IgA Nephropathy: “The Times They Are a-Changin”

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Abstract

Background: Primary IgA Nephropathy (IgA N) is a very common and often progressive glomerular disease. At present, the diagnosis of IgA N is totally dependent on kidney biopsy, but the prospect for a future diagnosis by means of a “liquid” biopsy is promising. A great deal is now understood regarding its diverse clinical and pathological features as well as its epidemiology, genetics, prognosis, and pathogenesis. Treatment approaches are now on increasingly solid evidence-based grounds, but many uncertainties continue to be devil the field. Better means of categorization of patients into a hierarchy of progression risk at the time of diagnosis will undoubtedly refine and personalize treatment decisions. Summary: The panorama of treatment strategies is undergoing a rapid transformation, largely due to an increase in large randomized clinical trials testing available agents and novel therapeutic classes. It is anticipated that the combination of better prognostic tools and new strategies for treatment of IgA N will alter the landscape of therapeutic algorithms for patients with IgA N. Key Messages: This review seeks to describe some of the evolutionary changes in the approach to treatment of IgA N, to place them in the context of current management, and to identify knowledge gaps that need to be addressed.

Introduction

In the fall of 1963, the future Nobel Laureate in Literature, Bob Dylan, penned the lyrics of a song that was to become emblematic of a generation. “The times they are a-changin” is a suitable metaphor for what is currently happening in the field of IgA Nephropathy (IgA N), slightly more than 50 years since its original description as a clinico-pathological entity by Berger and Hinglais [1]. We now understand its frequency in global populations, its origins in genetic ecology, its most common pathogenesis, and its diversity of clinical and pathological forms [2]. A kidney biopsy is still required for diagnosis, but promise exists for noninvasive (“liquid” biopsy) diagnostic approaches in the not too distant future. At present, estimates of the prevalence of IgA N in specific geographical area will vary according to the prevailing (local) indications for performance of a kidney biopsy among patients suspected of harboring the disease. Less selective approaches, including preimplantation biopsies of kidneys donated by living or deceased individuals, give a much higher prevalence of “lanthanic” IgA deposition (up to 24%) than that generated by studies of clinically indicated kidney biopsies [3]. In such “lanthanic IgA deposition, C3 is commonly, but not universally, co-depos-
ited, but IgG is not [3], implying a possible pathogenic role of co-deposition of IgG, perhaps related to the presence of IgG anti-gd1aGAl autoantibodies (see below).

We are also getting ever better at predicting outcomes in individual patients and cohorts by use of biochemical parameters (such as estimated glomerular filtration rate [eGFR] and protein excretion) combined with classifications of pathological findings (such as the OXFORD-MEST-C system, and patterns of deposition of C3 or C4) [4, 5]. Two areas have lagged behind these advancements; namely, as stated above, we still must rely on a kidney biopsy for diagnosis and treatment remains an unsettled area in many clinical circumstances. But, recent events driven by numerous well-designed and executed interventional trials are beginning to clear the haze of uncertainty that has clouded a vision of clarity in therapy of IgA N. The field is brimming with exciting new developments, novel strategies, and critical reexamination of older treatment modalities. There is an air of optimism that we may yet conquer the tendency of this chronic disease process to progress toward kidney failure. This brief review will highlight some of these advances, and identify some of the major knowledge gaps that need to be filled.

Risk-Prediction: An Art Becoming a Science

The assessment of the “natural history” of a disease is a vital, indeed irreplaceable, part of therapeutic decision-making and interventional trial design. This is especially true in IgA N because of its clinical, pathological, and possibly pathogenic heterogeneity. Many efforts to create a systematic ranking system for likely prognosis, focused primarily on the end point of kidney failure (end-stage kidney disease) [2, 4, 6]. These systems have been useful in predicting outcomes in large cohorts, but not unexpectedly, less useful at the individual patient level. Long-term studies have shown that for the great majority of adult patients with IgA N a slow, but variable, progression to kidney failure is the rule with about 10–60% of patients reaching kidney failure after a decade of follow-up, averaging about 1.5–2% per year [7, 8]. Much faster progression is seen in those uncommon patients with extensive crescentic disease [9] and much slower progression, if any, in those patients with very minor clinical expression or the small number of patients with steroid-responsive Nephrotic syndrome [10]). Superimposed lesions, like Alport syndrome, LECT2 Amyloidosis, anti-GBM disease, or thrombotic microangiopathy with minimal histological change nephropathy, can markedly affect prognosis [11]. Whether a discrete “point-of-no-return” really exists in IgA N is not certain [12], but most studies suggest that progression to kidney failure is inexorable once the eGFR falls below 20–30 mL/min/1.73 m² in the presence of advanced chronic changes in kidney biopsy.

The field of risk stratification in IgA N has been greatly benefitted by the recent development of a new international risk-prediction tool from the International IgA Network [4]. This tool, employing combined clinical and histological variables (specifically the OXFORD-MEST classification system), can predict the kidney-specific end points of a 50% decline in kidney function or kidney failure (ESKD) with quite reasonable accuracy. It was developed and validated in large, multiethnic cohorts (n = 3,927). The variables used in the predictive modeling were (1) age; (2) eGFR, mean arterial pressure and proteinuria at biopsy; (3) OXFORD-MEST score; (4) use of renin-angiotensin system inhibitor; and (5) immunosuppression use at biopsy (a web-based tool is available at QxMD- https://qxmd.com/calculate-by-qxmd). Models with and without ancestry/ethnicity were developed for prediction of patient-centered kidney end points at 5 years after the diagnostic biopsy. Interestingly, crescents (the C category in the MEST-C score) were not included in the final model as this lesion was highly correlated with ancestry/ethnicity and with immunosuppression use. Other studies have somewhat inconsistently shown that the degree of crescents (C0 none, C1 1–24% and C2 ≥25% of glomeruli involved with cellular or fibro-cellular crescents; not counting fibrous crescents) correlate independently with outcomes, namely, in C1 lesions without immunosuppression, and C2 lesions with or without immunosuppression [9]. Nevertheless, this highly refined but very practical tool showed that low, intermediate, higher, and highest risk groups to have a 1.5, 4.7, 13.9, and 46.5% 5-year risk of the kidney endpoints in the ancestry/ethnicity risk-adjusted model [4]. A recent simulation study has shown that use of this International IgA N prediction tool for making treatment decisions (use of immunosuppressive agents) leads to improved outcomes relative to the use of proteinuria alone as the prediction parameter [13]. It is also important to point out that a low and intermediate-risk pool would not be good candidates for enrollment in a 3 year trial of a new therapy for IgA N unless very large numbers of patients are randomized (high risk of a Type 2 error).

In sum, risk-prediction in IgA N has become a practical clinical and morphologic exercise with a high degree of sophistication, reliability, and clinical decision-making utility. Whether newer prognostic biomarkers, like plasma suPAR, complement activation assessment, urinary matrix metalloproteinase-7, urinary proteomics, sophis-
ticated morphologic analysis of pathology (beyond OXFORD-MEST-C), or quantification of hematuria as well as others [14–20], will achieve clinical utility in risk-prediction for IgA N remains for future study, but they will all have to be compared with the current “gold-standard” provided by the International IgA N prediction tool. In particular, the persistence and magnitude of hematuria, not currently a part of the international IgA N prediction tool, needs much more attention as a potential prognosis determining variable in IgA N [18]. Measurement of IgG auto-antibody targeted to aberrant galactose deficient (gd) IgA1 may be the best serological marker of progression risk [16] and the risk of posttransplant recurrence of IgA N [21], but these assays are not yet commercially available. Serum levels of gd IgA1 are not consistently associated with a worse prognosis, and it is unclear if these levels can be used to probe the efficacy of therapy in IgA N [19]. It is useful to recall an observation from more than 3 decades ago that phenytoin is very effective in lowering the serum IgA concentration (and presumably the gd IgA1 levels as well) and circulating immune complex levels, but aside from a diminution in episodes of hematuria has no beneficial impact on pathology [22]. Such studies have generally been underpowered to examine impact on patient-centered outcomes. Many challenges lie ahead in efforts to bring serum and/or urine biomarkers in IgA N to a level of validation and utility comparable to other autoimmune glomerular diseases, such as membranous nephropathy, ANCA-vasculitis, and anti-GBM disease.

**Therapy of IgA N: The Pipeline Expands Rapidly**

For many decades, the therapeutic armamentarium for the intermediate to high-risk patient with IgA N was rather limited. Renin-angiotensin system inhibition (RASI; with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were widely adopted for those patients with persisting proteinuria >0.75–1.0 g/d, largely on the basis of pioneering studies of Praga et al. and Woo et al. [23, 24]. This treatment approach is only effective for curtailing the development of progression to more advanced forms of CKD or kidney failure if the proteinuria decreases persistently to less than 0.75–1.0 g/d. Combinations of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker were suggested to have greater efficacy in the COOPERATE trial, but this report was later retracted for concerns about validity. A benefit of dual RASI therapy could not be demonstrated in a retrospective examination of the STOP-IgA N trial (see below) [25]. Some studies combining direct renin inhibitors combined with angiotensin receptor blockers have been conducted but these are generally short term and this combination is not currently recommended for treatment of IgA N [26]. Whether RASI inhibition is also of value in low-risk patients with <0.75 g/d accompanied by histological signs of chronicity is uncertain as this would require large trials of very prolonged duration. Blood pressure control with systolic blood pressures of 120–130 mm Hg is also desirable, especially in patients at high risk of cardiovascular disease, primarily to avoid premature mortality from stroke and/or heart failure. It is of interest that the risk of mortality among patients with IgA N compared to age-adjusted controls is not increased until the patients have reached kidney failure [27].

**Steroid Therapy of IgA N: Yes or No and if Yes, When?**

While a substantial (30–50%) fraction of patients with noncrescentic IgA N will respond to optimized regimens of RASI with a persisting diminution of proteinuria to <0.75–1.0 g/d and thereby have an improved prognosis [28], those that do not experience such an anti-proteinuric effect, are “at risk” for a progressive course, ending in kidney failure. Steroid administration, added to RASI, seems to be beneficial in such cases. Observational studies have suggested a beneficial effect of steroids added to RASI, but only when the proteinuria is >1.0 g/d [29]. Such beneficial effects are only present after 5–6 years of follow-up when the proteinuria is between 1 and 3 g/d, and after about 2–3 years of follow-up in those with proteinuria >3 g/d [29]. Large meta-analyses of trials involving steroids, usually given in initially high doses and then a tapering schedule over 6 months have shown a weighted mean reduction of protein excretion of about 0.4–0.45 g/d and a reduced relative risk of kidney failure to about 0.39 (95% CI = 0.19–0.79) compared to controls [30]. A recent Cochrane Collaboration analysis has also suggested efficacy for steroid therapy [31]. But many trials are small and of short duration. In addition, some, but not all, studies have shown an increased risk of adverse events, mainly infection, with high-dose of steroids [30, 31]. Recently, the large STOP-IgA N and the TESTING (high-dose) (TESTING-I) RCTs have raised additional issues and concerns regarding the safety and efficacy of short-term, high-dose steroid therapy in IgA N (unresponsive to optimal supportive therapy with RASI, with proteinuria >0.75 and >1.0 g/d, respectively) [28, 32]. The STOP-IgA N trial (n = 162) included patients assigned to supportive care only (n = 80) and those assigned to supportive care plus immunosuppression (n = 82). The immunosuppression group included a steroid monotherapy group (n = 56), all with eGFR ≥60 mL/min/1.73 m² and a combined
immunosuppression group \((n = 26)\) – sequential cyclophosphamide and azathioprine (AZA) – with an eGFR of <60 mL/min/1.73 m\(^2\). STOP IgA N was conducted in an open-label fashion in European Caucasians only [28]. Here, we will only consider the steroid monotherapy group. This group had a baseline eGFR of >60 mL/min/1.73 m\(^2\) (averaging 73 ± 11 mL/min/1.73 m\(^2\)) and a baseline urinary protein excretion of 1.6 ± 0.8 g/d. The cyclical steroid regimen of Pozzi et al. [33] (combining IV and oral steroids) was used for steroid-related immunosuppression. The follow-up was 36 months, and the OXFORD-MEST-C scores were not initially reported or used for stratification (but were subsequently analyzed in a post hoc fashion) [34].

The TESTING-I (high-dose) trial \((n = 262\), 95% Chinese) employed a Manno et al. [35] style steroid regimen (0.4–0.6 mg/kg/d, maximum dose = 48 mg/d for 2 months, then tapered over 4–6 months), in a masked, double-blind, placebo-controlled fashion [32]. The baseline proteinuria was >1.0 g/d in all subjects and averaged 2.4 ± 1.2 g/d (50% higher than in STOP-IgA N), and the baseline eGFR was 59 ± 25 mL/min/1.73 m\(^2\) (20% lower than STOP IgA N). The follow-up was only 2.1 years as the trial was stopped prematurely for safety (infections, mainly pneumocystis pneumonia with deaths). Pneumocystis prophylaxis was not routinely employed in either the STOP-IgA N or TESTING trials. The OXFORD-MEST-C scores were not reported in the TESTING-I trial.

The outcomes of these 2 large trials were quite different in several respects [36]. In STOP IgA N, clinical remissions (reductions in proteinuria/hematuria) were more common in the steroid-treated group than the control group, but a progressive loss of renal function (>−15 mL/min of eGFR) was not different in the steroid-treated and nonsteroid-treated groups at the end of follow-up. Perhaps no effect on kidney function decline would be expected by 3 years considering the rather low levels of sustained proteinuria at baseline. Adverse events were increased in the steroid-treated group, but none were serious and no deaths were reported. In a 10-year follow-up of 149/162 subjects randomized in the STOP-IgA N trial, Rauen and colleagues report that no differences in outcome were observed between the supportive care only and the supportive care plus immunosuppression (steroids only and sequential CYC-AZA combined) [37]. However, in those subjects with an eGFR of <60 mL/min/1.73 m\(^2\) in whom a regimen of sequential CYC-AZA was employed, a trend toward poorer outcomes at between 2 and 6 years but not at last follow-up, was seen in the immunosuppressive treated compared to the supportive care only group. The opposite was observed in the group with eGFR ≥60 mL/min/1.73 m\(^2\), where those treated with steroids seemed to have better outcomes at between 2 and 6 years of follow-up but not at the last follow-up. Although the OXFORD-MEST-C scores were not reported initially in the STOP-IgA N study, this deficiency has been partially remedied by a post hoc analysis of 70 biopsies in the original cohort of 162 patients [34]. In those with a C0 lesion \((n = 48)\), the eGFR loss >15 mL/min was seen in 6 of 24 subjects (25%) given supportive care only and in 10 of 24 subjects (42%) given immunosuppression (steroids or CYC-AZA) plus supportive care. In those with a C1/2 lesion \((n = 22)\), the eGFR loss of >15 mL/min was seen in 5 of 8 subjects (63%) given supportive care and in only 2 of 14 subjects (14%) given immunosuppression (steroids or CYC-AZA). Overall, although the numbers of patients studied are small, this post hoc analysis did not suggest efficacy of immunosuppression in IgA N without crescents (C0), and however, it suggests that immunosuppression might be beneficial in those patients with C1/2 lesions, and this finding deserves further study in larger numbers of subjects.

In the TESTING-I high-dose trial (prematurely stopped for safety reasons after 2.1 years), the findings were, similar to the STOP-IgA N trial in some respects only [32]. Steroid therapy (oral methyl-prednisolone in high doses) was associated with a decrease on proteinuria (as also seen in the STOP-IgA N trial), but in addition, eGFR was better preserved and doubling of the serum Cr was less often observed in the steroid-treated group. However, the decline in eGFR was much higher in the control arm \((-6.95\) mL/min/1.73m2\) of the TESTING-I high dose trial than the STOP-IgA N supportive care only group \((-1.6\) mL/min/1.73m2\) after a comparable follow-up period. This may have been due to the different ancestral make-up of the 2 trials (Asian vs. Europeans) and/or the higher level of baseline proteinuria in the TESTING-I high dose trial. Nevertheless, because of the premature stoppage due to safety issues generated by infectious complication of steroid use, the findings are mainly hypothesis generating. Subsequent to these findings a second TESTING trial (TESTING-II- low dose) was designed and initiated. This placebo-controlled double-blind RCT trial (NCT# 01,560,052) is still in progress. The TESTING trials are the largest ever conducted in IgA N (N = 502), 262 from the original high-dose cohort and a further 240 from the low-dose cohort, with randomized subjects mainly from China, Australia, India, South Asia, Canada – not USA, or Europe. Stratification by OXFORD-MEST-C scores will be employed. All randomized
patients will have a baseline proteinuria of >1.0 g/d after rigorous RASt pre-randomization therapy. eGFR ranges between 20 and 120 mL/min/1.73 m² will be allowed. The steroid (oral methyl-prednisolone) treatment regimen used is 0.4 mg/kg/d (maximum dose 24–32 mg/d) for 2 months then tapered over 6–9 months. Pneumocystis pneumonia prophylaxis is used in all randomized subjects. The primary outcome (examined after 1–5 years of follow-up) is a 40% decline from baseline eGFR, ESKD, or renal death and in the low-dose cohort a decline in urine protein to Cr ratio and change in eGFR at 6 and 12 months. The TESTING-II low-dose trial is fully recruited and initial results are expected in 2021. This trial will hopefully answer questions regarding the safety and efficacy of a lower dose, systemically acting, and steroid regimen and will also help to clarify the role of OXFORD-MEST-C scoring in making treatment decisions at the time of diagnostic kidney biopsy.

The STOP-IgA N and TESTING trials have been pre-occupied by an examination of the efficacy and safety of systemically acting steroid preparations, their dosing requirements and tolerance. Simultaneously, a very novel approach was taken focusing on the formulation of the steroid and the site of action of the agent. Nefecon is a specially formulated version of budesonide (a very potent steroid 2-3X more active than Prednisone) designed to release the active steroid in the ileum, where it can act on Peyer patches to impact lymphoid tissue elaboration of potentially pathogenic IgA1 and subsequently enter the portal circulation and undergo “first-pass” hepatic metabolism into inactive conjugates, thus minimizing systemic steroid exposure [38]. A preliminary Phase 2b, double-blind, placebo-controlled trial (NEFIGAN) demonstrated reduced protein excretion and stabilization of eGFR in 100 subjects allocated to an 8 or 16 mg/d dose of Nefecon compared to 50 subjects receiving a placebo [38]. The NEFIGAN trial (Calliditas Therapeutics; www.Calliditas.com). This may mean that a new era of a special formulation for steroid administration for IgA N might emerge.

One way or the other, we are getting very close to some definitive answers to the question posed at the beginning of this section. At this moment, my own impression is that the answer is YES-steroids work in reducing long-term risks of ESKD, but with some caveats about patient selection, role of OXFORD-MEST-C scores, the application of prognostic tools, and about optimum steroid dosage, formulations, regimens, duration of therapy, and overall safety. These caveats may be clarified very soon. Stay tuned.

Nonsteroid Therapy of IgA N: Lots of Promise, but the Devil Is in the Details!

Once 1 move beyond RASts and steroids for treatment of IgA N the level of uncertainty increases substantially, but the level of hope and promise also elevates. A number of commercially available agents, including mycophenolate mofetil (MMF), AZA, mizoribine leflunomide, cyclophosphamide, cyclosporin, tacrolimus, everolimus, AC-THAR gel, rituximab (RTX), and hydroxychloroquine, have been tried with varying degrees of success or failure [39]. Space does not permit a comprehensive and detailed examination of all such trials, so only a few will be examined in some detail. Choosing 1 or another of these agents is a difficult dilemma as the evidence underpinning their safety and efficacy is generally weak and influenced greatly by the clinical and pathological characteristics of individual patients.
Antimetabolites

Mycophenolic acid salts (MMF and Mycophenolate sodium) have been most extensively studied, including in RCT [40]. The results have been quite mixed, with favorable results (in terms of decreased proteinuria and suppression of progression) seen in Asians, and lack of efficacy in non-Asians (European and American cohorts). The reasons for these discrepant results based on geography or ancestry are poorly understood. None of these trials have used histological criteria for inclusion or outcomes, and re-biopsy has usually not been a part of the study. This deficiency was in part remediated by a retrospective study from the Imperial College in London [41]. Treatment with MMF has been employed since 2,006 by this group for treatment of IgA N when endothelial hypercellularity is seen on initial biopsy (E = 1 by the OXFORD-MEST-C classification). In a small cohort (n = 18), in whom a re-biopsy was performed 24 months (median) after MMF therapy, improvement in histology, and IgA deposition was observed [41]. In the absence of a control group, it is hard to know what this really means over the long-term, but it raises the possibility that histological criteria may have utility in selecting patients for “personalized” therapy protocols. In addition, some studies (in Chinese) have suggested that MMF may exert a steroid sparing effect (particularly when active “proliferative” lesions are present in the initial biopsy) [42]. The combination of MMF with low-dose prednisone might be as effective as high-dose prednisone alone—thus obviating the adverse side effect profile of high-dose prednisone, alluded to above. However, if the TESTING-II (low-dose) trial shows efficacy and safety, any advantage of MMF will be canceled. Clearly, much more work is needed to fully clarify the role of MMF in treatment of IgA N, particularly among non-Asians.

AZA (a purine synthesis inhibitor) has no proven value in IgA N and may actually be harmful [43, 44] Leflunomide seems to be efficacious and safe, but all of the studies so far have been carried out in Asians [45]. Leflunomide also seems to show a “steroid-sparing” effect like MMF [46]. Mizoribine, an agent with biological effects similar to AZA, has been commonly used in Japan to treat IgA N, but the paucity of well-controlled RCTs make it difficult to assess the efficacy and safety of this approach [47]. The effect of inhibitors of the mammalian target of rapamycin in IgA N have not been adequately evaluated, but posttransplant immunosuppression with Everolimus + steroids seems to reduce the risk of recurrence of IgA N in kidney transplants [48].

Calcineurin Inhibitors

The beneficial effects and safety of calcineurin inhibitors (CNI; cyclosporin, tacrolimus, and voclosporin) have been inadequately evaluated in IgA N [49]. A recent Cochrane Collaboration analysis failed to find any convincing evidence of efficacy [31]. Small RCTs of relatively short duration have shown an anti-proteinuric effect of CNIs in IgA N [31], but long-term benefits on progression to ESRD and the potential for cumulative nephrotoxic effects are largely unknown.

Cytotoxic Agents

The principal cytotoxic agent used in IgA N is cyclophosphamide (CYC; IV or oral). Early encouraging studies of sequential CYC – AZA therapy in patients with slowly progressive (noncrescentic) disease [50] could not be confirmed by the STOP-IgA N trial (see above), even after a follow-up of up to 10 years [37]. As noted above, observational studies patients with IgA N and a C-1 lesion (1–24% crescents) seem to progress less rapidly when immunosuppression (including steroids in high dosage) is utilized compared to conservative (supportive) treatment alone; whereas, those with C-2 lesions (≥25% crescents) seem to have similar rates of progression, with or without immunosuppressive therapy [9]. These observations promote a hypothesis that there may be a “window of opportunity” for immunosuppression in patients with a C-1 lesion, but the efficacy of this approach is in doubt because of the findings in the STOP-IgA N trial after up to 10 years of follow-up (see above) [37]. As stated above, patients with C1/2 lesions might be benefited by immunosuppression [34], but this is based on only a small number of patients (n = 22) studied in a post hoc fashion. Patients with rapidly progressive glomerulonephritis (RPGN) and extensive crescents (>50% of glomeruli involved) are very uncommon in IgA N, and few studies have been performed to help guide evidence-based therapy for this exceptional group [51], but by analogy to other forms of extensive crescentic disease with RPGN, aggressive treatment with pulse methyl-prednisolone, oral prednisone, cyclophosphamide and sometimes plasma exchange (PLEX) are often employed (more out of desperation than high-level evidence guided) (see below) [52, 53].

Procedures

Tonsillectomy combined with steroid pulse therapy is commonly used for treatment of moderate to severe IgA in some prefectures of Japan, but seldom used elsewhere. The evidence for efficacy is weak and largely observational [54, 55]. Two RCTs showed a possible effect on protein-
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43 ± 12 mL/min/1.73 m² and median urinary ACR = 0.92 enrolled 4,304 patients with CKD (baseline mean eGFR = shown in a landmark RCT (DAPA-CKD) [61]. This study specifically dapagliflozin, was strongly and unexpectedly below). A possible role for SGLT2 inhibitors (SGLT2i), specifically in ANCA-vasculitis [58] cannot be extrapolated to the use of this modality in IgA N with RPGN.

Biologic Immunomodulation

Only one small (pilot) controlled trial of RTX in IgA N has been reported [59]. No benefits were observed, including no effects on circulating anti-gd IgA1 autoantibodies. On the other hand, other studies have suggested a beneficial effect of RTX in the related condition of IgA vasculitis [60]. The utility of biologic immunomodulators remains as a topic of great interest, due to the well-established autoimmune nature of the disease, and the failure of RTX to modify the course of IgA N in a single study should not be taken as evidence for lack of efficacy for whole class of biologic immunomodulatory agents (see below).

Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

A possible role for SGLT2 inhibitors (SGLT2i), specifically dapagliflozin, was strongly and unexpectedly shown in a landmark RCT (DAPA-CKD) [61]. This study enrolled 4,304 patients with CKD (baseline mean eGFR = 43 ± 12 mL/min/1.73 m² and median urinary ACR = 0.92 g/g) randomized to receive dapagliflozin (10 mg/d) or a placebo in addition to standard of care (such as RASi). 34% of the randomized subjects were Asian. The primary end points were a sustained decline of eGFR of at least 50% from baseline values, kidney failure or death from kidney or cardiovascular causes. The follow-up was only 2.4 years as the trial was stopped for “overwhelming efficacy.” Of the randomized subjects, 2,906 had Type 2 Diabetes mellitus (T2DM); 1,398 had nondiabetic CKD. 270 patients had IgA N (38 with concomitant T2DM and 232 with IgA N only). This makes DAPA-CKD 1 of the largest RCTs of therapy for IgA N yet conducted. At the end of the trial, the hazard rate for the composite primary end point was 0.64 (95% CI = 0.52–0.798, p < 0.001) in those with T2DM and 0.50 (95% CI = 0.35–0.72, p < 0.001) for those participants without T2DM. A detailed prespecified subgroup analysis of the DAPA-CKD trial also showed a hazard ratio for the composite primary end point of 0.43 (95% CI = 0.26–0.71) in subjects with glomerulonephritis (n = 695, including IgA N) [62]. Thus, SGLT2i (dapagliflozin) in conjunction with RASi has a strong rationale for addition to the roster of effective agents for IgA N (possibly with eGFR > than about 20–30 mL/min/1.73 m²) with persisting proteinuria after an adequate course of RASi). Additional agents (such as canagliflozin and empagliflozin) in the same therapeutic class may soon be added. These striking results are likely to have a profound impact on the design and execution of future trials of novel agents for treatment of IgA N, depending on whether a RCT of SGLT2i was carried out specifically in IgA N with stratification according to the international risk-prediction tool confirms the dramatic findings of DAPA-CKD.

Other Agents

ACTHAR gel has been studied in 1 small uncontrolled (pilot) trial [63]. An effect to decrease proteinuria was noted but the long-term effects on progression and relapse rates were not studied. A well-powered RCT with a follow-up of at least 3–5 years is needed to clarify the potential role of ACTHAR gel in management of IgA N. Hydroxychloroquine was shown to be effective in IgA N in a small (n = 60) placebo-controlled RCT from China [64]. The baseline eGFR was 54 mL/min/1.73 m² and urinary albumin to Cr ratio was 0.93 g/g. Ninety-eight percent of patients were receiving RASi. An anti-proteinuric effect was noted at 6 months. This study needs to be confirmed in non-Asians and long-term follow-up is needed.

Novel Agents under Investigation: A Powerhouse Pipeline!

The “treatment gaps” identified in the prior discussion has generated much interest in developing novel strategies for the treatment of IgA N, resistant to conventional measures, such as RAS inhibition. The stunning results of the DAPA-CKD trial [61, 62], and the anticipated results of the ongoing NEFIGARD and TESTING-II trials may have a profound effect on the design and execution of trials of novel agents that are emerging in increasing numbers, particularly if a new “standard-of-care” emerges. Table 1 provides a summary of the extent and character of these trials that focus on immunomodulation, inhibition of complement activation, and hemodynamic intervention, among others. Space does not permit a detailed analysis of each and every trial, but the next few years may bring new paradigms in management of IgA N.
Table 1. A compilation of selected novel nonsteroid-related studies in progress for treatment of IgA N

<table>
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<th>Therapeutic class (route)</th>
<th>NCT# (expected date of completion)</th>
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<tr>
<td>OMS-721-narsoplimab (Omeros)</td>
<td>3</td>
<td>Complement Inhibitor-MASP inhibitor (ARTEMIS-IgA N) (IV)</td>
<td>03608033 (4/2023)</td>
</tr>
<tr>
<td>ALN-CC5-Cemdisarin (Alnylam)</td>
<td>2</td>
<td>Complement Inhibitor-C5 inhibitor (SC)</td>
<td>03841448 (2/2023)</td>
</tr>
<tr>
<td>CCX-168-avacopan (Chemocentryx)</td>
<td>2</td>
<td>Complement inhibitor-C5a receptor inhibitor (oral)</td>
<td>02384317 (12/2016 – completed)</td>
</tr>
<tr>
<td>Ravulizumab (Alexion/Astra-Zeneca)</td>
<td>2</td>
<td>Complement inhibitor-C5 inhibitor (IV)</td>
<td>04564339 (7/2023)</td>
</tr>
<tr>
<td>APL-2 (Apellis)</td>
<td>2</td>
<td>Complement inhibitor-C3b inhibitor (SC)</td>
<td>03453619 (12/2022)</td>
</tr>
<tr>
<td>CHK-01-atresentan (Chinook)</td>
<td>3/2</td>
<td>Endothelin A receptor inhibitor (oral)</td>
<td>04573478 (12/2025)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>04573920 (12/2023)</td>
</tr>
<tr>
<td>Sparsentan (Travere/Retrophin)</td>
<td>3</td>
<td>Combined endothelin A/angiotensin II receptor inhibitor–PROTECT (oral)</td>
<td>03782850 (4/2023)</td>
</tr>
<tr>
<td>RTA-402-bardoxolone methyl (Reata)</td>
<td>2</td>
<td>Nuclear factor erythroid-derived 2-related factor 2 (Nrf-2) agonist – PHOENIX (oral)</td>
<td>03366337 (1/2019 – completed)</td>
</tr>
</tbody>
</table>

IV, intravenous; SC, subcutaneous.
Conclusions

IgA N is without doubt a very common, organ-specific autoimmune glomerular disease of reasonably well-defined pathogenesis diagnosed (presently) only by kidney biopsy including immunofluorescence microscopy. In many, but not all, cases progression toward kidney failure is noted, and this can be predicted by a multivariable prognostic tool, allowing for the practice of “personalized” management. A persistent reduction in proteinuria by 25% or more from baseline values (and perhaps a remission of hematuria as well) seems to reduce the likelihood of progression. Good blood pressure control (<120–130 mm Hg, systolic) and use of RAS inhibition is the first step in treatment of moderate-to-severe proteinuria persists (>0.75–1.0 g/d), and kidney biopsy shows features indicative of a poorer prognosis. However, adjunctive treatment with SGLT2i looms as a new regimen for IgA N. Steroid treatment of those who do not respond to aggressive supportive therapy (RASi and possibly SGLT2i) and who are classified as high risk by the International IgA N prediction tool is the most likely next step, but considerable uncertainty exists concerning optimal dosing, duration, drug formulation, and regimens. These uncertainties will likely be resolved in the next few years as pivotal trials record their results. The milieu for therapeutic strategies beyond aggressive supportive therapies and steroids remains rather murky and seems likely to be conditioned by classification of the renal histological lesions, clinical course, and promising biomarkers of poor outcomes. The pipeline of novel agents involving immunomodulation, complement inhibition, inflammation, and hemodynamic intervention is deep and very encouraging. Taking the clinical characteristics and pathological heterogeneity among patients IgA N into account, it is very difficult to generate an algorithm for management that could be used in individual patients with IgA N, with reasonable prospects that it would not become obsolete soon after its development. This is the reason why this communication does not advance a new algorithm. An update of the KDIGO Clinical Practice Guidelines for IgA N will likely be published soon [65] and will serve as the reference manual for management of IgA N, at least for a while. But, guidelines for treatment of IgA N in children will still be missing [66].

The entire field of IgA N therapeutics seems to be moving in the direction of “personalized medicine” based on individualized risks of progression using relatively simple and available clinical and pathological tools, as modified by demographics (age, gender, and ancestry). The efficacy and safety of individual treatment regimens and agents (and their combination or sequential use) informed by rigorously designed RCT will then allow the selection of a regimen that is optimally positioned to yield patient-centered benefits in a safe manner. Data concerning the latter component of personalized medicine is expanding rapidly, yet we do not yet have full agreement on what constitutes “optimal” management for individuals embraced within the wide spectrum of patients with IgA N. Novel paradigms of treatment are very likely to appear in the next few years – a very gratifying change after decades of very slow progress.

Conflict of Interest Statement

The author discloses the following interests: Compensated Consulting agreements with Chemocentryx, Ionis, Horizon Pharma, Omeros, BioCryst, Apellis, Calliditas, Traverce (formerly Retrophin), Equilibrium, Novartis. The author owns <100 shares of Reta, Inc. The authors hold no relevant patents or external funding. The author receives a semiannual Stipend and Royalties from Editorial services rendered to UpToDate (Wolters-Kluwer) and Karger, Inc, and Royalties from Oxford Medical Publisher for a book on Treatment of Primary Glomerulonephritis.

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Author Contributions

The author takes sole responsibility for the content of the manuscript. The author conceived, wrote, and edited the manuscript.

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