An update on the treatment of IgA nephropathy

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Purpose of review
The treatment of IgA nephropathy (IgAN) has been limited by several controversies in the literature, including the benefits of corticosteroids in addition to optimized renin–angiotensin system blockers (RASBs), in those with lower estimated glomerular filtration rate (eGFR), or in different ethnic groups. Recent studies have attempted to address these issues.

Recent findings
Two observational studies suggest the efficacy of corticosteroids in those with lower eGFR, but with a higher risk of adverse events. The Supportive versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial compared immunosuppression with supportive care in addition to optimized RASB, and suggests that corticosteroids (but not cyclophosphamide/azathioprine) may reduce proteinuria but the effect on renal function is not clear, that immunosuppression is associated with a high risk of adverse events and that optimal RASB is very effective at lowering proteinuria and the short-term risk of renal function decline. The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) trial compared corticosteroids with placebo in addition to optimized RASB, and demonstrated a decreased risk of renal function decline and lower proteinuria, but a higher risk of adverse events. Additional trials demonstrate the potential efficacy of enteric-budesonide but not rituximab on proteinuria reduction, and conflicting findings with mycophenolate mofetil.

Summary
Until less toxic therapies for IgAN are available, treatment with corticosteroids will need to be made in the context of conflicting evidence, and should likely be limited to patients at highest risk of disease progression who understand the significant risk of adverse events.

Keywords
budesonide, corticosteroids, cyclophosphamide, IgA nephropathy, mycophenolate mofetil, rituximab, treatment

INTRODUCTION
IgA nephropathy (IgAN) is characterized by dominant or codominant mesangial IgA deposits on kidney biopsy, and is the most common type of glomerular disease worldwide \cite{1–3}. Although variants of IgAN exist with more extreme clinical presentations, it is most commonly a slowly progressive form of proteinuric kidney disease. IgAN is significantly heterogeneous, with a highly variable risk of progression to end-stage renal disease (ESRD) ranging between less than 10\% and more than 60\% after 10 years \cite{4} and substantial ethnic variation with Asian populations having a higher incidence of disease and a higher risk of renal function decline \cite{5–7}. These features have contributed to a dearth of high-quality clinical trials in IgAN and ongoing uncertainty regarding the optimal treatment strategy with immunosuppressive medications. This review will briefly summarize the evidence available at the time of the 2012 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for slowly progressive IgAN \cite{8–12}, and then will provide a critical appraisal of several recent clinical trials and observational studies that attempt to address prior controversies in the treatment of IgAN \cite{13\*,14\**,15\*,16}. This discussion does not relate to crescentic or minimal-change variants of IgAN.

CORTICOSTEROIDS IN IgAN
Although there are multiple studies that have investigated corticosteroids for the treatment of IgAN,
KEY POINTS

- Recent studies have addressed some of the existing controversies in the treatment of IgAN, including the uncertain benefit of corticosteroids in those with low eGFR, in different ethnic groups, or in addition to optimized RASB.
- Observational analyses suggest that corticosteroids may reduce the risk of renal function decline and improve proteinuria in patients with eGFR less than 60 ml/min/1.73 m², but with an increased risk of adverse events.
- The STOP-IgAN trial suggests that corticosteroids in addition to optimized RASB may reduce proteinuria but are associated with a high risk of adverse events, that optimization of RASB is highly effective at reducing proteinuria and the short-term risk of renal function decline, and that combination corticosteroids with cyclophosphamide followed by azathioprine is not effective.
- The TESTING trial suggests that corticosteroids in addition to optimized RASB may reduce the risk of renal function decline and improve proteinuria (including in those with lower eGFR), but was stopped early because of a significant increase in adverse events in the corticosteroid group; a second phase of the TESTING trial will study the efficacy of a lower dose of corticosteroids in a more multiethnic cohort.
- Until these results are available, the treatment of IgAN with corticosteroids should likely be limited to patients at highest risk of disease progression who understand and accept the significant risk of adverse events.

three clinical trials have historically contributed to the majority of evidence, and the baseline patient and study characteristics are shown in Table 1 [9–12]. The Pozzi trial randomized 86 Italian patients from 1987 to 1995 to receive either corticosteroid treatment for 6 months or supportive care. Because of the era in which the trial was conducted, very few patients were treated with renin–angiotensin system blockers (RASBs). After 5 years, the risk of doubling serum creatinine was 5% in the corticosteroid group compared to 26% in the control group (P = 0.005). Patients were subsequently followed in a posthoc observational study that confirmed a sustained benefit after 10 years in those treated with corticosteroids (3 vs. 47%, P = 0.0003) [17]. The Manno trial recruited 97 Italian patients with grade G2 lesions on renal biopsy within 1 year of recruitment. Although the histologic classification used in the trial has not been validated and is not routinely available in clinical practice [18], it was nonetheless used to augment clinical criteria to identify patients at high risk of disease progression. All patients had RASB withdrawn and were randomized to receive ramipril and 6–8 months of prednisone, or ramipril alone. After 8 years, the risk of either doubling serum creatinine or ESRD was 14.8% in the corticosteroid group compared to 47.9% in the control group (P = 0.003). The Lv trial recruited 63 Chinese patients, and similar to the Manno trial RASBs were withdrawn and patients were randomized to cilazapril and prednisone, or cilazapril alone. After 3 years, the risk of a 50% increase in serum creatinine was 3.4% in the corticosteroid group compared to 33.8% in the control group (P = 0.006).

All three trials have significant limitations, including open-label nonblinded designs and small sample sizes with relatively few outcome events. Baseline renal function was preserved in all three studies, so the benefit of corticosteroids in patients with lower estimated glomerular filtration rate (eGFR) is unknown. Given the known ethnic variability of IgAN, the generalizability of trial results from homogenous study populations is not clear. The use of RASB was either infrequent, or they were withdrawn prior to study entry. It is therefore uncertain if corticosteroids are effective after optimal RASB targeting blood pressure and proteinuria reduction. Importantly, none of the trials systematically captured and reported adverse events, so that the risks of treatment could not be weighed against the potential benefit. A meta-analysis of nine published corticosteroid trials in IgAN revealed suboptimal study designs with a high risk of bias, and suggested that corticosteroids were associated with a pooled relative risk of 0.32 [95% confidence interval (CI) 0.15–0.67] for halving eGFR or ESRD, but with more common adverse events (24 vs. 14%) [19]. As a result of these limitations, significant equipoise remained regarding the potential benefits of corticosteroids in IgAN.

CYCLOPHOSPHAMIDE IN NONCRESCENTIC IgAN

A single trial has suggested benefit from sequential treatment with corticosteroids and cyclophosphamide followed by azathioprine [12]. The Ballardie trial was a single-centre study from the United Kingdom that recruited 38 patients with serum creatinine 130–250 μmol/l that had increased by at least 15% over 1 year, and who were randomized to receive supportive care, or prednisolone with cyclophosphamide for 3 months followed by azathioprine. The study cohort was not well described (Table 1); however, baseline proteinuria was between 4.4 and 4.8 g/day and no patient had glomerular crescents on biopsy. After 5 years, renal failure was significantly less common in the treatment compared to control group (28 vs. 95%,
There are many limitations to this study, including suboptimal trial design with a high risk of bias, no background use of RASB, unclear generalizability because of limited description of the study cohort and incomplete reporting of adverse events. Two additional small randomized trials compared cyclophosphamide, dipyridamole and warfarin with supportive care, with no improvement in renal outcome [20,21].

However, multiple areas of uncertainty remain. What is the benefit of corticosteroids in those with eGFR less than 50 ml/min/1.73 m², or in addition to maximum RASB? What are the risks of corticosteroids? Are corticosteroids beneficial in all ethnic groups? Several recent studies have attempted to answer some of these questions, and are reviewed next.

### KDIGO GUIDELINE RECOMMENDATIONS

The 2012 KDIGO clinical practice guidelines for IgAN make the following recommendations [8]:

- Patients with persistent proteinuria at least 1 g/day after 3–6 months of optimized supportive care (including RASB) and eGFR more than 50 ml/min/1.73 m² can be treated with 6 months of corticosteroids (grade 2C).

- Noncrescentic IgAN should not be treated with corticosteroids combined with cyclophosphamide or azathioprine (grade 2D).

- Patients with eGFR less than 30 ml/min/1.73 m² should not be treated with immunosuppression (grade 2C).

### OBSERVATIONAL STUDIES

The Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA) study was a retrospective multicentre cohort study of 1147 mostly White patients from Europe that validated the Oxford MEST histologic score [22]. A recent secondary analysis of the VALIGA cohort sought to investigate the association between corticosteroid treatment and renal outcomes in those with lower eGFR [15]. One hundred eighty-four patients treated with corticosteroids and RASB were propensity score matched to 184 controls treated with RASB alone, in whom corticosteroid use was associated with a reduced risk of a 50% decline in eGFR or ESRD (hazard ratio (HR) = 0.48 (95% CI 0.28–0.82,
The benefit of corticosteroids was similar in the subgroup with baseline eGFR less than 50 ml/min/1.73 m^2 (HR = 0.38, 95% CI 0.18–0.82, \( P = 0.01 \)). A second study performed a patient-level meta-analysis of 325 patients from three randomized trials that compared supportive care with immunosuppression (corticosteroids alone or with azathioprine) [16]. Proteinuria over time did not change in the supportive care group but decreased in those given immunosuppression, a pattern which was similar in all three subgroups of baseline eGFR (<30, 30–60 and >60 ml/min/1.73 m^2). However, this effect may have been confounded by large differences in the use of RASB, and the risk of immunosuppression-related serious adverse events increased substantially from 2.3 to 15–30% with progressively lower eGFR. Although these observational analyses have limitations and do not replace the need for prospective randomized trials, they nonetheless provide valuable insight into the potential efficacy of immunosuppression in patients with lower renal function who were not included in previous trials, but this may come at the cost of increased toxicity and adverse events.

STOP-IgAN TRIAL

The multicentre Supportive versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial from Germany was the first immunosuppression study to emphasize optimization of supportive care prior to randomization, and to systematically capture and report adverse events [13*]. The trial included patients with proteinuria at least 0.75 g/day and either eGFR less than 90 ml/min/1.73 m^2 or hypertension, who subsequently underwent a 6-month run-in period during which RASB was maximized to control proteinuria and blood pressure. After the run-in period, patients were eligible to enter the trial if proteinuria was 0.75–3.5 g/day and eGFR had not declined to less than 30 ml/min/1.73 m^2 or by more than 30% from baseline, and were randomized to either continue supportive care or to immunosuppression based on the level of eGFR (>60 ml/min/1.73 m^2 received a ‘Pozzi’ corticosteroid regimen, and <60 ml/min/1.73 m^2 received a ‘Ballardie’ regimen of corticosteroids with cyclophosphamide followed by azathioprine). There were two primary outcomes evaluated after 3 years: clinical remission (PCR <0.2 g/g and eGFR within 5 ml/min/1.73 m^2 of baseline) and an eGFR decline at least 15 ml/min/1.73 m^2 from baseline. It should be emphasized that the trial was powered for clinical remission, and not for eGFR decline.

The trial enrolled 337 patients, of whom 162 ultimately underwent randomization (Table 2 [13*,14**] for baseline characteristics). During the run-in period, 106 patients achieved proteinuria reduction to less than 0.75 g/day, underscoring the efficacy of optimizing RASB and supportive measures. The primary analysis for the trial combined the two treatment groups. After 3 years, clinical remission occurred in 5% of the control group and 17% of the combined immunosuppression group (odds ratio (OR) = 4.82, 95% CI 1.43–16.30, \( P = 0.01 \)). This was
due predominantly to a reduction in PCR less than 0.2 g/g (Table 3 [13**]), with no difference between the
groups in stable eGFR within 5 ml/min/1.7 m$^2$ of
baseline. Mean proteinuria at 12 months was signifi-
cantly lower in the combined immunosuppression
group, but after 3 years the difference was no longer
significant (Table 3). However, there may have been a
differential proteinuria response depending on the
type of immunosuppression; there was a sustained
reduction in proteinuria over 3 years in the steroid
group but not in the cyclophosphamide/azathiop-
rine group. There was no difference between groups
in the risk of eGFR decline at least 15 ml/min/1.73 m$^2$
from baseline (OR $= 0.89$, 95% CI 0.44–1.81,
$P = 0.75$), or in the absolute reduction in eGFR ($= 4.7$
vs. $= 4.2$ ml/min/1.73 m$^2$, $P = 0.32$). Serious
adverse events were accurately captured, and were
more common than in prior trials occurring in 35% of
patients treated with immunosuppression including
one death due to sepsis.

Although the STOP-IgAN trial has been inter-
preted as a negative study that does not support the
use of immunosuppression [23,24], there are some
limitations that need to be considered. The study
pooled the two immunosuppression treatment
groups, which may not be appropriate if there is a
differential effect on the primary outcome such as
proteinuria, as suggested in Table 3. One expla-
nation for the lack of efficacy in the cyclophospha-
maine/azathioprine group may be a systematic
difference in patient characteristics compared to
the population studied in the original Ballardie trial,
including baseline proteinuria (2 vs. 4.4–4.8 g/day)
and the exclusion of patients with decreasing renal
function. The STOP-IgAN trial was primarily pow-
ered to detect a difference in clinical remission,
which it did in favour of immunosuppression. Al-
though this was due predominantly to changes in
proteinuria, a recent patient-level meta-analysis
validated short-term reduction in proteinuria as a
surrogate outcome in IgAN [25**]. Conversely, small
approximately 25% relative changes in eGFR, equiv-
alent to an absolute decline of 15 ml/min/1.73 m$^2$ as
used in the primary outcome, were not supported as
valid surrogate outcome measures by a joint
National Kidney Foundation and Food and Drug
Administration working group [26]. The trial was
too short and underpowered to detect larger
changes in renal function that are more established
outcome measures, such as a 50% decline in eGFR
that occurred in only 9% of the control group. The
low risk of renal function decline may be because of
the modest degree of proteinuria during the follow-
up period (PCR $= 1$ g/g over time in the control
group, equivalent to $= 1–2$ g/day). Proteinuria is
one of the strongest risk factors for disease pro-
gression in IgAN [27], and a recent observational
study demonstrated that although patients with
sustained proteinuria between 1 and 2 g/day have
an increased 10-year risk of poor renal outcome,
they have a very low risk within the short-term 3-
year follow-up duration of the STOP-IgAN trial
(Fig. 1) [27,28]. However, this also demonstrates
the benefit of aggressive optimization of supportive
measures that result in a sustained reduction in
proteinuria and a low short-term risk of renal
function decline.

**TESTING TRIAL**

The Therapeutic Evaluation of Steriods in IgA
Nephropathy Global (TESTING) trial is an inter-
national multicentre placebo controlled double
blind trial that has been presented in abstract format
but is not yet published (data provided by personal
communication with V. Perkovic) [14**]. Patients
underwent a 4-month run-in period to optimize
RASB, and were then randomized to 6 months of
methylprednisolone (0.8 mg/kg/day then tapered)
or placebo (Table 2). The study was stopped early

### Table 3. Proteinuria over time in the STOP-IgAN trial

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Combined IS group</th>
<th>Steroid group</th>
<th>CYC+Aza group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR (g/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.0</td>
<td>1.1</td>
<td>0.98*</td>
<td>1.2*</td>
</tr>
<tr>
<td>12 months</td>
<td>0.80*</td>
<td>0.57*</td>
<td>0.50</td>
<td>0.74</td>
</tr>
<tr>
<td>36 months</td>
<td>0.85**</td>
<td>0.76**</td>
<td>0.57</td>
<td>1.27</td>
</tr>
<tr>
<td>PCR $&lt; 0.2$ g/g (%)</td>
<td>11.3%</td>
<td>24.4%</td>
<td>30.9%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

*PCR values were not provided in the original article, and were instead estimated from the reported 24-h proteinuria values.

$P = 0.01$

$P = 0.66$

Aza, azathioprine; CYC, cyclophosphamide; IS, immunosuppression; N/a, not available.
after recruitment of only 262 mostly Chinese patients because of a significantly higher risk of serious adverse events in the corticosteroid group (14.7 vs. 3.2%, HR 4.95, 95% CI 1.87–17.0, \( P = 0.003 \)), including 11 serious infections, two of which were fatal. However, the corticosteroid group had a lower risk of a 40% decline in eGFR, ESRD or death due to renal disease (5.9 vs. 15.9%, HR 0.37, 95% CI 0.17–0.85, \( P = 0.019 \)), a slower rate of eGFR decline and lower proteinuria over time. This study had lower baseline eGFR than the Pozzi, Manno or Lv trials [9–11], and would have been able to address the controversy of treatment in those with reduced renal function. Although the interim results suggest a benefit of corticosteroids using a validated renal outcome measure, the substantial risk of serious adverse events raises doubts about the balance between safety and efficacy. A second phase of the TESTING trial is planned with more multiethnic representation and will compare lower dose methylprednisolone with placebo in hopes of maintaining efficacy while improving toxicity.

**OTHER TRIALS**

Altered function of gut-associated lymphoid tissue may play an important role in the immunopathogenesis of IgAN [29]. An enteric formulation of budesonide has been developed that targets release of the drug in the distal ileum wherein it affects local lymphoid tissue, with theoretically high first-pass metabolism in the liver resulting in low systemic exposure [30]. The NEFIGAN trial has been presented in abstract format, and compared enteric-budesonide with placebo [31]. The treatment group experienced not only a significant reduction in proteinuria, but also a substantial risk of steroid-related adverse events suggesting that there may be more systemic drug exposure than anticipated. Additional studies will be needed to determine if enteric-budesonide can improve renal outcome without the risk of systemic toxicity that was observed in the STOP-IgAN and TESTING trials. There have been several small trials studying mycophenolate mofetil (MMF) in IgAN with conflicting results [32–34]. A recent trial compared MMF with placebo in addition to RASB and fish-oil in 52 children and adults with IgAN [35]. The treatment group experienced not only a significant reduction in proteinuria, but also a substantial risk of steroid-related adverse events suggesting that there may be more systemic drug exposure than anticipated. Additional studies will be needed to determine if enteric-budesonide can improve renal outcome without the risk of systemic toxicity that was observed in the STOP-IgAN and TESTING trials. There have been several small trials studying mycophenolate mofetil (MMF) in IgAN with conflicting results [32–34]. A recent trial compared MMF with placebo in addition to RASB and fish-oil in 52 children and adults with IgAN [35]. The treatment group experienced not only a significant reduction in proteinuria, but also a substantial risk of steroid-related adverse events suggesting that there may be more systemic drug exposure than anticipated. 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Additional studies will be needed to determine if enteric-budesonide can improve renal outcome without the risk of systemic toxicity that was observed in the STOP-IgAN and TESTING trials.

**CONCLUSION**

Although recent studies were meant to address historical controversies in the treatment of IgAN, significant uncertainty remains. The existing data suggest that corticosteroids may be effective at lowering proteinuria when added to optimized RASB, but at the expense of a 15–30% risk of serious adverse events. The long-term follow-up and second phase of the TESTING trial will be required to confirm a benefit on renal function decline in a multiethnic population and in those with lower
eGFR, which can then be weighed against the short-term risks of treatment complications. Importantly, the STOP-IgAN trial demonstrates the impressive benefits of optimizing supportive care and provides further evidence in favour of the 2012 KDIGO guideline recommendations that cyclophosphamide followed by azathioprine should not be used in noncrescentic IgAN. Given that IgAN is largely asymptomatic and slowly progressive, new treatments are clearly required with more favourable safety profiles. Until these are available, clinical decisions regarding immunosuppression will need to be made in the context of conflicting evidence, and treatment with corticosteroids should likely be limited to patients at highest risk of disease progression, who accept the current uncertainty regarding long-term benefit, and who understand the risk of adverse events.

Acknowledgements
None.

Financial support and sponsorship
S.B. has a salary support award from the Michael Smith Foundation for Health Research.

Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• of outstanding interest


13. Randomized trial suggesting that optimization of RASB is highly effective at lowering proteinuria, that corticosteroids in addition to optimal RASB reduce proteinuria but with frequent adverse events and that cyclophosphamide/azathioprine is not effective. This is the first trial to use corticosteroids in addition to optimal RASB, and to accurately capture adverse event data.


16. Observational analysis suggesting that corticosteroids may be effective in those with lower eGFR.


Randomized trial comparing MMF with placebo that was stopped early because MMF failed to show a reduction in proteinuria, further contributing to the literature suggesting MMF is not effective in IgAN.
**Special commentary**


Randomized trial comparing MMF with low-dose steroids to high-dose steroids and showed a high but similar risk of proteinuria remission and no difference in adverse events, providing additional conflicting evidence regarding the use of MMF in IgAN.


Randomized trial comparing two doses of rituximab with supportive care, and failed to show any difference in proteinuria, eGFR, Gd-IgA1 or anti-Gd-IgA1 antibody levels. This contradicts the hypothesis that targeting B cells may be effective in IgAN.