Treatment of IgA Nephropathy

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IgA nephropathy remains the most common primary glomerular disease worldwide. It affects children and adults of all ages, and is a leading cause of end-stage kidney disease, making it a considerable public health issue in many countries.

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1. Introduction

IgA nephropathy (IgAN) remains the most common primary glomerular disease in the world. It often affects younger adults, and in approximately 30% of patients it progresses to end-stage kidney disease (ESKD) within 20 years of diagnosis, placing a considerable burden on individuals, carers and healthcare systems globally. To date there is no approved disease-specific treatment available. The role of corticosteroids in the management of IgAN is uncertain, and there has been no consistent evidence to support the use of other existing immunosuppressive agents. Over the past few decades, significant advances have been made in understanding the complex pathogenesis that underlies IgAN. This has driven an explosion of interest in developing new therapeutic strategies for this condition, and several global phase II and phase III clinical trials are currently underway.

2. Current Treatment Strategies

Despite advances in the understanding of the underlying pathogenic mechanisms in IgAN, there are currently no approved treatments that can specifically alter the production of galactose-deficient IgA1 (Gd-IgA1) nor its corresponding autoantibody that are central to the disease process, IgA1-immune complex formation, or their deposition within the glomerular mesangium.

Long-term registry data have shown that patients with IgAN who have preserved kidney function, non-visible haematuria and minimal proteinuria <0.5 g/day are at low risk of progressive kidney disease, and do not require disease-specific treatment [1]. However, these patients should be followed up at least annually, so that any worsening of proteinuria, development of chronic kidney disease (CKD) or hypertension can be detected and managed appropriately.

The primary focus of management for those who have proteinuria above this threshold should be on optimized goal-directed supportive care. This includes renin-angiotensin-aldosterone system (RAAS) blockade, with either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), but not both, to the maximum tolerated amount, and addressing overall cardiovascular risk, including strict blood pressure control (to a recommended target of <130/80 mm Hg for those with proteinuria > 0.3 g/day and <125/75 mm Hg when proteinuria is >1 g/day) [2], dietary sodium reduction, smoking cessation if appropriate, weight control, and exercise. The Supportive versus immunosuppressive Therapy for the treatment of Progressive IgA Nephropathy (STOP-IgAN) trial has provided robust evidence to support this approach [3]. All participants in this trial underwent a 6-month run-in period, where an intensive program of supportive care was provided utilizing the measures outlined above. A key finding was that around one-third of participants, originally thought by their treating nephrologist to be suitable for treatment of their disease with immunosuppression, were no longer eligible to continue in the trial after this period, as proteinuria had fallen to below the set criteria to proceed.

A substantial proportion of patients will have persistent proteinuria of >1 g/day despite these measures, and observational data have demonstrated that these patients are at high risk of progressive kidney disease and ESKD. Reducing proteinuria to below this threshold is also associated with improved renal outcomes [4]. Long-term follow-up data from the STOP-IgAN trial have shown that IgAN still has a poor prognosis in those with persistent proteinuria, even with optimized supportive care, with almost half of the participants reaching the composite of death, ESKD, or decline in estimated glomerular filtration rate (eGFR) of over 40% over a median time interval of 7.4 years [5]. In the next sections, we will discuss potential additional treatments to supportive care.

3. Systemic Corticosteroid Treatment

Corticosteroids have long been used in the management of IgAN, due to their anti-inflammatory and immunosuppressive effects, but their role is controversial. Many of the clinical trials that have supported their use were conducted at a time when the concept of optimized supportive care was not well established, meaning that trial participants were not consistently treated to strict blood pressure targets and the use of RAAS inhibitors was variable. In addition, data regarding adverse events were often not systematically collected.

In an early randomized controlled trial by Pozzi et al., treatment with corticosteroids resulted in significantly reduced proteinuria and prevented progression to ESKD over a 10-year follow-up period [6]. The treatment regimen included pulsed IV methylprednisolone at induction, and at months 2 and 4, with alternate day oral prednisolone for 6 months. This would be expected to be associated with significant toxicity, yet only one significant adverse event of steroid-induced diabetes mellitus was recorded. In keeping with standard of care at the time, RAAS blockade use was low and the achieved blood pressure was higher than current treatment targets. Subsequent studies by Manno et al. and Lv et al. also reported a beneficial effect from a 6-month course of corticosteroids in high-risk patients, defined by having proteinuria > 1 g/day [7][8]. However, temporary discontinuation of RAAS blockade was mandated before re-introduction at baseline in both trials, and it is possible that a number of included patients would have responded to optimized RAAS blockade and supportive care alone.

Two recent RCTs have addressed these points, the STOP-IgAN and the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) studies, by including a run-in period where supportive care could be optimized. STOP-IgAN, conducted in Germany, compared intensive supportive care to immunosuppressive therapy (corticosteroids if estimated glomerular filtration rate (eGFR) was ≥60 mL/min/1.73m^2, or cyclophosphamide followed by azathioprine with prednisolone if eGFR was between 30–59 mL/min/1.73m^2) in patients at high risk of progressive kidney disease [3]. Although a reduction in proteinuria was observed in the immunosuppressed group compared to supportive care alone, there was no difference in eGFR decline between the groups, and more episodes of infection (with one fatal pneumonia) and other adverse events, including malignancy, impaired glucose tolerance and weight gain, occurred in those receiving immunosuppression. In a follow-up study, no significant difference in renal outcomes was observed between the immunosuppressed and supportive care groups at a median of 7.4 years follow-up [5]. The TESTING trial, conducted mainly in centers in China, of oral methylprednisolone vs. placebo in IgAN patients at high risk of progression was stopped early due to an excess of serious adverse events in the methylprednisolone group, including one fatal case of *Pneumocystis jirovecii*, although interestingly, there was a significant reduction in those reaching the composite renal outcome (40% reduction in eGFR, ESKD, or death due to renal failure) in this group [9]. Important differences between these two RCTs have been discussed in detail previously [10].

Currently, the risk-benefit ratio for corticosteroids in the treatment of IgAN remains uncertain, and significant questions remain regarding their optimum dose and duration, and patient selection. The TESTING low-dose study will assess whether a lower dose of methylprednisolone together with *Pneumocystis jirovecii* prophylaxis can be beneficial while avoiding the rate of serious adverse events observed in the earlier trial, and this is due to be reported in 2023 (ClinicalTrials.gov Identifier: NCT01560052). It should also be noted that corticosteroids are typically pursued as part of treatment in the rare circumstances where IgAN is associated with nephrotic syndrome, or with rapidly progressive glomerulonephritis. Both scenarios have been excluded from clinical trials addressing the benefit of steroids in the treatment of IgAN.

Forthcoming Kidney Disease: Improving Global Outcomes (KDIGO) guidelines emphasize that although patients with IgAN who have proteinuria >1 g/day despite 90 days of optimized supportive care can be considered for corticosteroid therapy, their clinical benefit is not established, and that it is much preferred that such patients be offered an opportunity to take part in a therapeutic clinical trial.

4. Clinical Trial Design in IgAN

There has been a welcomed increase in the number of clinical trials being performed in IgAN over the past decade. However, a number of difficulties are inherent to studying this disease. Firstly, it should be recognized that IgAN may not be a single disease, but instead may represent a common histological endpoint towards which distinct pathogenic mechanisms may contribute [11]. Its clinical presentation and rate of progression is highly variable between individuals, with evidence that these factors vary according to geographical location and ethnicity. The implication of this is that findings from trials conducted in certain populations may not be applicable to others. Secondly, in most cases, IgAN is a slowly progressive disease, where the traditional renal endpoints of death, dialysis, or doubling of serum creatinine may

take many years to occur. This has previously meant that clinical trials have been prohibitively expensive and difficult to conduct, especially as IgAN is a rare disease. Incorporation of a ‘pre-‘ and ‘post-treatment’ kidney biopsy in clinical trials can yield significant mechanistic insights into a certain drug’s effectiveness, although this is an invasive procedure that is associated with a small risk of complications, and would not be accepted by all participants. Recent data have demonstrated that proteinuria reduction and the rate of change/slope of eGFR decline are accurate surrogate endpoints for these renal outcomes [12][13]. Trial-level analysis of 13 controlled trials in IgAN by a Kidney Health Initiative workgroup demonstrated an association between proteinuria reduction and effects on a composite of time to doubling of serum creatinine, ESKD or death, that was independent of the therapeutic intervention used [13]. These endpoints have recently been approved by the US Food and Drug Administration (FDA) for use in clinical trials in IgAN, generating further interest in drug development in this field.

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