Articles

Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

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Summary

Background IgA nephropathy is thought to be associated with mucosal immune system dysfunction, which manifests as renal IgA deposition that leads to impairment and end-stage renal disease in 20–40% of patients within 10–20 years. In this trial (NEFIGAN) we aimed to assess safety and efficacy of a novel targeted-release formulation of budesonide (TRF-budesonide), designed to deliver the drug to the distal ileum in patients with IgA nephropathy.

Methods We did a randomised, double-blind, placebo-controlled phase 2b trial, comprised of 6-month run-in, 9-month treatment, and 3-month follow-up phases at 62 nephrology clinics across ten European countries. We recruited patients aged at least 18 years with biopsy-confirmed primary IgA nephropathy and persistent proteinuria despite optimised renin-angiotensin system (RAS) blockade. We randomly allocated patients with a computer algorithm, with a fixed block size of three, in a 1:1:1 ratio to 16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, or placebo, stratified by baseline urine protein creatinine ratio (UPCR). Patients self-administered masked capsules, once daily, 1 h before breakfast during the treatment phase. All patients continued optimised RAS blockade treatment throughout the trial. Our primary outcome was mean change from baseline in UPCR for the 9-month treatment phase, which was assessed in the full analysis set, defined as all randomised patients who took at least one dose of trial medication and had at least one post-dose efficacy measurement. Safety was assessed in all patients who received the intervention. This trial is registered with ClinicalTrials.gov, number NCT01738035.

Findings Between Dec 11, 2012, and June 25, 2015, 150 randomised patients were treated (safety set) and 149 patients were eligible for the full analysis set. Overall, at 9 months TRF-budesonide (16 mg/day plus 8 mg/day) was associated with a 24·4% (SEM 7·7%) decrease from baseline in mean UPCR (change in UPCR vs placebo 0·74; 95% CI 0·59–0·94; p=0·0066). At 9 months, mean UPCR had decreased by 27·3% in 48 patients who received 16 mg/day (0·71; 0·53–0·94; p=0·0092) and 21·5% in the 51 patients who received 8 mg/day (0·76; 0·58–1·01; p=0·0290); 50 patients who received placebo had an increase in mean UPCR of 2·7%. The effect was sustained throughout followup. Incidence of adverse events was similar in all groups (43 [88%] of 49 in the TRF-budesonide 16 mg/day group, 48 [94%] of 51 in the TRF-budesonide 8 mg/day, and 42 [84%] of 50 controls). Two of 13 serious adverse events were possibly associated with TRF-budesonide—deep vein thrombosis (16 mg/day) and unexplained deterioration in renal function in follow-up (patients were tapered from 16 mg/day to 8 mg/day over 2 weeks and follow-up was assessed 4 weeks later).

Interpretation TRF-budesonide 16 mg/day, added to optimised RAS blockade, reduced proteinuria in patients with IgA nephropathy. This effect is indicative of a reduced risk of future progression to end-stage renal disease. TRF-budesonide could become the first specific treatment for IgA nephropathy targeting intestinal mucosal immunity upstream of disease manifestation.

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Introduction

Primary IgA nephropathy is the most prevalent chronic glomerular disease worldwide, with patients often diagnosed as young adults.[1] About 20–40% of patients progress to end-stage renal disease within 10–20 years of diagnosis.[2–4] Major risk factors for progression to end-stage renal disease are persistent proteinuria, hypertension, and reduced glomerular filtration rate (GFR).[1,3,5,6] Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for glomerulonephritis recommend renin-angiotensin

system (RAS) blockade with angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line treatment for patients with IgA nephropathy with proteinuria of more than 1 g/day (recommendation level 1B), and suggest up-titration as far as tolerated to the maximum recommended dose to achieve proteinuria of less than 1 g/day (recommendation level 2D).[7] For patients with persistent proteinuria of more than 1 g/day and GFR greater than 50 mL/min per 1·73 m² despite 6 months' optimised RAS blockade, KDIGO

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Research in context

Evidence before this study
We searched PubMed up to April 26, 2016, with no start date restrictions, for published papers with no language restrictions about targeted-release formulation (TRF) of budesonide using the following search terms "targeted-release", "budesonide", "TRF-budesonide", and "NEFECON". We identified one relevant paper. In 2011, Smerud and colleagues reported an open-label, uncontrolled, exploratory phase 2a trial, in which 16 patients with IgA nephropathy received TRF-budesonide. Treatment for 6 months resulted in a statistically significant reduction in proteinuria and was well tolerated.

Added value of this study
To our knowledge, this phase 2b trial is the only randomised, double-blind, placebo-controlled trial to investigate and show that TRF-budesonide, additional to optimised renin-angiotensin system blockade, reduced proteinuria and stabilised estimated glomerular filtration rate in patients with immunoglobulin A

(IgA) nephropathy at risk of progression to end-stage renal disease. At 9 months, mean urine protein creatinine ratio had decreased by 24% in all TRF budesonide-treated patients combined versus an increase of 3% in placebo-treated patients. The effect was sustained throughout follow-up; mean urine protein to creatinine ratio (UPCR) decreased by 32% from baseline at 12 months for 16 mg/day versus <1% for placebo. Changes in 24-h protein excretion, urine albumin to creatinine ratio, and 24-h albumin excretion were consistent with the UPCR data. For 9 months, eGFR was stable with TRF-budesonide but decreased 10% with placebo. These effects are indicative of a reduced risk of future progression to end-stage renal disease.

Implications of all the available evidence
TRF-budesonide has the potential to become the first IgA nephropathy-specific treatment targeting intestinal mucosal immunity upstream of disease manifestation, reducing the risk of progression to end-stage renal disease.

suggest 6 months' treatment with high-dose systemic corticosteroids (recommendation level 2C).[7] However, use of high-dose systemic corticosteroids is associated with increased risks of adverse events and sequelae such as serious infections, hypertension, weight gain, diabetes, and osteoporosis.[8–10] The benefit of systemic immunosuppression, in addition to dietary restrictions and use of multiple drugs to optimise the RAS blockade has recently been questioned in the STOP-IgAN trial.[11] A targeted treatment with a favourable risk–benefit profile is needed for patients with IgA nephropathy who are at risk of progression to end-stage renal disease.

Evidence suggests a role for the mucosal immune system in the pathogenesis of IgA nephropathy.[1,12,13] In patients with IgA nephropathy, mucosal B lymphocytes located in Peyer's patches are thought to be primed to produce IgA1 that is galactose deficient (GdIgA1), which can form large immune complexes with anti-glycan IgG antibodies in the circulation.[1,14–16] These complexes can bind to glomerular mesangial cells resulting in stimulation of cell proliferation, release of inflammatory mediators that promote proteinuria, and fibrotic remodelling, ultimately leading to loss of renal function.[1,15] This pathogenesis suggests that local immunosuppression of mucosal B-lymphocyte activation and proliferation in Peyer's patches could attenuate GdIgA1 production,[17] thereby reducing subsequent pathophysiological changes, assessed as a reduction in protein excretion by the kidneys.

A novel, oral, targeted-release formulation of the glucocorticosteroid budesonide (TRF-budesonide; Nefecon [Pharmalink AB, Stockholm, Sweden]) was developed to release the drug in the distal ileum, which has a high density of Peyer's patches. The safety profile of TRF-budesonide was anticipated to be superior to high-dose systemic corticosteroids because of its extensive first-pass metabolism—less than 10% of budesonide enters

systemic circulation.[18] In a previous exploratory phase 2a trial,[19] 16 patients with IgA nephropathy received TRF-budesonide (8 mg/day) for 6 months. The treatment resulted in a statistically significant reduction in proteinuria and was well-tolerated. In this phase 2b trial we aimed to evaluate the safety and efficacy of two different doses of TRF-budesonide in patients with IgA nephropathy who were at risk of progression to end-stage renal disease due to persistent proteinuria despite optimised RAS blockade therapy.

Methods

Study design

We did a randomised, double-blind, placebo-controlled phase 2b trial in patients with biopsy-confirmed primary IgA nephropathy and overt proteinuria considered at risk of progressing to end-stage renal disease. This trial was done at 62 nephrology clinics across ten European countries (Belgium, Czech Republic, Denmark, Finland, Germany, Italy, Spain, Sweden, the Netherlands, and the UK; appendix). The competent authorities and ethics committees for participating centres approved the trial, which was conducted from Dec 11, 2012, to June 25, 2015, in accordance with Good Clinical Practice and the Declaration of Helsinki, 2008.

Patients

We recruited men or women aged at least 18 years with biopsy-confirmed primary IgA nephropathy and overt proteinuria for the run-in phase. All patients provided written informed consent before enrolment. Inclusion criteria for randomisation to treatment included estimated GFR (eGFR) of at least 45 mL/min per 1·73 m² and a urine protein creatinine ratio (UPCR) of more than 0·5 g/g or urinary total protein of at least 0·75 g/day—levels that would be considered to increase the risk of

See **Online** for appendix

progression to end-stage renal disease.[20] We used either 24-h protein excretion or UPCR on the 24-h collection of urine to determine eligibility to overcome possible collection errors and deviations from normal creatinine excretion (eg, physically active and muscular men), thus minimising the risk of unintentionally excluding patients. Full eligibility criteria are in the appendix.

Procedures

Trial medication was an oral capsule formulation of TRF-budesonide (Nefecon) or placebo, designed to provide sustained release of active compound that was delayed until the capsule reached the distal ileum,[21] targeting the site with a high density of Peyer's patches.

After screening, eligible patients were enrolled into a 6-month run-in phase, a 9-month treatment phase, and a 3-month follow-up phase; patient eligibility was assessed before run-in and treatment phases. During run-in, RAS blockade was optimised by up-titrating ACEIs and ARBs to a maximum recommended dose or maximum tolerated dose (in keeping with established clinical practice), to a target blood pressure of less than 130/80 mm Hg, UPCR of less than 0·5 g/g, and urine protein of less than 0·75 g/day. At the end of run-in, patients with persistent proteinuria (UPCR ≥0·5 g/g or proteinuria ≥0·75 g/day) despite optimised RAS blockade, eGFR (estimated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] serum creatinine equation,[22] ≥45 mL/min) or measured GFR ≥45 mL/min per 1·73 m², and blood pressure 160/100 mm Hg or less were eligible for randomisation to treatment. Run-in phase directives are detailed in the appendix.

An independent Data and Safety Monitoring Board (DSMB) monitored all safety issues and reviewed data at the interim analysis.

Randomisation and masking

Patients were stratified according to their baseline UPCR (≤0·9 g/g and >0·9 g/g) at month 0 (baseline). We randomly allocated patients to treatment groups using a computer algorithm method of permuted blocks. Within each block, patients were allocated in a 1:1:1 ratio to 16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, or placebo. All patients continued optimised RAS blockade treatment throughout the trial. Randomisation was done by Pharma Consulting Group AB (Uppsala, Sweden).

The trial was double-blind. Therefore, throughout the trial and the analyses, allocation to treatment groups was unknown to each patient, all trial staff (including the investigators and other staff who performed the randomisation and analyses), the sponsor, and the DSMB (the DSMB reviewed masked safety data and unmasked data were available should there be concerns).

To ensure masking, placebo capsules provided by the sponsor had the same appearance and route of administration as the active capsules. Patients self-administered masked capsules, once daily, 1 h before breakfast during the treatment phase. During follow-up (months 9–12), patients who received 16 mg/day TRF-budesonide during months 0–9 were tapered to 8 mg/day for 2 weeks while all other patients (ie, those who received TRF-budesonide 8 mg/day or placebo during months 0–9) received placebo to maintain masking. No further trial medication was administered after tapering.

Treatment code envelopes were provided for each randomised patient. In case of emergency, the code envelope could be opened. Any unmasked patient had to be withdrawn from the trial.
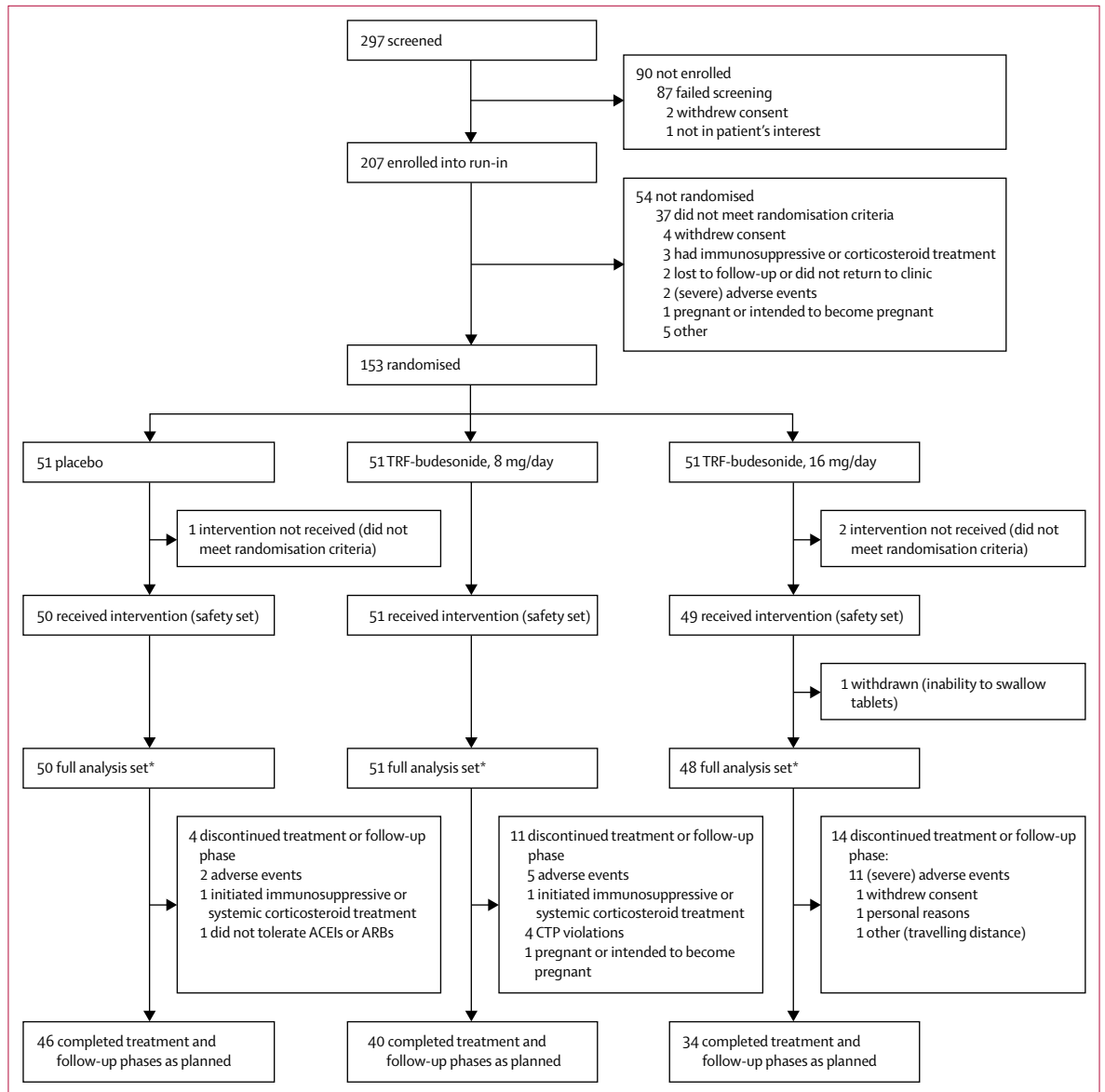
Outcomes

Our primary outcome was mean change from baseline in UPCR over the 9-month treatment phase. For primary analysis, we compared mean change from baseline in UPCR at 9 months between TRF-budesonide-treated patients (16 mg/day and 8 mg/day combined) and placebo-treated patients.

Secondary outcomes, assessed at various timepoints, were mean changes from baseline in UPCR at 12 months, eGFR, 24-h urine protein excretion, urine albumin creatinine ratio (UACR), and 24-h urine albumin excretion, which we calculated from measured 24-h urine samples. The tertiary outcome, the presence or absence of microhaematuria, was assessed by dipstick.

Patients attended screening visits to assess eligibility to enroll into the run-in phase. Patient's attended between 2–6 visits in the run-in phase and subsequent visits at 0, 1, 3, 6, and 9 months in the randomisation and treatment phase and at 10·5 and 12 months in the follow-up phase. We used standardised questionnaires at each visit to ask patients about the presence of specific gastrointestinal-related and corticosteroid-related adverse events. All solicited and spontaneously reported adverse events were recorded from screening until the end of trial, and coded using the Medical Dictionary for Regulatory Activities (version 16.0E). Vital signs, clinical chemistry, and haematology parameters were also assessed at each visit.

Statistical analysis

We used individual patient data from other relevant studies[23,24] to estimate UPCR variability and the expected change from baseline at 9 months in those taking placebo. On the basis of these studies, the estimated geometric mean ratio of 9-month to baseline UPCR values was 0·88 (log SD 0·597). The corresponding geometric mean ratio for TRF-budesonide was estimated from a previous exploratory phase 2a trial[19] as 0·60 (log SD 0·488). Sample size calculations were based on the hypothesis that the true difference between TRF-budesonide (16 mg/day and 8 mg/day combined) and placebo in log UPCR change from baseline was log(0·60)−log(0·88) corresponding to an absolute difference of (1−0·6)−(1−0·88)=28%. Thus, a trial with 150 patients (50 per treatment arm) would provide more than 90% power to detect this level of

***Figure 1:* Trial profile**
ACEI=angiotensin-converting-enzyme inhibitors. ARBs=angiotensin receptor blockers. CTP=clinical trial protocol. *Full analysis set corresponds with the modified intention-to-treat analysis set.

treatment effect for TRF-budesonide (16 mg/day and 8 mg/day combined) versus placebo at the one-sided 2·5% α level.

The primary outcome (mean change from baseline in UPCR over the 9-month treatment phase) was assessed on the full analysis set, defined as all randomised patients who took at least one dose of trial medication and had at least one post-dose efficacy measurement. A formal interim analysis of the primary outcome governed by the DSMB was prospectively planned and triggered when 90 patients completed 9 months' treatment, to ascertain whether the primary hypothesis could be rejected as well as to ensure patient safety and to exclude futility.

further statistical analyses were performed on the primary endpoint. All other statistical analyses were evaluated on final data.

The interim analysis was not a simple analysis of the 9-month datapoint in the first 90 patients. Rather, using mixed modelling methodology accepted by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), the interim analysis included all patients who were randomised at the time the 90th patient had completed 9 months' treatment, even if some of these patients had data only up to the 1-month, 3-month, or 6-month timepoint. The number of patients included in the interim analyses was therefore 149, of

	Placebo (n=50)	TRF-budesonide 8 mg/day (n=51)	TRF-budesonide 16 mg/day (n=48)	Total (n=149)
Age (years)	38·9 (12·0)	40·6 (13·0)	37·5 (11·9)	39·0 (12·3)
Sex				
Male	35 (70%)	37 (73%)	33 (69%)	105 (71%)
Female	15 (30%)	14 (27%)	15 (31%)	44 (29%)
BMI (kg/m²)	27·5 (5·4)	26·5 (4·4)	27·8 (5·2)	27·3 (5·0)
Weight (kg)	85·2 (18·9)	80·9 (14·5)	86·7 (16·9)	84·2 (16·9)
Race				
Asian	1 (2%)	0 (0%)	1 (2%)	2 (1%)
Causcasian	48 (96%)	49 (96%)	47 (98%)	144 (97%)
Other	1 (2%)	2 (4%)	0 (0%)	3 (2%)
Ethnicity				
Hispanic/Latino	3 (6%)	11 (22%)	7 (15%)	21 (14%)
Non-Hispanic/non-Latino	47 (94%)	40 (78·4)	41 (85·4)	128 (85·9)
Blood pressure (mm Hg)				
Systolic	128·1 (11·9)	127·7 (13·6)	126·7 (11·6)	127·5 (12·3)
Diastolic	80·2 (10·1)	80·3 (9·7)	78·1 (9·6)	79·6 (9·8)
UPCR (g/g)	0·8 (0·5–1·6)	0·8 (0·5–1·2)	0·8 (0·5–1·3)	0·8 (0·5–1·3)
24-h protein excretion (g)	1·2 (1·0–3·2)	1·1 (0·9–1·8)	1·3 (0·9–2·1)	1·2 (0·9–2·01)
UACR (g/g)	0·7 (0·4–1·3)	0·7 (0·5–1·0)	0·7 (0·4–1·2)	0·7 (0·4–1·1)
24-h albumin excretion (g)	1·1 (0·8–2·2)	1·0 (0·7–1·6)	1·1 (0·8–1·8)	1·0 (0·8–1·8)
eGFR CKD-EPI (creatinine formula; mL/min per 1·73 m²)	76·5 (23·2)	74·1 (25·8)	83·8 (25·9)	78·3 (25·1)
Patients with microhaematuria	40 (80%)	32 (63%)	42 (88%)	114 (77%)
Time from diagnosis to start of treatment (days)	1101 (294–2870)	1972 (623–4188)	1219 (498–2573)	1499 (496–3162)
Patients who made lifestyle changes during the run-in phase*	16 (32%)	18 (35%)	14 (29%)	48 (32%)
Patients previously treated with corticosteroids or immunosuppressants	7 (14%)	14 (28%)	6 (13%)	27 (18%)
Patients on ACEI alone, n (%, % on MRD)	21 (42%, 28%)	25 (49%, 22%)	26 (52%, 29%)	72 (48%, 26%)
Patients on ARB alone, n (%, % on MRD)	16 (32%, 20%)	14 (28%, 16%)	14 (29%, 19%)	44 (30%, 18%)
Patients on ACEI and ARB, n (%, % on MRD of one or both)	13 (26%, 20%)	12 (24%, 22%)	8 (17%, 13%)	33 (22%, 18%)
Patients on MRD of ACEI or ARB or both	34 (68%)	30 (59%)	29 (60%)	93 (62%)

Data are n (%), mean (SD), or median (IQR) unless otherwise stated. ACEI=angiotensin-converting-enzyme inhibitor. ARB=angiotensin receptor blocker. BMI=body-mass index. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration Equation. eGFR=estimated glomerular filtration rate. MRD=maximum recommended dose. TRF-budesonide=targeted-release formulation-bedesonide. UACR=urine albumin creatinine ratio. UPCR=urine protein creatinine ratio. *Including salt intake, fluid intake, protein intake, fish oil intake, smoking, and exercise.

Table 1: Patient demographics and baseline characteristics (full analysis set)

whom 90 had a 9-month measurement, with the remainder having some data at an earlier timepoint. We did mixed modelling analysis by assessing the patients' proteinuria profile up to the 9-month timepoint. The treatment effect and p value at 9 months were extracted to provide the interim analysis result. This pre-planned approach offers more power than a simple analysis of the 9-month datapoint in the first 90 patients. We set the threshold for significance for TRF-budesonide (16 mg/day and 8 mg/day) versus placebo on the primary outcome at 1·58% one-sided; futility could also be declared if predictive power was 5% or less. The α level applied at final analysis was 1·52% one-sided to ensure an overall type I error rate of 2·5% one-sided.

We prospectively planned that if statistical significance for the primary outcome was met during the interim analysis, the trial would continue, thereby allowing all patients to complete the trial and the analysis of additional endpoints on final data. All secondary and tertiary endpoints were thus analysed during the final analysis after all patients had completed the trial.

We defined several post-hoc analyses after the interim analysis, and before the final database lock: treatment effects on UPCR and eGFR, CKD-EPI as a function of baseline UPCR, and eGFR.

All efficacy data were analysed using mixed-effect model repeated-measures analysis with fixed-effect terms for baseline log UPCR, randomised treatment group,
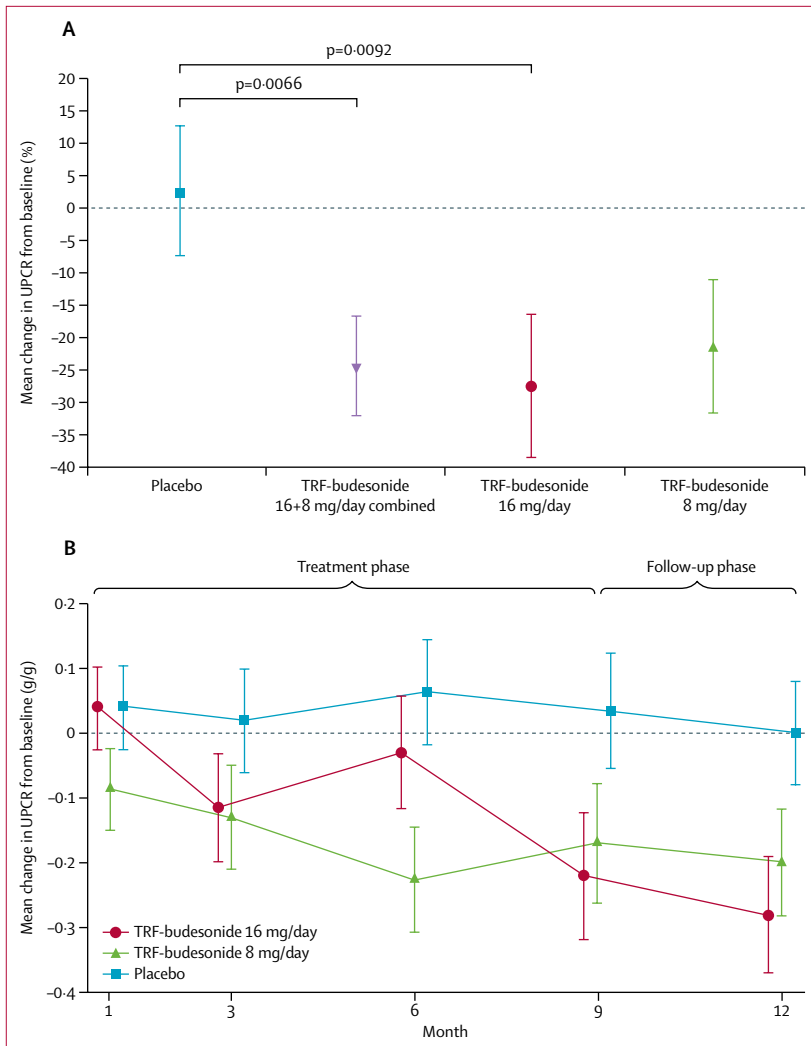
Figure 2: Change in UPCR from baseline
Data are from all 149 patients in the full analysis set and are expressed as mean (bars show standard error of the mean). (A) Change in UPCR from baseline in patients after receiving placebo or TRF-budesonide (16 mg/day and 8 mg/day combined, 16 mg/day, and 8 mg/day) for 9 months at the interim analysis (primary outcome). (B) Absolute mean change in UPCR from baseline in patients receiving 16 mg/day or 8 mg/day TRF-budesonide or placebo for the 9-month treatment phase and 3-month follow-up phase. UPCR=urine protein creatinine ratio.

UPCR stratification level (UPCR ≤0·9 g/g and >0·9 g/g), visit, and visit by treatment group interaction. Patient and region were included as random effects. Region was defined on the country level, although Denmark was combined with Sweden and Belgium with the Netherlands due to small patient numbers per country. Restricted maximum likelihood estimation was used and inference on the fixed effects was based on robust (sandwich) variance estimation. Statistical analyses were performed using SAS version 9.3. This trial is registered with ClinicalTrials.gov, number NCT01738035.

Role of the funding source

The sponsor oversaw all study processes. AM is an employee of the sponsor, who contributed to the study design, provided study oversight, participated in data analysis, data interpretation, and writing of the report. Both placebo and TRF-budesonide treatments were provided by the sponsor. Following database lock and unblinding, the sponsor and all investigators had access to analyses performed on trial data. BCF had final responsibility for the decision to submit for publication.

Results

297 patients were screened between Dec 11, 2012, and Dec 26, 2013, and 207 patients were enrolled into the run-in phase (figure 1). Following run-in, all patients eligible for randomisation to treatment received either a maximum tolerated dose or maximum recommended dose of ACEIs, or ARBs, or both. The last patient visit was on June 25, 2015. 150 randomised patients received masked trial medication; 149 comprised the full analysis set (one patient was unable to swallow capsules; figure 1, appendix). Trial drug exposure is described in the appendix. Treatment groups (16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, and placebo) were similar in demographic and baseline characteristics, with all patients using RAS blockade therapy (table 1). Patients maintained optimised RAS blockade treatment throughout the trial. In a few patients, changes in dose or drug were made in their RAS blockade (17 [11%] patients) or diuretics (ten [7%] patients). The frequencies of changes were comparable across the TRF-budesonide and placebo treatment groups (appendix).

In the pre-planned interim analysis (figure 2), the primary outcome of geometric least-squares mean UPCR at 9 months was reduced from baseline by 24·4% (–0·212 g/g) in all TRF-budesonide-treated patients combined versus an increase of 2·7% (0·024 g/g) in placebo-treated patients ([1–0·244]/[1+0·027]=0·74; 95% CI 0·58–0·94; p=0·0066; figure 2). All point estimates and 95% CIs are in the appendix. Hence, the primary objective of the trial was met at the interim analysis and the corresponding null hypotheses rejected. Geometric least-squares mean changes from baseline were –27·3% for 16 mg/day TRF-budesonide and –21·5% for 8 mg/day TRF-budesonide. The difference in UPCR at 9 months was significant for 16 mg/day TRF-budesonide versus placebo (0·71; 0·53–0·94; p=0·0092), but not for 8 mg/day TRF-budesonide versus placebo (0·76; 0·58–1·01; p=0·0290), which did not meet the adjusted p value at interim analysis (p≤0·0158).

Secondary and tertiary endpoints and post-hoc analyses were evaluated using the final analysis data. Change in UPCR from baseline at 9 months in the final analysis, when all patients had completed the trial (figure 2, appendix), was consistent with the change at 9 months in the interim analysis (figure 2, appendix).

Analysis of the reduction in UPCR at 9 months versus baseline showed that TRF-budesonide had a consistent effect on the relative change in UPCR regardless of baseline UPCR levels (appendix). Upon completion of the 3-month follow-up, after cessation of trial medication, the

geometric least-squares mean reduction was sustained in the 8 mg/day TRF-budesonide group (–22·6% change from baseline) and decreased further in the 16 mg/day group (–32·0% change from baseline) versus an increase of 0·5% for placebo (figure 2 and appendix). Compared with placebo, the changes in UPCR at 12 months in both active treatment groups were statistically significant (16 mg/day vs placebo 0·68, 95% CI 0·57–0·96, p=0·0005; 8 mg/day vs placebo 0·77, 0·62–0·96, p=0·0101; appendix).

Changes from baseline at 9 months and at 12 months in 24-h urine protein excretion, UACR, and 24-h urine albumin excretion (appendix) were consistent with the UPCR data (appendix). In the final analysis, changes in geometric least-squares-mean from baseline at 9 months in the 16 mg/day group versus placebo were UPCR 0·72 (95% CI 0·56–0·92; p value not estimated); 24-h urine protein excretion 0·69 (0·53–0·91; p=0·0040); UACR 0·68 (0·50–0·91; p=0·0053); 24-h urine albumin excretion 0·66 (0·48–0·89; p=0·0035; appendix).

eGFR remained stable in the TRF-budesonide groups but decreased in the placebo-treated group during the treatment phase in the final analysis, as shown by percentage changes at 9 months (figure 3) and by absolute mean changes in eGFR from baseline across the 12 months (figure 3, appendix). Mean percentage change from baseline in eGFR at 9 months was –9·8% for placebo, 0·6% for 16 mg/day, and –0·9% for 8 mg/day (figure 3). Comparisons with placebo achieved statistical significance at 9 months (16 mg/day vs placebo 1·12%, 95% CI 1·03–1·205, p=0·0026; 8 mg/day vs placebo 1·10%, 1·02–1·18, p=0·0064). eGFR levels in the TRF-budesonide 16 mg/day group were sustained throughout the trial (mean percentage change from baseline at 12 months, 0·7% vs –10·9% for placebo; 1·11; 1·01–1·225; p=0·0134; appendix).

No participants died and none progressed to end-stage renal disease. 14 patients (three patients who received 16 mg/day TRF-budesonide, four who received 8 mg/day TRF-budesonide, and seven who received placebo) reported treatment-emergent adverse events associated with worsening of renal function, or received high-dose systemic corticosteroid therapy, or both.

11 patients reported 13 treatment-emergent serious adverse events (appendix). Two were considered possibly associated with TRF-budesonide by investigators masked to trial medication: deep vein thrombosis (16 mg/day); and unexplained worsening of renal function, reported during follow-up after tapering from 16 mg/day to 8 mg/day. Two serious adverse events in the placebo-treated group were considered possibly associated with trial medication: both cases of increased proteinuria, one with a decline in renal function (details on adverse event reporting are in the appendix).

Total incidence of treatment-emergent adverse events was similar across treatment groups (table 2). The most frequently reported adverse event, nasopharyngitis, was reported by similar percentages of patients in each group.
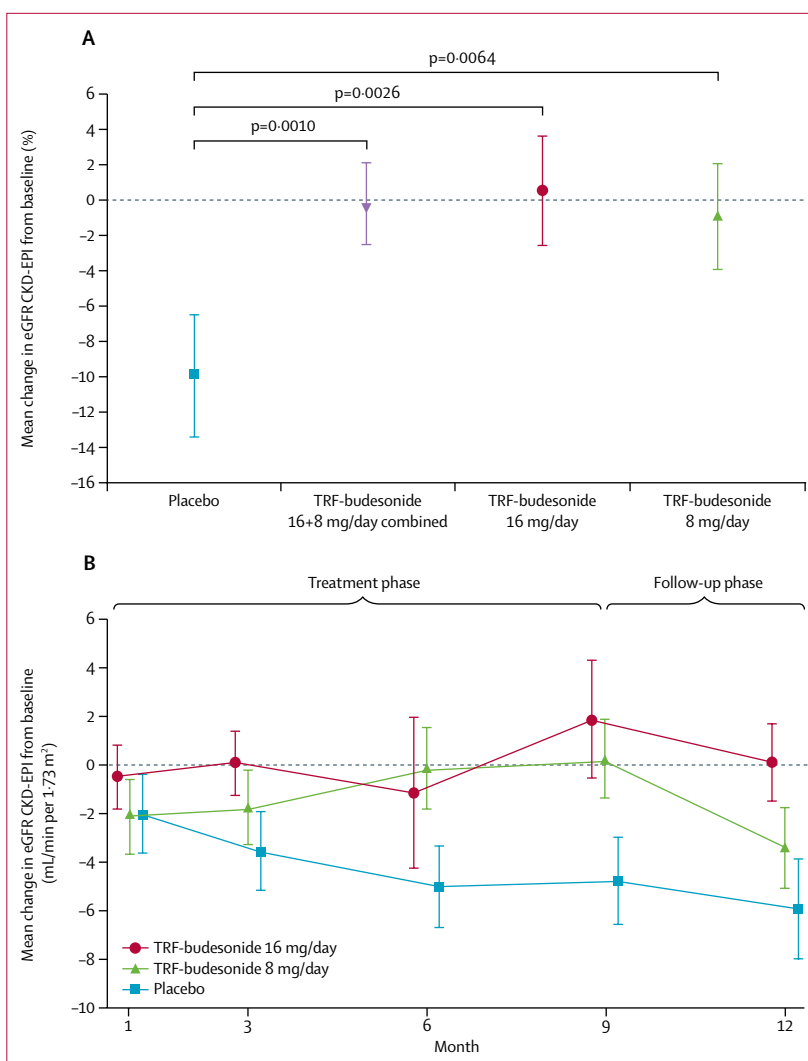
Figure 3: Change in eGFR from baseline
Data are from all 149 patients in the full analysis set and are expressed as mean (bars show standard error of the mean). (A) Change in eGFR CKD-EPI from baseline in patients after receiving placebo or TRF-budesonide (16 mg/day and 8 mg/day combined, 16 mg/day, and 8 mg/day) for 9 months. (B) Absolute mean change in eGFR CKD-EPI from baseline in patients receiving TRF-budesonide 16 mg/day, 8 mg/day or placebo over the 9-month treatment phase and 3-month followup phase. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration Equation. eGFR=estimated glomerular filtration rate.

Bodyweight, blood pressure, and glycated haemoglobin (HbA$_{1c}$) values did not significantly change from baseline in either TRF-budesonide group compared with placebo at the end of treatment (appendix, post-hoc analysis). Two patients receiving TRF-budesonide, both with a body-mass index of 36 kg/m² at baseline, had increases in HbA$_{1c}$ into the diabetic range (≥48 mmol/mol) at the end of treatment or during follow-up (appendix). We saw no other clinically relevant changes in clinical chemistry variables in any treatment group (the full list of clinical chemistry variables investigated is in the appendix). The incidence of gastrointestinal-related adverse events was similar in TRF-budesonide-treated and placebo-treated patients (appendix).

	Placebo (n=50)		TRF-budesonide 8 mg/day (n=51)		TRF-budesonide 16 mg/day (n=49)		Total (n=150)	
	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
Any adverse event	42 (84%)	162	48 (94%)	270	43 (88%)	305	133 (89%)	737
Nasopharyngitis	10 (20%)	14	8 (16%)	16	10 (20%)	16	28 (19%)	46
Acne*	3 (6%)	3	8 (16%)	9	9 (18%)	10	20 (13%)	22
Joint swelling	2 (4%)	2	8 (16%)	8	9 (18%)	14	19 (13%)	24
Cushingoid*	3 (6%)	3	5 (10%)	5	8 (16%)	8	16 (11%)	16
Insomnia*	2 (4%)	2	6 (12%)	6	8 (16%)	9	16 (11%)	17
Diarrhoea	7 (14%)	9	1 (2%)	1	5 (10%)	5	13 (9%)	15
Dyspepsia†	4 (8%)	5	2 (4%)	2	7 (14%)	9	13 (9%)	16
Headache	3 (6%)	4	3 (6%)	3	6 (12%)	6	12 (8%)	13
Alopecia*	2 (4%)	2	4 (8%)	5	4 (8%)	4	10 (7%)	11
Back pain	1 (2%)	1	6 (12%)	8	3 (6%)	3	10 (7%)	12
Mood swings*	2 (4%)	2	3 (6%)	3	5 (10%)	5	10 (7%)	10
Oedema peripheral	2 (4%)	3	2 (4%)	3	6 (12%)	9	10 (7%)	15
Blood creatine phosphokinase increased	3 (6%)	3	3 (6%)	4	3 (6%)	3	9 (6%)	10
Hirsutism*	1 (2%)	1	3 (6%)	3	5 (10%)	5	9 (6%)	9
Hypertension	1 (2%)	1	3 (6%)	3	5 (10%)	5	9 (6%)	9
Muscle spasms	2 (4%)	3	5 (10%)	5	2 (4%)	2	9 (6%)	10
Abdominal pain†	1 (2%)	1	4 (8%)	4	3 (6%)	4	8 (5%)	9
Nausea	1 (2%)	1	4 (8%)	4	3 (6%)	5	8 (5%)	10
Upper respiratory tract infection	3 (6%)	3	2 (4%)	3	3 (6%)	3	8 (5%)	9

Adverse events reported by ≥5% of the total patient population. TRF-budesonide=targeted-release formulation-budesonide. *Corticosteroid-related adverse events solicited by questionnaire at every visit. †Gastrointestinal-related adverse events solicited by questionnaire at every visit.

Table 2: Treatment-emergent adverse events reported by ≥5% of all patients by preferred term (safety set)

Solicited corticosteroid-related adverse events were more frequently reported by TRF-budesonide-treated patients (appendix). 18 patients experienced adverse events that led to discontinuation of treatment (11 in the 16 mg/day group, five in the 8 mg/day group, two in the placebo group). Most patients who discontinued in the TRF-budesonide groups experienced corticosteroid-related adverse events (appendix).

When assessed as a tertiary outcome in the final analysis, the proportion of patients with microhaematuria in the 16 mg/day TRF-budesonide group significantly decreased from 42 (88%) of 48 patients at baseline to 21 (44%) of 48 at 9 months compared with 37 (74%) of 50 placebo-treated patients at 9 months (odds ratio 0·22, 95% CI 0·07–0·68; p=0·0041) but remained unchanged in the 8 mg/day-treated and placebo-treated groups.

Exploratory post-hoc analyses suggested that stabilisation of eGFR in TRF-budesonide-treated groups was independent of baseline UPCR and eGFR values, and that the degree of eGFR reduction in the placebo-treated group appeared related to the magnitude of baseline UPCR (appendix). To determine whether there was an influence of the extent of RAS blockade on eGFR, we compared eGFR changes in placebo-treated patients receiving maximum recommended dose versus the maximum tolerated dose of RAS blockade. This post-hoc analysis showed that the

magnitude of decline in eGFR was comparable in placebo-treated patients receiving RAS blockade therapy at the maximum recommended dose (–4·9 mL/min per 1·73 m² [SD 12·685]) versus at the maximum tolerated dose (–4·4 mL/min per 1·73 m² [9·187]).

Discussion

We report the results of the NEFIGAN trial in which 9 months' treatment with TRF-budesonide resulted in a significant reduction in UPCR versus placebo in patients with primary IgA nephropathy. This primary outcome was met in a prespecified interim analysis of data from the full analysis set population. The effect of TRF-budesonide was dose-dependent and time-dependent. Upon completion of the 3-month follow-up, after cessation of trial medication, the mean percentage reduction in UPCR was sustained in the 8 mg/day TRF-budesonide group and continued to decrease in the 16 mg/day group. The reductions in UPCR were consistent with changes in 24-h urine protein and albumin excretion and UACR, which were all sustained during the 3-month follow-up. This persistence of effect following cessation of treatment suggests a disease modifying effect.

Patients entering the treatment phase of this trial were at risk of progression to end-stage renal disease due to persistent proteinuria despite optimised RAS blockade.

The further reduction in proteinuria was achieved by targeting an alternative pharmacological mechanism, using TRF-budesonide, irrespective of baseline UPCR, eGFR, and time since diagnosis of IgA nephropathy (appendix). Our findings support the generally accepted hypothesis that mucosal immune system dysfunction has a significant role in the pathogenesis of IgA nephropathy because TRF-budesonide targets the region of the gastrointestinal tract where Peyer's patches reside at high density. Evidence and general acceptance is increasing that a reduction in proteinuria is associated with a reduced risk of end-stage renal disease in patients with IgA nephropathy, and time-averaged proteinuria is predictive of renal survival in these patients—the rate of decline of renal function and subsequent risk of renal failure are associated with higher levels of time-averaged proteinuria.[5,20] A meta-analysis[25] of trials for IgA nephropathy used contemporary statistical methodology to assess the possible surrogacy of the effect of treatment intervention (RAS blockade, fish oil, immunosuppression, and steroids) on proteinuria at 9 months to predict the effect of the intervention on clinical outcomes in end-stage renal disease. The analysis suggested that an improvement in proteinuria at 9 months for a drug compared with control would be positively associated with an improvement in longer term end-stage renal disease outcome. For patients in the 16 mg/day TRF-budesonide group, proteinuria in the form of UPCR and 24-h urine protein excretion both decreased by about 30%, compared with the placebo-treated group. This level of proteinuria reduction is comparable with that conferred by RAS blockade in patients with IgA nephropathy,[25] and in other chronic kidney diseases such as diabetic nephropathy.[26] Proteinuria reduction was significantly associated with outcomes in end-stage renal disease in another meta-analysis[26]—for each 30% reduction in proteinuria by drugs that intervene in the RAS, the risk of end-stage renal disease (non-significantly) decreased by 32% (95% CI –55 to 2).[26] A treatment-induced decrease in proteinuria of 30% would result in a comparable reduction in the risk of end-stage renal disease.[25]

In our trial eGFR declined in the placebo-treated group but remained stable in the TRF-budesonide groups following 9 months' treatment, an effect that persisted throughout follow-up in the 16 mg/day group. Stabilisation of eGFR in patients with IgA nephropathy is likely to predict a favourable outcome. All patients were on a maximum recommended dose or maximum tolerated dose of ACEI, or ARB, or both (as assessed by their investigator); thus, RAS blockade therapy remained optimised throughout the trial, with no dose changes during the treatment phase, except in a small number of individuals (percentage of maximum recommended dose of RAS blockade was increased for five of 150 patients and decreased for six of 150 patients), distributed across the three treatment groups (appendix). Despite the maintenance of rigorous RAS blockade, the rapid rate of loss of eGFR observed in the placebo-treated group was greater than that seen in the STOP-IgAN study[11] but consistent with other studies in patients with IgA nephropathy receiving optimised RAS blockade, albeit with generally higher levels of baseline proteinuria.[24,27] A post-hoc analysis showed that the eGFR reduction in the placebo-treated group was related to baseline proteinuria, indicating that the response of this group of patients is consistent with the expectation that higher levels of proteinuria are associated with greater loss of eGFR (appendix). Because histological data are not available for the patients in all of these studies, speculation on the contribution of histopathological changes to the rate of eGFR decline is difficult. However, the deterioration in eGFR illustrates that this patient population is at risk of disease progression, current standard-of-care therapy is insufficient, and alternative interventions for patients with IgA nephropathy and persistent proteinuria are needed.

High-dose systemic corticosteroids and other potent immunosuppressive treatments have been studied in a number of randomised controlled trials with varying results.[28] A consequence of these trials has been the necessity to test interventions in patients on optimised standard-of-care RAS blockade, as we did in this trial, and the investigators of the TESTING trial (a randomised controlled trial evaluating high-dose systemic corticosteroid therapy versus placebo [recruitment was stopped early and randomised treatment discontinued due to safety concerns, interim results published]),[29] and the STOP-IgAN trial also did.[11] The STOP-IgAN trial[11] assessed the potential benefit of systemic immunosuppression in addition to dietary restrictions and polypharmacy upon optimised RAS blockade, and was the first study in patients with IgA nephropathy to use such comprehensive supportive care. No difference in the rate of decrease in eGFR was observed between groups for the 3-year period of the trial.[11] The slow annual loss of eGFR in the intensive supportive care group (1·6 mL/min per 1·73 m²) in the STOP-IgAN trial contrasts with the more rapid rate of loss of eGFR shown in other studies,[24] including ours, in which a 6-month run-in phase was used to optimise RAS blockade. In our study, 62% of patients received the maximum recommended dose of ACE or ARB drugs (or both; table 1) and, on average, patients received 79% of the maximum recommended dose. In the placebo-treated group, 68% of patients received the maximum recommended dose of RAS blockade (table 1). By comparison, in the STOP-IgAN trial, 76% of patients in the supportive care group were on a maximum recommended dose of an ACEI or ARB. Whether this difference in RAS blockade is sufficient to account for the different rates of loss of renal function or whether other factors such as polypharmacy and the more rigorous application of dietary restrictions in the STOP-IgAN trial (including limited salt intake) played a greater

part cannot be discerned from the available data. In our trial, a post-hoc analysis showed that eGFR was unlikely to be affected substantially by whether patients received the maximum recommended dose or maximum tolerated dose of RAS blockade therapy, because the magnitude of decline in eGFR was comparable in placebo-treated patients at the maximum recommended dose versus at the maximum tolerated dose.

16 mg/day TRF-budesonide resulted in a significant reduction in the presence of microhaematuria at 9 months compared with placebo. Although the prognostic significance of haematuria disappearance in patients with IgA nephropathy has not been prospectively investigated, clinical and experimental studies suggest that haematuria is associated with glomerular and tubulointerstitial damage in IgA nephropathy and other glomerular diseases.[30,31]

In this trial, TRF-budesonide appeared to be safe and generally well-tolerated, although there was a dose-dependent trend in the incidence of solicited corticosteroid-related adverse events and in discontinuations due to these events (appendix). Budesonide, administered in a targeted-release oral dosage form, is subject to high first-pass metabolism, resulting in low systemic exposure (about 10% of administered dose).[18] Some degree of systemic exposure was reflected in reduced cortisol excretion (data not shown) and the aforementioned dose-dependent trend in the incidence of solicited corticosteroid-related adverse events. However, several studies[11,32] have reported higher incidences of diabetes mellitus or impaired glucose tolerance, hypertension, and weight gain in high-dose systemic corticosteroid-treated patients. Furthermore, increased incidences of serious and fatal infections were documented with high-dose systemic corticosteroid therapy in the STOP-IgAN trial[11] (one of 55 patients) and TESTING trial[29] (12 of 236 patients, including two deaths). By contrast, no serious infections were attributed to TRF-budesonide in our trial and no statistically significant changes were observed for blood pressure, HbA$_{1c}$, or bodyweight with TRF-budesonide versus placebo. Systolic and diastolic blood pressure levels were non-significantly higher in the 16 mg/day TRF-budesonide group at the end of treatment compared with baseline values (appendix). Our trial data indicate that TRF-budesonide might elicit fewer and less severe systemic effects and have a preferable tolerability profile than has previously been reported for high-dose systemic corticosteroid regimens, when used to treat patients with IgA nephropathy at risk of progression to end-stage renal disease, many of whom are young adults.[11,32] However, this tolerability needs to be confirmed in larger studies than this phase 2b trial.

Proteinuria is a major risk factor for renal failure in IgA nephropathy.[3,5] As addressed by Rauen and colleagues,[11] clinically significant proteinuria has been arbitrarily defined as an excretion level greater than 1 g/day (KDIGO guidelines).[7] However, evidence from epidemiology studies[20,33] indicates that patients with IgA nephropathy with proteinuria of 0·5 to 1 g/day are at increased risk of renal failure. Thus, to evaluate TRF-budesonide in a clinically relevant high-risk IgA nephropathy population, we selected a proteinuria threshold of either 0·75 g/day or 0·5 g/g UPCR (on a 24-h collection). A threshold level of 0·75 g/day was similarly applied in the STOP-IgAN trial.

This trial is one of the largest randomised controlled trials in patients with IgA nephropathy in which RAS blockade was optimised before adjunct therapy. The primary objective of this trial was to assess the effect of TRF-budesonide on UPCR at 9 months, a proteinuria-based measure and surrogate endpoint for renal failure. Although both a reduction in UPCR and stabilisation of eGFR were shown, the magnitude of relative risk reduction associated with TRF-budesonide treatment in patients with IgA nephropathy at risk of progression to end-stage renal disease needs to be quantified in a larger trial of longer duration. Another limitation of the present trial is that the patient population treated was almost exclusively white, thus the results also need to be confirmed in other populations. Additionally, allowing entry of patients into the study regardless of time since biopsy meant recent histopathology data were unavailable for all patients before randomisation. This absence prevented the implementation of a stratification strategy to discount imbalance of renal histology scores as a potential confounder. To our knowledge, no published pharmacokinetic data exist for TRF-budesonide in patients with IgA nephropathy. Patients with severe hepatic impairment were excluded from the study but whether patients with IgA nephropathy are subject to higher systemic exposure due to increased mucosal gastrointestinal absorption is unknown. Increased exposure of budesonide has been observed in chronic inflammatory bowel disease (11–21% vs 9–12% in healthy volunteers) but systemic exposure normalises after 8 weeks of treatment.[34]

This trial showed that 9 months' treatment with TRF-budesonide resulted in reduced proteinuria and stabilised eGFR in patients with IgA nephropathy at risk of progression to end-stage renal disease. The observed effect was additive to optimised RAS blockade and supports the use of TRF-budesonide as adjunct therapy in patients with IgA nephropathy with persistent proteinuria. TRF-budesonide has the potential to become the first disease-specific treatment for IgA nephropathy, with a risk-benefit profile supportive of its use early in the course of disease.

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