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What does STOP-IgAN tell us about how to treat IgA nephropathy?

[1]E Rutherford, [2]PB Mark
[1]*Clinical Research Fellow, Division of Cardiovascular and Diabetes Medicine, Medical Research Institute, University of Dundee, Dundee, UK;*
[2]*Clinical Reader in Nephrology, Institute of Cardiovascular and Medical Sciences, BHF Glasgow Clinical Research Centre, University of Glasgow, Glasgow, UK*

TITLE Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

AUTHORS Rauen T, Eitner F, Fitzner C et al.

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***Correspondence to** E Rutherford*
Division of Cardiovascular and Diabetes Medicine
Medical Research Institute
Ninewells Hospital & Medical School
Dundee DD1 9SY
UK

***e-mail** e.rutherford@dundee.ac.uk*

SUMMARY

The Intensive Supportive Care plus Immunosuppression in IgA Nephropathy (STOP-IgAN) trial was designed to investigate the outcomes of immunosuppressive therapy, when added to maximal supportive care, in patients with IgA nephropathy (IgAN). This was a multicentre, open-label, randomised, controlled trial with a two-group, parallel group design.

Following screening, 337 participants were recruited from 32 nephrology centres across Germany. The main inclusion criteria were biopsy confirmed primary IgAN, age 18–70 and a proteinuria level above 0.75 g/day plus hypertension, impaired renal function (estimated glomerular filtration rate [eGFR] <90 ml/min/1.73m^2), or both. Patients with eGFR <30 ml/minute/1.73 m^2, those with rapidly progressive crescentic IgAN, secondary IgAN and other chronic renal diseases, or who had previously received immunosuppression were excluded.

The first stage of the trial involved a six-month run-in phase where all patients received intensive supportive care including renin angiotensin system (RAS) blockade to lower blood pressure (BP) to a target below 125/70 mmHg. If proteinuria persisted above 0.75 g/day once this target BP was achieved, the dose of RAS blocker (either angiotensin converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB] or both) was increased as tolerated up to the maximum approved dosage. Participants were seen seven times during this period. In total, 34% of patients had a response to supportive care during this period with proteinuria falling to below 0.75 g/day. These responsive patients were excluded from the randomisation phase of the study.

Following the run-in phase, 162 participants with persistent proteinuria more than 0.75 g/day but less than 3.5 g/day were randomised to the 3-year study phase. These participants were randomly assigned either to continue with maximal supportive care alone (80 participants), or to receive maximal supportive care plus immunosuppressive therapy (82 participants).

Depending on the eGFR, the immunosuppression given in the immunosuppression arm of the study varied. Patients with eGFR between 30 and 59 ml/min/1.73m^2 received cyclophosphamide (1.5 mg/kg/day) for 3 months, followed by azathioprine (1.5mg/kg/day) during months 4–36, plus oral prednisolone initially at dose of 40 mg/day, tapered to 7.5 mg/day by month 6 of the study and continued on this dose until the study end. Those with eGFR of ≥60 ml/min/1.73m^2 received glucocorticoid monotherapy for six months. They received intravenous methylprednisolone (1 g/day) as three pulsed doses at the start of months 1, 3 and 5 and oral prednisolone (0.5 mg/kg) every 48 hours on the other days.

The primary outcomes of the study were i) full clinical remission defined as proteinuria with a protein:creatinine ratio of <0.2 and stable renal function with decrease in the eGFR of <5 ml/min/1.73m^2 from the baseline eGFR at the end of the 3 year trial phase and ii) a decrease in the eGFR of at least 15 ml/min/1.73m^2 from baseline eGFR.

After three years, 14 participants in the immunosuppression group met the first primary outcome measure of full clinical remission, compared to only four participants in the supportive therapy alone group. This difference was statistically significant (p = 0.01). However, participants who had a full clinical remission had lower baseline levels of proteinuria than those who did not. There was no statistical difference in the number of patients in each group with a decrease in eGFR of at least 15 ml/min/1.73m^2 (28% in the supportive

care group vs 26% in the immunosuppression group) with no significant difference in the rate of decline of eGFR between groups.

There were more episodes of infection (including one fatal pneumonia) in the immunosuppression group, of which 25% were considered directly related to immunosuppression. There were also more episodes of neoplasia, impaired glucose metabolism and bodyweight gain in the immunosuppression arm.

The investigators stated, 'We could not confirm our hypothesis that additional immunosuppressive therapy would provide substantial kidney-related benefits in patients with high risk IgAN.'

OPINION

IgAN is the most common primary glomerulonephritis in the world (including Scotland).[1] Approximately one quarter of individuals diagnosed with IgAN with significant proteinuria will progress to end stage renal disease requiring dialysis or a kidney transplant within 20–25 years of presentation.[1] The prognosis is worse for those patients with persistent proteinuria.[1–3] In this group, approximately 50% may reach end stage renal disease within 10 years.[3] RAS blockade to aggressively control BP and reduce proteinuria is the mainstay of treatment. Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines also recommend use of immunosuppression with glucocorticoids if proteinuria remains above 1 g/day with maximally tolerated RAS blockade.[4] However, with the exception of those with nephrotic range proteinuria (>3.5 g/day),[5] the evidence base behind this strategy is relatively weak.[6] The STOP-IgAN trial addresses this area of uncertainty.[7]

The first piece of knowledge we gain from this study is that immunosuppression in patients with stage 1–3 chronic kidney disease caused by IgAN without nephrotic range proteinuria is of very limited benefit when added to maximal supportive therapy.[7] Previous studies, which inform the KDIGO guidelines, have shown some benefit from immunosuppressive therapy.[4,8–12] However, as the STOP-IgAN investigators highlight, these studies lacked a run-in period where RAS blockade was maximised, and RAS blockade was either temporarily stopped pre-baseline or was inconsistent throughout the studies.[6–12]

Further questions remain unanswered about immunosuppression in IgAN. First, the follow up in STOP-IgAN was too short to determine if there is longer-term benefit gained from remission of proteinuria, which was achieved in a greater proportion of patients treated with immunosuppression.[7] Second, due to the indolent yet progressive nature of IgAN, patients present at different stages in the disease. Some patients may have had haematoproteinuria for years prior to diagnosis. For immunosuppression to be effective there should be minimal irreversible renal fibrosis present. Finally, the individual subgroups treated with the various immunosuppressive regimens were small.[7] It is also unclear if more specific future immunosuppressive regimes (e.g. blisibimod, spleen tyrosine kinase inhibition) in the era of 'precision medicine' may be more effective than the broad based immunosuppressive regimens employed in STOP-IgAN. The experience of STOP-IgAN highlights the challenges of testing new therapies in IgAN.

Perhaps the real success of this trial is the demonstration that traditional supportive therapy for IgAN is effective in the medium term – 34% of participants in STOP-IgAN achieved significant reduction in proteinuria.[7] With effective RAS blockade and BP control, proteinuria can be reduced significantly. Furthermore, with reduction in proteinuria one can expect an improved longer-term prognosis with slower rate of decline of eGFR.[7,13] Remarkably, mean BP in STOP-IgAN was 126/78 mmHg.[7] The investigators must be commended on this achievement; unfortunately real life rarely replicates the controlled environment of a clinical trial. This trial[7] does provide further evidence that we should be aggressively pursuing lower BP targets and maximising RAS blockade to reduce proteinuria even if, or when, these BP targets are achieved.

It is notable that approximately 42% of randomised participants in STOP-IgAN received both ARB and ACEI therapy simultaneously.[7] Subsequent to three recent trials,[14–16] the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a warning against this combination, because of increased risk of hyperkalaemia, hypotension and impaired renal function.[17] STOP-IgAN had only one serious adverse event (in the supportive arm) associated with increased serum creatinine and potassium.[7] The lack of serious complications of simultaneous ARB and ACEI in STOP-IgAN is probably due to intensive study monitoring. In clinical practice, where this level of monitoring is impractical, clinicians pursuing dual RAS blockade in this patient group would be contravening MHRA advice. We recommend maximal single-agent RAS blockade while heeding MHRA guidance.

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