prevent the development of renal symptoms but was effective in treating them. Finally, Jauhola et al. reported 223 newly diagnosed pediatric IgA patients [44]. There was no difference in the clinical course (abdominal or joint pain, and renal involvement) between the prednisone-treated and non-treated patients during the 6-month follow-up.

These studies displayed some limitations, including diagnosis of IgA vasculitis not biopsy-proven, inclusion of patients with mild forms and patients with severe forms of vasculitis, very short duration of corticosteroids, and follow-up duration lower than 1 year.

Pulses of methylprednisolone (MP) have been evaluated in retrospective or open-label series in pediatric patients, often in association with others’ therapy [45–47]. In adults, a prospective study of 86 patients with primary IgA nephropathy (IgAN) with mild involvement (urine protein excretion of 1 to 3.5 g/d, and serum creatinine levels <1.5 mg/dL), patients were randomized to receive steroids or supportive therapy alone. The patients randomized to the steroid group received 1 g of MP for 3 consecutive days before the initiation of oral prednisone and additional pulses 2 and 4 months later, and received low dose prednisone (0.5 mg/kg/day) for 6 months [48]. Ten-year renal survival was significantly better in the steroid group than in the control group (97% versus 53%; p = 0.0003).

This «Locatelli» schedule, with combination of pulses of MP and low dose prednisone, is frequently used for the treatment of IgA nephropathy to reduce cumulated dose of steroids. The 2012 KDIGO guidelines recommended to treat patients with IgA nephropathy with persistent proteinuria >1 g/day despite 3–6 months of optimized supportive care (including renin–angiotensin–aldosterone system inhibition and blood pressure control), and eGFR >50 mL/min, with 6-month course of such steroid therapy [49]. However, these guidelines do not concern IgAV, but IgA nephropathy.

Finally, a prospective study was performed to evaluate whether early administration of prednisone could be useful in preventing the development of IgA nephropathy in a pediatric population without signs of nephropathy and followed up for 24–36 months [50]. Patients received or not prednisone 1 mg/kg/day for 2 weeks. None of the patients treated with steroids and 12% of the control patients developed nephropathy 2–6 weeks after the initial flare.

6.6. Azathioprine

Azathioprine has not been evaluated in adults with IgA vasculitis. In pediatric population, combination of azathioprine and corticosteroids could be beneficial by improving clinical course of severe IgA nephritis
and histological features, but studies were of small sample sizes or without control groups [51,52].

6.7. Mycophenolate mofetil

Ren et al. compared combination of mycophenolate mofetil with low-dose prednisone and full-dose prednisone alone as induction therapy for IgA nephritis with large proteinuria (>2.0 g/24 h) [53]. Fifty-three adults were included and divided into two groups: patients who received oral mycophenolate mofetil 1.0 g/day with low-dose prednisone (0.4–0.5 mg/kg/day), and patients who received full-dose prednisone (0.8–1.0 mg/kg/day). At 6 months, the remission rate was 76.9% in the full-dose prednisone group and 55.5% in the mycophenolate mofetil group (not significant difference). After a median follow-up of 28 months in both groups, the overall remission rate was 80.8% in the full-dose prednisone group and 77.8% in the mycophenolate mofetil group, suggesting that mycophenolate mofetil could be useful for inducing remission and as steroid-sparing agent.

6.8. Cyclosporin A

Kalliaxman et al. reported 5 adults with nephritic range proteinuria, treated with cyclosporin A (CsA) in combination with corticosteroids [54]. All patients showed complete or partial remission of nephrotic syndrome and preserved stable renal function over a follow-up period of 5 years. Other studies concerned pediatric population. Jauhola et al. have compared CsA and MP for the treatment of severe IgA vasculitis, including 24 pediatric patients with nephrotic range proteinuria or crescentic nephritis in kidney biopsy [55]. All patients receiving CsA achieved remission of nephrotic range proteinuria within 3 months, while the response was slower in those receiving methylprednisolone. Additional immunosuppressive treatment was needed in six patients treated with MP compared to none with CsA.

6.9. Cyclophosphamide

By analogy with other severe autoimmune diseases, cyclophosphamide (CYC) has been used in patients with organ- or life-threatening manifestations. In adults, Pillebout et al. compared corticosteroids without or with CYC in adults with severe IgA vasculitis in a 12-months, multicenter, prospective, open-label trial. Fifty-four patients with biopsy-proven IgA vasculitis and severe manifestations, including proliferative glomerulonephritis and/or severe visceral manifestations, were included [56]. At 12 months, no difference was found between the 2 groups (remission rate, renal outcomes, deaths and adverse events). This study should however be analyzed with cautions. First, only 54 patients out of the 200 initially planned were included, explaining why the trial does not have sufficient statistical power to detect any difference between the arms of treatment. Second, overall survival at 12 months was 96% with corticosteroids plus CYC compared to 79% with corticosteroids alone (p = 0.08). In pediatric population, the prospective and randomized study by Tarshish et al. in 27 children with severe IgA nephritis, comparing supportive therapy with or without oral CYC, did not find any difference between the 2 groups for the rate of end stage renal disease after 14 years of follow-up [57].

6.10. Rituximab

Rituximab, a chimeric anti-CD20 monoclonal antibody, was successfully used in different forms of vasculitis associated with pathogenic antibodies or immune complexes deposition, such as ANCA-associated vasculitis [58] or cryoglobulinemia vasculitis [59]. Rituximab, depleting B cells, may reduce immune complexes containing IgA during IgA vasculitis and reduce disease activity. Only 4 case series of patients treated with rituximab are reported in the literature. Pillebout et al. described an adult with moderate nephritis and severe skin vasculitis treated in first line with rituximab without corticosteroids, the patient achieving

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complete and sustained skin and renal remission [60]. Pindi Sala et al. reported a 49-year-old patient treated with rituximab because for relapsing and corticosteroid dependent disease [61]. Successful outcome was observed during the two years of follow-up. Ishiguro et al. reported a 68-year-old woman with nephritis and skin involvement refractory to corticosteroids plus cyclophosphamide, treated with rituximab leading to complete remission [62]. Finally, the efficacy of rituximab in refractory chronic purpura has been recently reported in three children with intestinal or neurological involvement without serious adverse events [63]. Further studies are thus required to evaluate the efficacy of rituximab in IgAV, in patients with refractory disease or as first-line therapy.

6.1.1. Other immunomodulatory approaches

The use of intravenous immunoglobulin (IVIg) for the treatment of IgA vasculitis has been anecdotally reported as being effective for abdominal pain or to reduce proteinuria. In an open prospective trial of 14 adults with stage III glomerulonephritis on histology and normal renal function, Rostoker et al. evaluated high-dose immunoglobulins (2 g/kg each month) for 3 successive months, followed by intramuscular immunoglobulins (0.35 mL/kg every 15 days) for another 6 months. Both proteinuria, hematia, histologic activity index and immune deposits improved in the majority of cases [64]. The benefit of plasma exchange has been poorly evaluated, mainly in severe manifestations. Augusto et al. reported 11 consecutive adults with severe and newly diagnosed IgA vasculitis who were treated with steroids and plasma exchange, with fast improvement and good long-term outcome [65].

6.1.2. Treatment algorithm

Based on previous studies and data in children, we proposed a treatment algorithm for the management of IgA patients according to organ involvement in Fig. 1. For the management of renal involvement, therapeutic strategy according to histologic class and proteinuria, as proposed in Table 2, could be helpful to determine initial treatment [24].

7. Conclusion

Management of IgA vasculitis is mainly symptomatic in cutaneous and/or articular forms. Treatment of severe involvement is in contrast more complex and remains controversial, with no evidence that corticosteroids or immunosuppressive agents improved long-term outcome. Prospective, randomized, controlled trials are thus needed to analyze the benefit–risk ratio of such treatments.

Take-home messages

- IgA vasculitis is a systemic vasculitis characterized by purpura, arthralgia or arthritis, gastrointestinal involvement and glomerulonephritis.
- IgA vasculitis is rare in adults but more severe than in children.
- Management of IgA vasculitis in adults is rendered difficult because of the absence of correlation between the initial presentation of the disease and the long-term outcome of renal involvement.
- Treatment remains controversial, with no evidence that immunosuppressive agents improved long-term outcome.

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