Should immunosuppressive therapy be used in slowly progressive IgA nephropathy?

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IgA nephropathy is the most common glomerulonephritis worldwide and an important cause of ESRD. IgA nephropathy (IgAN) has variable clinical presentation: it is of minimal clinical significance in many people and rarely may cause rapidly progressive kidney failure in others. Typical however in nephrology practice is *a slowly progressive course*, characterised initially by hematuria and persistent proteinuria before arterial hypertension, followed by a progressive fall in GFR, supervenes.

Treatment of IgA nephropathy remains uncertain. By 2009 there had been five published randomised controlled trials (RCTs) of glucocorticoids with inconsistent findings leaving an unresolved controversy which explains the cautious advice given by the KDIGO Clinical Practice Guideline for

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Glomerulonephritis: "*We suggest that patients with persistent proteinuria ≥1 g/d despite 3-6 months of optimized supportive care (including ACE inhibitor or angiotensin receptor blocker and blood pressure control) and GFR >50 mL/min receive a 6 month course of corticosteroid therapy (2C).*" [1]

The STOP-IgAN trial [2] published in July 2015 adds valuable new information which should influence the views of clinicians and researchers on this issue.

What does this important study show?

STOP-IgAN tested the hypothesis that immunosuppressive therapy slows kidney disease progression effect in individuals who are at high risk of progression (assessed by persistent proteinuria >0.75g/24hr) despite receiving maximal supportive care focused on tight blood pressure (BP) control and minimization of proteinuria through optimal renin-angiotensin system (RAS) blockade over a 6 month run-in phase.

Recruited from 32 German centers between February 2008 and October 2011, 309 patients completed the run-in phase. While all had proteinuria >0.75g/24hr at the start of the run-in phase, proteinuria fell and remained below 0.75g/24hr in 94 patients (30%), who, based on the protocol, were not randomized due to lower risk for progression. All patients entering STOP-IgAN had already been under the care of a nephrologist, and 95% were already receiving RAS blockade; even so 30% responded to optimisation of supportive therapy with a reduction in proteinuria below the threshold for randomization. In addition, 38 were ineligible due to proteinuria above 3.5 g/day, estimated glomerular filtration rate (eGFR) below 30 ml/min per 1.73m^2, or a >30% increase in eGFR with run-in phase treatments. Of 177 eligible participants, the 162 who consented to randomisation either continued maximal supportive therapy or were randomized to one of two immunosuppressive regimens based on baseline eGFR. For those with eGFR > 60ml/min/1.73m^2, the immunosuppressive regimen was the 'Pozzi' regimen [3] of intravenous

and oral glucocorticoids for 6 months (methylprednisolone 1g daily for 3 days at the beginning of months 1,3, and 5 with oral prednisolone 0.5 mg/m^2 every 48 hours on the other days during the 6 month treatment period), then continuing supportive therapy alone until 36 months. For those with eGFR 30-59 ml/min/1.73m^2, the immunosuppressive regimen described by Ballardie et al was used [4] (oral cyclophosphamide 1.5 mg/kg/day for 3 months followed by azathioprine 1.5mg/kg/day from month 4 to month 36 accompanied by oral prednisolone at an initial dose of 40mg/day tapered over 36 months). For both eGFR ranges, supportive therapy included RAS blockers with other anti-hypertensive agents as necessary to achieve a target BP < 125/75 mm Hg. If proteinuria remained >0.75g/24hr despite BP control, the RAS blocker was increased to the maximum approved daily dose or to the highest dose at which patients did not have unacceptable side-effects.

Two primary end points were assessed at 36 months in hierarchical order: firstly, full clinical remission at the end of the trial (urine protein-creatinine ratio <0.2g/g and stable kidney function, defined by a fall in eGFR of less than 5ml/min/1.73m^2); secondly, a decrease in eGFR of at least 15ml/min/1.73m^2 from baseline to the end of the trial. If the first endpoint was statistically significant, the second endpoint was evaluated. Improvement in both endpoints was required to consider immunosuppressive therapy beneficial. Among those randomized, 95% of participants completed the 3-year trial. Overall event rates were low, with only 4 of 80 (5%) participants randomized to supportive care and 14 of 82 (17%) randomized to immunosuppression having full clinical remission at the final study visit (p=0.01). This higher rate of clinical remission with immunosuppression related exclusively to remission of proteinuria There was no significant difference in the number of participants with eGFR decline of 15 ml/min/1.73 m^2 between randomized groups [22 of 80 (28%) vs. 21/82 (26%), respectively, p=0.75]. Although the total number of serious adverse events was not higher with immunosuppression, there was a significant

increase in infections attributable to trial medication (including one death due to infection); additionally, especially with glucocorticoid monotherapy, participants had greater weight gain and impaired glucose tolerance. In sum, the authors concluded that STOP-IgAN did not support the hypothesis that immunosuppressive therapy slows kidney disease progression in the setting of optimised intensive supportive care. The remainder of this editorial discusses the strengths and limitations of STOP-IgAN and review the clinical implications in interpreting and implementing its findings.

1. *Was the ideal primary outcome measure used in STOP-IgAN?*The chosen primary outcomes included both changes in proteinuria and eGFR, and there was a divergent response to immunosuppression, complicating interpretation of the findings. There were more full clinical remissions based on reduction in proteinuria in those receiving immunosuppression. The proteinuria response however was heterogeneous; remissions of proteinuria were more likely in those with lower baseline proteinuria, while mean proteinuria for the entire study population was not different at 36 months. Althoughobservational data from other studies indicate that a sustainedreduction in proteinuria is predictive of improved outcome in IgAN [5], in STOP-IgAN there was no beneficial effect of immunosuppression on eGFR. We share the authors' interpretation of these study findings that remission of proteinuria without protection of eGFR is not a worthwhile goal given the adverse effects of the chosen immunosuppressive regimens.
2. *Was the choice of immunosuppressive regimens ideal?* The choice of two different regimens based on eGFR level is perhaps surprising, but these were the two most successful regimens in the literature in 2007 when the study protocol was approved. STOP-IgAN might be considered underpowered if each of the chosen regimens is considered separately: 55 had eGFR >60ml/min/1.73m^2 and received glucocorticoid monotherapy while 27 had lower eGFR levels and received combination immunosuppression. Nevertheless the original RCTs showing benefit for these regimens in the absence of intensive supportive care were smaller: only 43 patients

were randomised to glucorticoid monotherapy in the Pozzi trial [3] while only 19 received combination immunosuppression in the Ballardietrial [4]. The STOP-IgAN trial plan chose to analyse all of those receiving immunosuppressive therapy as a single group, and the complete absence of any trend towards benefit for either immunosuppressive regimen does not suggest any *post hoc* alternative analysis is justified.

3. *Was the study long enough?* A follow up period of only 36 months is relatively short in a slowly progressive entity like IgAN, and it should be noted that, in the Pozzi trial, there was growing kidney survival advantage as far as 10 years [3]. Nevertheless in STOP-IgAN there is not even evidence of a trend towards slowing eGFR decline at 36 months
4. . *Which patients were excluded?* STOP-IgAN provides no information on the treatment of patients with eGFR <30ml/min/1.73m^2 or with proteinuria >3.5g/24hr at the end of the run-in period as individuals with these characteristics were excluded from randomization.

How does this study compare with prior studies?

Five RCTs of glucocorticoids in IgAN had been published by 2009 reporting a benefit either in short term reduction of proteinuria or protection from ESRD in those receiving glucocorticoids [3, 6-9]. However the shared limitations of all these studies include the lack of uptitration of RAS blockade to minimise proteinuria, and the absence of a run-in period using supportive care alone before randomisation; this suggests that some of the benefit might be attributable to RAS blockade as much as to glucocorticoids. An entry criterion in all these studies was GFR> 50ml/min/1.73m^2.

Only one RCT had evaluated immunosuppression in IgAN with GFR 30-60ml/min/1.73m^2; this trialdemonstrated a benefit of cyclosphosphamide followed by azathioprine combined with oral glucocorticoids for 36 months. However in this study BP control was well above currently accepted

goals, and the use of RAS blockade was not reported [4]. Other recent RCTs of immune modulating therapy have used supportive therapy as 'standard of care' including three small studies of mycophenolate; among these trials, one, conducted in a Chinese population, indicated benefit [10] while two others, both in European populations, did not [11,12].

STOP-IgAN is the first published RCT of immunosuppressive therapy in IgAN to include a 6 month run-in period before randomisation in which supportive care, including blood pressure control and anti-proteinuric therapy using RAS blockade, was intensively optimised. It sets the standard for design of any study of a novel intervention in slowly progressive glomerulonephritis.

What should clinicians and researchers do?

When the management of slowly progressive IgAN is discussed by clinicians, the most frequently posed question is 'Should I *treat* this patient?' That phrasing itself is revealing since the question actually being posed is usually 'Should I *treat* this patient with glucocorticoids or another immunosuppressive regimen?' It seems that some clinicians do not regard intensive supportive care, as utilised in STOP-IgAN, as sufficient *treatment*and feel that perhaps more should be done, suggesting that immunosuppressive therapy is regarded by some as essential and effective in patients at high risk of progression.

The results of STOP-IgAN should make all clinicians caring for adults with IgAN re-evaluate their management approach. Where the findings of STOP-IgAN appear at conflict with previous literature, then STOP-IgAN should be given considerable weighting, given its use of intensive supportive care before randomization. For now a focus on intensive supportive care should be regarded as the most

powerful available treatment for slowly progressive proteinuric IgAN, and it should be deployed with intensity and attention to detail by all who treat this common glomerular disease.

For clinical triallists designing RCTs of immunosuppressive and other novel therapies in IgAN, the impact of intensive supportive care and its low toxicity should ensure it is the standard of care to which all novel agents are added. Happily our review in January 2016 of published protocols of ongoing trials in IgAN using www.clinicaltrials.gov indicates the near universal requirement for supportive therapy for several months before selecting those with persistent proteinuria as candidates to be randomised to any novel intervention. Nevertheless the requirement for supportive care to be optimized as in STOP-IgAN is not always explicit in these protocols, and it is to be hoped that investigators will apply supportive care with the same rigor shown in STOP-IgAN in order to be able to test new therapies with confidence.

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