Immunosupression in IgA Nephropathy

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ABSTRACT

IgA Nephropathy (IgAN) is one of the most frequent types of glomerulonephritis encountered in adults from Western countries and Asia. IgAN is responsible for approximately 40% of end-stage renal disease (ESRD) mediated by glomerular impairment. The majority of adult IgAN patients present a slowly progressive pattern towards ESRD. Current types of treatment are based mainly on supportive care: i.e., life style risk factors, measures that lower blood pressure and reduce proteinuria, weight loss, smoking cessation or glycaemia control. Because IgAN is an immune complex-mediated disease, immunosuppression therapy gains more and more attention as a modality of treatment. Despite the beneficial effects, the value of immunosuppression remains controversial due to high rates of adverse reactions. The aim of this review is to highlight the benefits and limitations of promoting immunosuppression in IgAN with mild to moderate proteinuria despite supportive antiproteinuric therapy up titrated to maximum tolerated doses.

Keywords: IgA nephropathy, supportive care, immunosuppression, adverse effects, outcome

INTRODUCTION

Named also Berger's disease, IgA nephropathy (IgAN) is a common glomerular disease seen more frequently in Asian and European population with a prevalence of 45 cases per million in Japan and respectively 31 cases per million in France [1]. The peak disease incidence is in the second and third decade of life, but symptoms may be encountered at any age [2]. Clinical manifestations vary from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis (RPGN). By far the most frequent forms are asymptomatic hematuria and slowly progressive renal impairment with a reported renal survival of 57-91% in 10 years [3]. Other less frequent clinical presentations of IgAN can be associated with nephrotic syndrome (defined by proteinuria > 3.5 g/day, serum albumin < 2.5 g/dL and dyslipidemia), often with podocyte involvement on renal biopsy which is suggesting a minimal change disease nephropathy (MCD) overlap. Under the revised KDIGO (*Kidney Disease Improving Global Outcomes*) guideline for management of glomerular disease, these cases should be treated like any other MCD. Another type of presentation can be with nephrotic range proteinuria without nephrotic syndrome, suggesting either chronic lesions given by substantial glomerulosclerosis and tubulointerstitial fibrosis or a secondary focal and segmental glomerulosclerosis (FSGS) overlap [4]. In addition, IgAN can be associated with acute kidney injury (AKI). If AKI occurs with gross hematuria, frequently associated with an upper respiratory tract coinfection, usually suggests tubular involvement (intraluminal obstructive red blood cell casts and acute tubular necrosis). In this case, management of AKI with IgAN is provided by AKI supportive care, usually, with a resolution up to 75% within two weeks [5]. Additionally, presentations with IgAN and AKI can

be encountered in the absence of macroscopic hematuria, as a form of RPGN with extensive crescent formation (generally more than 50% of glomeruli involvement). Researchers recommend that IgAN with rapid progressive pattern to be treated with glucocorticoids and cyclophosphamide as in ANCA associated vasculitis protocol [6]. Our focus on this brief review is the treatment of IgAN with high risk progression to CKD, defined as patients with persistent proteinuria > 0.75 mg/day, despite maximal supporting therapy, given by antihypertensive control (blood pressure target < 130/80 mmHg) with angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), sodium restriction, dyslipidemia control and smoking cessation, for more than 3 months [4].

Risk and progression in IgAN

IgAN can be diagnosed only by renal biopsy. The only true serum biomarkers of IgAN risk and progression are proteinuria and estimated glomerular filtration rate (eGFR) [6]. Recent studies succeed to manage a histological classification named **MEST-C score**, which is able to stratify the prognostic risk in IgAN, but the impact of the treatment cannot be determined. The Oxford Classification for IgAN or **MEST-C** established the presence of mesangial hypercellularity with **M1** and the absence with **M0**, presence of endocapillary hypercellularity with **E1** and the absence with **E0**, presence of segmental glomerulosclerosis with **S1** and respectively **S0** in absence, three grades of tubular fibrosis (**T1:** < 25%, **T2:** 25-50%, **T3:** > 50%) and **C** from crescents. It has been established that M1, S1, T2-T3 are risk factors for poor renal prognosis [7]. **E1** revealed no predictive value for eGFR decrease. Instead, E1 findings on biopsy were associated with improvements in eGFR decline in patients with immunosuppressive treatment, in contrast with those only on supportive care therapy. A recent study comprising a large cohort of patients with IgAN from four retrospective studies: VALIGA study [8], Oxford classification [9], and two large Asian databases [10, 11], which included all patients with IgAN, without age, eGFR or rapid progressive clinical course limitations, found that active crescents (fibrocellular or cellular) were present in 36% (1,118) from total biopsies (3,096). The study suggested a cut-off for crescents of more than one forth active crescents to be associated with a faster glomerular function decline. I was also noticed that active crescents in less than one fourth of glomeruli is an independent factor for renal function decline but not on patients under immunosuppression therapy, rather than active crescents in more than one fourth of glomeruli which is a predictor of renal function decline with or without immunosuppression. Thereby the study proposed a cres-

cents classification to the old MEST score – **C0:** no crescents, **C1:** crescents in less than one forth, **C2:** crescents in more than one forth with increased renal risk even in immunosuppression clinical course [7]. Another option for IgAN risk assessment is represented by the International IgA Nephropathy Prediction Tool (IIgAN-PT), available as a mobile application and used to calculate the five-year risk in progression to end-stage renal disease (ESRD) or a 50% decline in eGFR. Main data which should be fill out are: eGFR, proteinuria, blood pressure, age, ethnicity, renin-angiotensin-system (RAS) blockers use, IgAN MEST score and immunosuppression use prior to biopsy. However, as MEST-C histology score, neither IIgAN-PT can indicate a solid 5-year risk threshold, in which a patient can be considered in high risk of progression to ESRD or to be included in immunosuppressive regimens [12].

Pathogenesis in IgAN

In order to use adequate treatment, it is necessary an adequate understanding of the mechanism incriminated in IgAN pathogenesis. The main finding in IgAN is IgA aberrant serum synthesis with mesangial deposition often along with IgG or C3. One of the "multihit" mechanisms is related to exposure to the environmental triggers like commensal or pathogenic bacteria witch may lead to uncontrolled production of IgA glycosylated from mucosal-associated lymphoid tissues. Pathogens like Epstein-Barr, Haemophilus parainfluenza, Parvovirus, Staphylococcus Aureus methicillin-resistant, or Helicobacter pylori were incriminated in IgA proliferations through T-cell and B-cell dependent processes [4]. Apparently, signaling receptors between IgA aberrant proliferation and B-cell activated, are APRIL (A-proliferation factor) and BAFF factors (B-cell activation factor of TNF family). Antigen-presenting cells express cytokines like BAFF and APRIL that play an important role in B-lymphocytes' development. Both of these cytokines are closely associated with different autoimmune diseases (i.e., lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome). In IgAN patients, serum levels of BAFF and APRIL were found to be elevated. High levels of BAFF and APRIL were associated with worse clinical outcomes in IgAN [13]. An *in vivo* study demonstrated that transgenic mice with overexpression of BAFF, induces high circulating levels of polymeric glycosylated IgA (Gd-IgA) which will induce B-cell activation with development of IgA or IgG antibodies against Gd-IgA [14]. Once formed, this immune-complexes will activate the complement and will stimulate pro-inflammatory factors with glomerular inflammation and mesangial proliferation. IgA can activate complement cascade through alternative and lectin pathway. Main factors contribut-

ing to complement activation are properdin and mannan-binding lectin (lectin pathway) [15] and complement factor H (CFH- major regulator of alternative complement pathway) [16].

Immunosuppressive regimen in IgAN

It seems logical to use immunosuppression for autoimmune mechanisms like in IgAN. However, mainstay treatment option in IgAN with asymptomatic hematuria or chronic progression to ESRD remains supportive therapy. In IgAN with high risk of progression to ESRD, it was considered adding immunosuppression regimens to supportive care therapy, after risks and side effects assessment.

The main immunosuppressive options studied are:

1. Corticosteroids

In the last 10 years two major trials involving corticosteroid treatment in IgAN, were published [4]. STOP IgAN trial (designed for 380 patients with IgAN) compared immunosuppression therapy with supporting therapy in patients with eGFR over 30 mL/min/1.73 m^2 and persistent proteinuria after 6-month premedication with ACEi/ARB (RAS blockade) for blood pressure control. Patients with eGFR over 60 mL/min/1.73 m^2 received corticosteroids (methylprednisolone 1 g in the first 3 days of the month 1, 3, 5 along with prednisolone 0.5 mg/kg/alternate day for 6 months) and patients with eGFR between 30-59 mL/min/1.73 m^2 received corticosteroids (prednisolone 40 mg/day tapered in the first 3 months until 10 mg/day, 10 mg/day during months 4-6 and continuing with 7.5 mg/day to complete 36 months) with cyclophosphamide (1.5 mg/kg for 3 months), followed by maintenance therapy with azathioprine (1.5 mg/kg from months 4-36). After 6 months of RAS blockade only 162 patients with persistent proteinuria (proteinuria between 0.75-3.5 g/day) were enrolled in immunosuppressive regimen (80 patients assigned to supportive group and 82 in the immunosuppressive group). In a 3-years follow-up 17% of patients with immunosuppression achieved clinical remission versus 5% patients randomized only with supportive therapy, but the differences between the rate of kidney function loss, were not significantly higher. Therefore, STOP IgAN trail found no significant benefit in intensive immunosuppression regimen in the treatment of IgAN. Furthermore, immunosuppressive regimen was associated with more adverse events, such as gastrointestinal and respiratory infection and also one death from sepsis in the cyclophosphamide regimen [17].

TESTING, the second trial, with the largest cohort of patients, was designed for 750 subjects but only 262 were enrolled in a proportion 1:1 (136 to methylprednisolone and 126 to placebo). The study criteria for enrolment were: persistent proteinuria (defined by TESTING over 1 g/day) after at least 3 months of RAS blockade, IgAN proved on kidney biopsy and eGFR between 20-120 mL/min/1.73 m^2. Patients randomized on immunosuppressive regimen received methylprednisolone 0.6-0.8 mg/kg/day (maximum 48 mg/day) for 2 months than tapered by 8 mg/month to complete 6-8 months. Due to high risk of serious adverse events in immunosuppressive group (14.7% versus 3.2%) the trial was stopped after 2 years. Until that point, TESTING demonstrated fewer events like death due to kidney failure, ESRD or a decrease more than 40% of eGFR in methylprednisolone group versus placebo group (5.9% versus 15.9%). The serious events reported were new onset diabetes, gastrointestinal hemorrhage, osteonecrosis with or without fracture, cardiovascular events, infections and two deaths. Because optimal glucocorticoids dosage is uncertain, another study, placebo controlled, with lower doses compared with TESTING is in progress (TESTING Low Dose Study) [18].

As a practice point, the current KDIGO guidelines indicate that glucocorticoids can be considered in patients who remain in high risk of progression (proteinuria > 0.75 g/day after at least 6 months of RAS blockade) after presenting the patients the possible adverse effects related to the therapy. In addition, KDIGO recommendations are to avoid the use of glucocorticoids in eGFR < 30 mL/min, diabetes mellitus, obesity, latent infections (i.e., viral infections, tuberculosis), gastrointestinal ulcerations, psychiatric diseases or severe osteoporosis. Other contraindications for glucocorticoids use are: small echogenic kidneys on abdominal ultrasound, evidence of severe glomerulosclerosis or severe tubulo-interstitial fibrosis [12]. As well, the use of prophylactic treatment for Pneumocystis Carinii pneumonia is suggested. Recommended doses used in the 3 most recent trials are:

- TESTING trial: oral methylprednisolone with start dose of 0.6-0.8 mg/day (maximum 48 g/day) for 2 months and then tapered with 8 mg/month, with total exposure of 6-8 months [18].
- Manno C et al study: prednisone 1 mg/kg/day (maximum 75 mg/day) for 2 months and tapered with 0.2 mg/kg/month until 6 months [19].
- Lv J et al study: prednisone 0.8-1 mg/kg/day for 8 weeks, tapered with 5-10 mg/day every two weeks with total exposure of 8 months [20].

There is no data regarding the superiority of one regimen to another.

2. Mycophenolate mofetil (MMF)

One trail published in 2005, randomized 40 Chinese patients (20 with MMF and supportive therapy versus 20 only on supportive care) with IgAN persis-

tent proteinuria (> 1 g/day) despite RAS blockade. Results were encouraging in the MMF group, with 80% partial (< 50% of proteinuria baseline reductions) and complete remission (proteinuria < 300 mg/day) versus 30% in standard care cohort, without serious adverse events in order to discontinue the treatment. Gastrointestinal adverse events were treated by increasing the administering interval, hemoglobin decreased with almost 1 g/dL but with recovery after 12 weeks post treatment interruption and also lymphocyte count dropped progressively during the treatment, with rebound after discontinuing. Patients in the MMF group received MMF 2 g/day for 24 weeks with a follow-up for 72 weeks [21]. A recent study, with a larger cohort of subjects demonstrated non-inferiority of MMF 1.5 g/day with prednisone 0.4-0.6 mg/kg for 2 months and tapered with 20%/month in the remaining 4 months versus only prednisone 0.8-1 g/day for 2 months and tapered with 20%/month in the remaining 4 months. The study randomized 176 patients (86 in MMF group versus 88 in prednisone group) with active crescents IgAN, but did not use RAS blockade as premedication or in normotensive subjects during the treatment [22]. Current KDIGO guidelines recommend MMF only in Chinese population with proteinuria >1 g/day and kidney biopsy showing proliferative histologic lesions (E or C lesions). The largest trial used MMF 1.5 g/day with prednisone 0.4-0.6 mg/kg for 2 months and tapered with 20%/month in the remaining 4 months. Nevertheless, MMF remains the preferred option in patients selected for immunosuppression with intolerance for corticosteroids. MMF is considered unsafe in pregnancy and should not be used [12].

3. Rituximab

Given the fact that IgA is provided by a subset of B cells, it seems appropriate to use Rituximab for trying depleting them. Despite the logical point of view, Rituximab treatment added to RAS blockade therapy failed to demonstrate the benefits regarding proteinuria, or eGFR in IgAN with persistent proteinuria [23]. In opposition to chronic clinical course, Rituximab showed benefits as immunosuppressive regimen either as monotherapy or added to corticosteroids and cyclophosphamide in IgA vasculitis as induction therapy or maintenance, in accordance with guidelines for ANCA-associated vasculitis [24].

4. Hydroxychloroquine (HCQ)

HCQ is recommended by KDIGO only in Chinese population with IgAN with persistent proteinuria despite RAS blockade. This suggestion was based on the evidence of a small cohort of 60 patients from China for whom HCQ demonstrated a reduction of

proteinuria by 48% versus 10% in placebo group, under 6-month follow-up treatment [25]. No clinical data are available in non-Chinese population.

5. Cyclophosphamide

It is recommended only in rapid progressive clinical course [11].

6. Calcineurin inhibitors

Showed nephrotoxicity and lack of efficacy [26].

7. Azathioprine

Combined with low-dose of prednisone showed no additional benefits in clinical course compared with placebo [27].

8. Leflunomide

Leflunomide combined with low-dose prednisone versus high-dose prednisone showed more serious adverse effects and similar efficacy [28].

9. Budesonide

It represents a synthetic second-generation corticosteroid with a coating pH-sensitive formula in order to deliver budesonide in the lower small intestine to the Peyer's patch areas (targeting gut lymphoid tissue). NEFECON, a patented oral formulation of budesonide demonstrated a dose depended proteinuria reduction (-27.3% with 16 mg/day Budesonide and -21.5% in 8 mg/day budesonide, treated for 9 months period) in a Phase II, placebo-controlled and double-blind trial, involving 150 subjects. A Phase III study (NEFIGARD) is ongoing since 2018 with NEFECON 16 mg/day versus placebo, in IgAN biopsy proven with persistent proteinuria (proteinuria > 1g/day) despite RAS blockade. Preliminary data from 200 subjects showed a mean proteinuria reduction of -31% in budesonide group versus +5% increment in placebo group. Final results are predicted for February 2023 [29].

10. Other ongoing clinical trials are included in Table 1.

CONCLUSIONS

Immunosuppression therapy can slow the progression to ESRD in IgAN cases with persistent proteinuria over 0.75 g/day, despite RAS blockers up titrated to maximal doses and hypertension control. This is mostly supported by corticosteroid regimens. MMF and HCQ may be an alternative immunosuppression treatment but larger cohorts with non-Chinese population are needed. Despite benefits from corticosteroid regimens, trials showed high risk of adverse effects, mostly in eGFR under 30 mL/min, diabetics, obesity, peptic ulcerations or osteoporotic

TABLE 1. Ongoing clinical trials with interim result

Study	Design	Pathway of action	No. of patients	Antiproteinuric effect	Adverse events
Atacicept [30] (NCT02808429)	Phase II study placebo controlled randomized 1:1:1 (25 mg/week:75mg/week:placebo)	Human TACI Ig fusion Inhibits B-cell stimulating factors (APRIL and BAFF)	16	Mean proteinuria reduction of -18.67% with 25 mg/week and -25.34% with 75 mg/week	none
Blisibimod [31] (BRIGHT-SC) (NCT020662684)	Phase I study placebo controlled multiple ascending doses (50;150;450;1350 mg/ monthly)	Monoclonal anti-body against BAFF	27	Significant proteinuria decrease	none
Adrenocorticotropic hormone [32] (ACTHAR) (NCT01103778)	Phase III study open label (80 mg twice weekly for 6 months)	Agonist melanocortin 1 receptor (MC1R) (B-cell inhibitor)	19	Mean proteinuria reduction of > -30%	weight gain hyperglycemia hypokalemia hypertension respiratory tract infections
Fosfamatinib [33] (NCT02112838)	Phase II study randomized 1:1:1 (100 mg BID/150 mg BID//placebo BID for 12 weeks)	Inhibitor of SYK (a cytosolic non-receptor protein tyrosine kinase with pro-inflammatory response)	76	No significant proteinuria decrease	8 serious adverse events 6 subjects discontinued the treatment
Sparsentan [34] (PROTECT study) (NCT03762850)	Phase III study randomized 1:1 (Sparsentan vs. Irbesartan)	Dual inhibitor of endothelin-1 and ANG II	380	Mean reduction of -30% proteinuria in 9 months	none
Iptacopan [35] (NCT04557462)	Phase II study placebo-controlled	C3 inhibitor by B factor inhibition (complement control factor)	112	Mean reduction of -23% proteinuria at 90 days of use	none
Narsoplimab [36] (NCT0222254)	uncontrolled	Monoclonal antibody against MASP-2 (Mannan binding lectin – associated serin proteases)	58	Mean reduction of -61.4% albuminuria	none
Ravulizumab [37] (NTC04564339)	Phase II study placebo controlled	Anti C5 complement factor Similar with Eculizumab	not yet recruiting	-	-

patients, therefore it should not be used for this population. Because almost 40% from IgAN biopsies showed active crescents, MEST-C classification with the latest proposed C-grading, may be an important tool in discovering the appropriate risk benefits balance and also patients suitable for this therapy. The new synthetic corticosteroid, budesonide, improved with a pH-sensitive coating formula, is a promising treatment in IgAN, with fewer adverse effects and a more targeted mechanism of action. Final results from phase III NEFIGARD study are awaited in the next year.

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