Budesonide versus systemic corticosteroids in IgA Nephropathy
A retrospective, propensity-matched comparison

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Abstract

IgA Nephropathy (IgAN) is characterized by mesangial deposition of dominant, polymeric, galactose-deficient IgA1 molecules of gut-associated lymphoid tissue origin. We sought to evaluate the efficacy of targeting the mucosal immune system dysregulation underlying IgAN pathogenesis with a pH-modified formulation of budesonide with a maximum release of active compound in the distal ileum and proximal colon.

We did a retrospective study evaluating the efficacy of budesonide (Budenofalk) in the treatment of IgAN. From a retrospective cohort of 143 patients with IgAN followed in our department we identified 21 patients that received treatment with budesonide. These patients received budesonide at a dose of 9 mg/d in the first 12 months, followed by a dose reduction to 3 mg/d for the subsequent period. Only patients that received a 24-month treatment with budesonide were included in the analysis (n = 18). We matched the budesonide-treated cohort to 18 patients with IgAN treated with systemic steroids from the same retrospective cohort. Efficacy was measured as change in proteinuria, hematuria and estimated glomerular filtration rate over a 24-month period.

Treatment with budesonide was associated with a 24-month renal function decline of -0.22 (95%CI, -8.2 to 7.8) ml/min/1.73m^2, compared to -5.89 (95%CI, -12.2 to 0.4) ml/min/1.73m^2 in the corticosteroid treatment group (p = 0.44, for between group difference). The median reduction in proteinuria at 24-month was 45% (interquartile range [IQR]: -79%; -22%) in the budesonide group and 11% (IQR: -39%; 43%) in the corticosteroid group, respectively (P = .009, for between group difference). The median reduction in hematuria at 24-month was 72% (IQR: -90%; -45%) in the budesonide group and 73% (IQR: -85%; 18%) in the corticosteroid group, respectively (P = .22, for between group difference). Treatment with budesonide was well tolerated with minimal side effects.

Budesonide (Budenofalk) was effective in the treatment of patients with IgAN at high-risk of progression in terms of reducing proteinuria, hematuria and preserving renal function over 24 months of therapy.

Abbreviations: eGFR = estimated glomerular filtration rate, GALT = gut-associated lymphoid tissue, Gd-IgA1 = galactose-deficient IgA1, IgAN = IgA nephropathy, IQR = interquartile range, IS = immunosuppressive.

Keywords: budesonide, corticosteroids, IgA Nephropathy, immunosuppression

1. Introduction

Immunoglobulin A Nephropathy (IgAN) is the most common primary glomerular disease diagnosed by percutaneous kidney biopsy worldwide.[1] Approximately 20% to 40% of patients will progress to end-stage renal disease within 20 years from diagnosis.[2] Despite that the treatment of IgAN has been a major focus of debate over the past decades there is still no consensus reached and we still await the approval of disease-modifying therapies.[2,3] The outdated recommendations of the 2012 KDIGO guidelines restrict the use of systemic corticosteroids to patients with persistent proteinuria and relatively preserved renal function.[4] However, two recent, large, randomized controlled trials that assessed the efficacy of immunosuppressive (IS) therapy by comparison to optimized supportive care revealed an excess of serious adverse events (mainly infections) with apparently no benefit with regard to retarding renal function decline.[5,6] Hence, the utility of systemic corticosteroids and other immunosuppressants were seriously questioned.[2]

IgAN is characterized by mesangial deposition of dominant or codominant polymeric IgA1-containing immune complexes of gut-associated lymphoid tissue (GALT) origin.[2] An altered

mucosal immune response is proposed to underlie this gut-renal connection.[7] In IgAN patients, B lymphocytes from Peyer's patches are primed to produce galactose-deficient molecules of IgA1 (Gd-IgA1) in response to microbial or dietary antigens and this is proposed to be the earliest pathogenic event.[2,7] These insights into IgAN pathogenesis offers the possibility for the development of novel agents with a more targeted effect.[2] As such, an enteric targeted-release formulation of budesonide (Nefecon) was developed in order to release the active drug in the distal ileum and proximal part of ascending colon, sites with the highest density of Peyer's patches.[8] In phase IIa[8] and IIb[9] trials, treatment with Nefecon determined a reduction of proteinuria and a stabilization of renal function, with fewer side effects than systemic steroids. Accordingly, a phase III trial was planned to further test the efficacy of targeting the GALT with Nefecon in IgAN.[10] However, other formulations of the locally acting glucocorticoid budesonide were previously developed and approved for the treatment of mild to moderate active Crohn's disease.[11] Budenofalk is a gastro-resistant, pH-modified formulation of budesonide with a maximum release of active compound in the distal ileum and proximal colon.[11] Additionally, it has an extensive first-pass metabolism and induces only mild and transient reductions in plasma cortisol levels, thus sparing the steroid-related side effects.[11]

We sought to evaluate the efficacy of targeting the mucosal immune system dysregulation underlying IgAN pathogenesis with a pH-modified formulation of budesonide (Budenofalk) by comparison to systemic steroids in a retrospective, propensity-matched analysis.

2. Material and methods

2.1. Study design and population

This is a retrospective study that assessed the efficacy of budesonide (Budenofalk) by comparison to systemic corticosteroids in the treatment of patients with primary IgAN. Since the initial publication of the NEFIGAN trial results,[9] we started treating patients with IgAN with a different formulation of budesonide (Budenofalk). From a retrospective cohort of 143 patients with IgAN followed in the Nephrology Department of Fundeni Clinical Institute, Bucharest, we identified 21 patients that had received budesonide (Budenofalk), as from March 2017. Patients considered for budesonide-treatment had an age between 18 and 70 years and a diagnosis of primary IgAN. Additionally, only patients considered at high-risk subsequently received budesonide treatment: those with persistent proteinuria over 1 g/d despite adequate renin-angiotensin-aldosterone system (RAAS) blockade or patients with proteinuria between 0.5 and 1 g/d if they had additional risk factors for progression (estimated glomerular filtration rate [eGFR] below 60 mL/min/L.73m^2, presence of proliferative lesions on kidney biopsy). We excluded patients with: age under 18 years, those with IgAN associated with other disorders (viral infections, autoimmune disorders, malignancy), those with an eGFR below 20 mL/min/L.73m^2, nephrotic syndrome or a rapidly progressive clinical course, patients with proteinuria below 0.5 g/d after adequate RAAS blockade, those with severe histological lesions of activity or chronicity (endocapillary hypercellularity in over 50% of examined glomeruli, crescents in over 30% of examined glomeruli, presence of fibrinoid necrosis, global glomerulosclerosis in over 50% of examined glomeruli), patients with diabetes

mellitus or active infections, patients that received prior immunosuppression. In addition, only those patients that had received treatment for a 24-month period were included in the final analysis. Similarly, we identified in the same retrospective cohort of patients those that received systemic corticosteroids and had similar characteristics with the budesonide-treated patients. Because the systemic steroids were given in a 6 to 8-month course regimens and the cohort of patients treated with budesonide received a 24-month treatment course, we included in the analysis only those patients that had at least 24 months of follow-up from corticosteroids initiation.

The study was conducted after institutional approval (The Ethics Council of Fundeni Clinical Institute, Registration number: 1975) aligned with the provisions of the Declaration of Helsinki and written consent to participate in the study was provided by all participating patients.

2.2. Treatment

All patients had received an angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy for a period of at least 3 months prior to IS therapy. The dose of angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker was titrated to a maximum tolerated dose in order to achieve a target blood pressure of 125/75 mm Hg or less and a proteinuria level below 0.5 g/d. In addition, the patients were advised on salt restriction, smoking and nonsteroidal anti-inflammatory agent avoidance.

Patients that after RAAS blockade initiation were considered to be at high-risk of progression were started on budesonide at a dose of 9 mg/d, for the first 12 months, followed by a subsequent dose reduction to 3 mg/d. Budesonide (Budenofalk)[11] is a controlled-release, gastro-resistant, pH-modified oral steroid formulation. It has a maximum release in the distal ileum and proximal colon and extensive first-pass metabolism, being associated only with mild and transient reductions in plasma cortisol levels and minimal steroid-related side effects.[11] Patients treated with systemic corticosteroids received either the "Pozzi regimen"[12] or "Manno regimen",[13] as originally described.

2.3. Study follow-up and data collection

The study follow-up period was 24 months. At baseline the following data were collected: age, gender, Charlson Comorbidity index, mean arterial pressure, renal function assessed by serum creatinine and eGFR (calculated with chronic kidney disease -EPI equation), serum uric acid, serum albumin, lipid panel, serum fibrinogen and hemoglobin, 24-hour proteinuria (g/d) and hematuria (cells/mmc). Only patients with a histological diagnosis of IgAN were considered for study inclusion. The diagnosis of IgAN was based on light microscopy, immunofluorescence (dominant IgA in the mesangium) and electron-microscopy (para-mesangial electron-dense deposits). All kidney biopsies were reviewed and scored according to the 2016 revised Oxford Classification.[14] All patients underwent a systematic screening for disorders reported to be associated with IgAN[15] and only those considered to have a primary form were finally included in the study. The histological assessment included the number of glomeruli with global glomerular sclerosis and the MESTC score. At each clinical visit (every 3 months in the first 6 months, and every 6 months thereafter), data regarding

evolution of renal function, proteinuria and hematuria were collected. Additionally, we reevaluated all the patients for the occurrence of any budesonide-related adverse events.

2.4. Study endpoints

The primary outcomes evaluated in this study were: the mean percentual change from baseline in 24-hour proteinuria and hematuria over the 24-month treatment period and the absolute change from baseline of eGFR. The secondary outcome evaluated the occurrence of budesonide-related adverse events.

2.5. Statistical analysis

Continuous variables were expressed as either mean (± standard deviation or 95% confidence interval) or median (interquartile range [IQR]: 25th–75th percentiles) and categorical variables as percentages. Differences between groups were assessed in case of continuous variables by Student t test or by Mann-Whitney test, according to their distribution, and in case of categorical variables by $\chi2$ test. When evaluating differences between the variables related to the outcome of the study, between group differences at each follow-up time point were assessed by Student t test or by Mann-Whitney test, according to their distribution, while within group differences (for comparison to baseline) were assessed by paired sample t-test or Wilcoxon Signed Rank Tests, according to the distribution of the variables.

We intended to compare the efficacy of treatment with budesonide with that of systemic corticosteroids in patients with primary IgAN. We used a propensity score to match the patients treated with budesonide with those treated with systemic steroids from a retrospective cohort of 143 patients with primary IgAN. We identified 18 patients treated with systemic corticosteroids with a similar risk of progression. The variables used to compute the propensity score were age, eGFR, proteinuria, hematuria and MEST score variables (Fig. 1). We matched patients with the closest propensity score with a maximum difference of ±0.5. In all analyses, P values are 2-tailed and all P values less than .05 were considered statistically significant. We calculated the 5-year risk of progression of IgAN with the new internationally validated risk prediction tool (the formulas for the calculation have been incorporated into mobile-app and web-based prediction tools, eg,: https://qxmd.com/calculateby-qxmd).[16]

Statistical analyses were performed using the SPSS program (SPSS version 20, Chicago, IL) and XLSTAT (Addinsoft 2019, XLSTAT statistical and data analysis solution. Available at: https://www.xlstat.com. Boston).

3. Results

3.1. Study population and baseline characteristics

Between March 2017 and December 2019, 21 patients with biopsy-proven primary IgAN had received treatment with budesonide. Of these, 18 patients received the treatment for a 24-month period (12 months with 9 mg/d followed by 12 months with 3 mg/d) and were included in the final analysis. Another 18 patients with primary IgAN treated with systemic steroids that had at least a 24-month follow-up period were retrospectively identified and included in the analysis as a comparison group (Fig. 1). All patients received adequate RAAS blockade prior to initiation of immunosuppression.

The baseline characteristics of the study groups are depicted in Table 1. The budesonide group had a median age at treatment initiation of 43 years (IQR: 37-47), a mean serum creatinine of 1.97 ± 0.81 mg/dL, 67% having an eGFR below 60 mL/min/$1.73m^2$, and median 24-hour proteinuria of 1.47 (IQR: 0.86-2.13) g/d. Six patients (33%) had an eGFR between 20 and 30 mL/min/$1.73m^2$ and 8 patients (44%) had an eGFR between 30 and 60 mL/min/$L.73m^2$. Twenty-seven percent of the patients had proteinuria over 2 g/d, while 3 patients had a proteinuria level over 3 g/d. Regarding the renal biopsy findings, these patients had 23% (IQR: 0-50%) of glomeruli with global sclerosis, 94% had mesangial hypercellularity, 22% had endocapillary hypercellularity, 72% had segmental sclerosis and 49% had at least 25% of the examined area with tubular atrophy and interstitial fibrosis. Sixteen percent of patients had crescents in at least 1 glomerulus, while only 1 patient had 25% of glomeruli with crescents. The corticosteroid group comprised 18 patients with similar baseline characteristics as the budesonide group. However, these patients showed a slightly better renal function, lower proteinuria and, on kidney biopsy, fewer patients showed segmental sclerosis or extracapillary hypercellularity (Table 1), but the differences did not reach any statistical significance. In order to evaluate the risk of progression of both treatment groups, we reevaluated all the patients according to the recently proposed and internationally validated risk prediction tool.[16] We identified a median 5-year risk of progression (50% decline of renal function or end-stage renal disease) of 24 (IQR:7-38), thus underlying the high risk of progression of both groups of patients (Table 1).

3.2. Primary outcomes

Treatment with budesonide was associated with a stabilization of renal function and a decrease of proteinuria and hematuria over the course of 24-months (Table 2, Fig. 2A and 2B). The eGFR at the time of treatment initiation was 49 ± 25 mL/min/$1.73m^2$ and the eGFR after the 24-month treatment period was 48.8 ± 26.8 mL/min/$1.73m^2$ ($P = .97$), corresponding to a 24-month renal function decline of -0.22 (95%CI, -8.2 to 7.8) mL/min/$1.73m^2$. The corticosteroid group, although starting at a higher eGFR (56 ± 36 mL/min/$1.73m^2$), had, after 24-months of follow-up and despite not reaching statistical significance, a faster decline of renal function of -5.89 (95%CI, -12.2 to 0.4) mL/min/$1.73m^2$ ($P = .44$, for between group difference).

The median reduction in proteinuria at 24-month was 45% (IQR: -79%; -22%; $P = .03$, for comparison to baseline) in the budesonide group and 11% (IQR: -39%; 43%; $P = .75$, for comparison to baseline) in the corticosteroid group, respectively ($P = .009$, for between group difference). Additionally, 12 patients (67%) in the budesonide group showed a decrease in proteinuria level below 1 g/d, while 6 of them having a proteinuria level below 0.5 g/d at the last-follow visit (Fig. 3). Correspondingly, 9 patients (50%) in the corticosteroid group had a proteinuria level below 1 g/d after 24 months of follow-up, 3 of them having a proteinuria below 0.5 g/d. The median reduction in hematuria at 24-month was 72% (IQR: -90%; -45%; $P = .002$, for comparison to baseline) in the budesonide group and 73% (IQR: -85%; 18%; $P = .04$, for comparison to baseline) in the corticosteroid group, respectively ($P = .22$ for between group difference). There was a complete disappearance of hematuria in 13 patients (72%) and 12 patients (67%) in the budesonide and corticosteroid group, respectively.
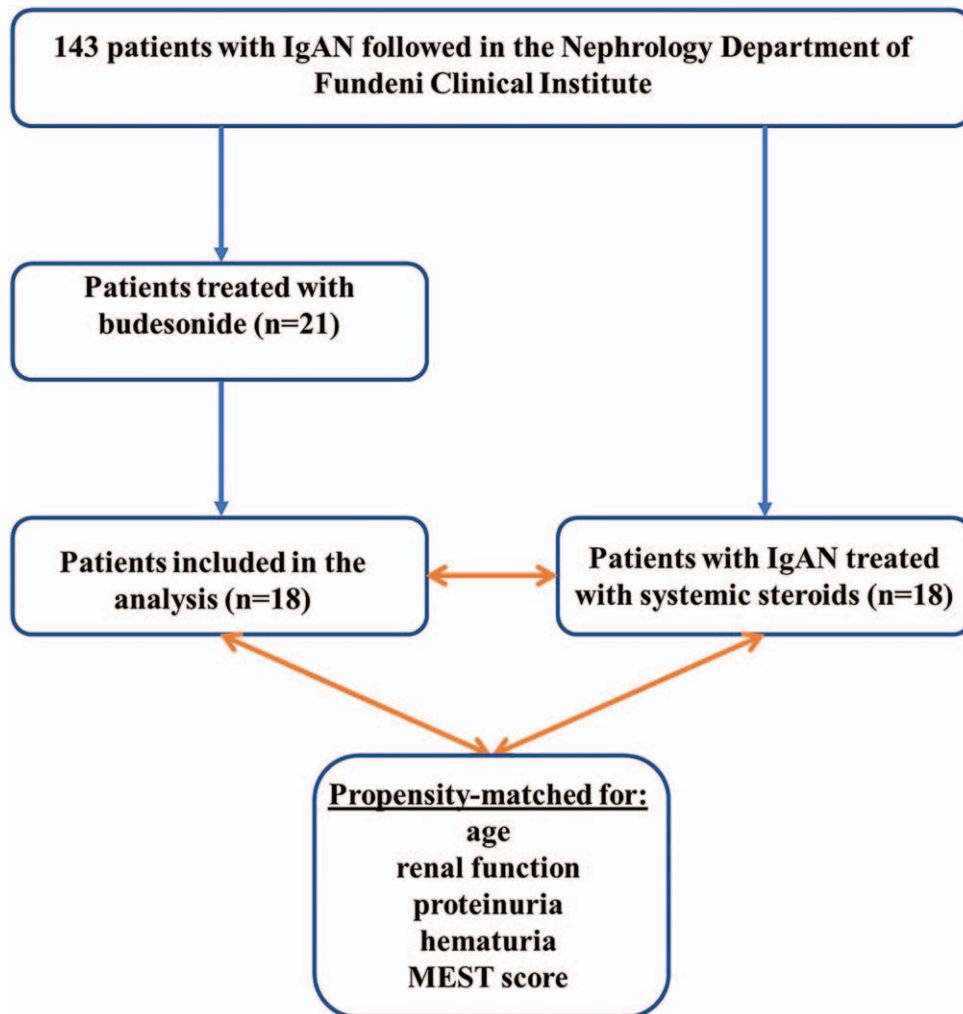
Figure 1. Study flow-chart.

3.3. Adverse events

Treatment with budesonide was well tolerated with minimal side effects encountered throughout the treatment period (Table 3). We noted 4 adverse events in the budesonide treatment group, 3 of which were mild. One patient had mild gastrointestinal complaints (nausea) at the initiation of treatment that subsequently resolved. One patient has an episode of mild oral candidiasis and 1 patient had a mild episode of upper respiratory tract infection (with a bout of macroscopic hematuria, that resolved with the resolution of the infection). The last patient had an episode of deep vein thrombosis complicated with pulmonary embolism. However, this patient was known to have a hereditary thrombophilia and had a previous thromboembolic event (prior to IgAN diagnosis). Thus, this event was considered unrelated to budesonide therapy.

4. Discussion

In this study we have shown a significant effect of budesonide (Budenofalk) in terms of reducing proteinuria and hematuria, along with a stabilization of renal function over a 24-month treatment period, in patients with IgAN at high risk of progression. Overall, budesonide determined a significant

reduction in proteinuria from a median 1.47 g to 1 g/d at 24 months ($P=.03$) that was accompanied by a mean absolute decline of eGFR of -0.22 mL/min/L.73m^2 over 24-month. In addition, we selected, from the same retrospective cohort, eighteen patients treated with systemic corticosteroids that had similar characteristics and at least 24 months of follow-up from treatment initiation and noticed only a non-significant proteinuria reduction ($P=.75$) and a mean absolute eGFR decline of -5.89 mL/min/L.73m^2 over 24 months. The treatment with budesonide was well tolerated with minimal side effects.

IgAN is characterized by mesangial deposition of polymeric IgA1-containing immune complexes, with a characteristic galactosylation defect in the hinge region of the molecule.[17] Emerging evidence supports the role of mucosal immune system in IgAN pathogenesis.[7,18] In patients with IgAN an exaggerated immune response is thought to occur to microbial or dietary antigens in which mucosal B lymphocytes from Peyer's patches are primed to synthesize Gd-IgA1.[7] The antigenic Gd-IgA1 molecule elicits an autoimmune response with production of specific IgG or IgA antibodies directed against the galactose-deficient hinge region of the molecule,[19] leading to immune complex formation that will subsequently bind to glomerular mesangial cells.[20] This triggers cell activation and proliferation

Table 1

Baseline patients' characteristics.

Variable	Whole cohort	Budesonide group	Corticosteroid group	P
Number of patients	36	18	18	
Gender (% male)	77%	83%	72%	.9
Age (yr)	43 (IQR:36-48)	43 (IQR:37-47)	44 (IQR:35-48)	.7
Charlson Comorbidity index	2 (IQR:0-2)	2 (IQR:0-2)	2 (IQR:0-2)	.5
MAP (mm Hg)	98 (IQR:90-107)	93 (IQR:90-107)	99 (IQR:90-107)	.8
Serum creatinine (mg/dL)	1.89 ± 0.83	1.97 ± 0.81	1.82 ± 0.88	.5
eGFR (mL/min/1.73m^2)	52 ± 30	49 ± 25	56 ± 36	.6
CKD stage (%)				.7
1	8.3%	5.6%	11.1%	
2	27.8%	27.8%	27.8%	
3	38.9%	33.3%	44.4%	
4	25%	33.3%	16.7%	
Uric Acid (mg/dL)	7.4 ± 2	7.5 ± 1.6	7.3 ± 2.4	.7
Total cholesterol (mg/dL)	204 ± 45	209 ± 45	199 ± 46	.5
Serum triglycerides (mg/dL)	137 ± 62	138 ± 68	136 ± 56	.9
Fibrinogen (mg/dL)	380 ± 102	375 ± 131	385 ± 64	.8
Hemoglobin (g/dL)	14 ± 2.1	14.7 ± 2.2	13.4 ± 1.9	.07
Serum albumin (g/dL)	4 ± 0.4	4.1 ± 0.3	4 ± 0.5	.7
24-h proteinuria (g/d)	1.3 (IQR:0.8-1.8)	1.47 (IQR:0.86-2.13)	0.95 (IQR:0.77-1.6)	.3
Hematuria (cells/mmc)	26 (IQR:17-69)	28 (IQR:15-79)	24 (IQR:18-59)	.8
Estimated 5-yr risk of progression	24 (IQR:7-38)	27 (IQR:8-45)	21 (IQR:8-31)	.4
Renal Biopsy Findings				
% of glomeruli with global sclerosis	22 (IQR:0-39)	23 (IQR:0-50)	22 (IQR:0-25)	.9
MESTC score (% of patients)				
M1	83%	94%	72%	.1
E1	22%	22%	22%	1
S1	61%	72%	50%	.1
T1/T2	27% / 19%	27% / 22%	27% / 16%	.9
C1/C2	8% / 2%	11% / 5%	5% / 0%	.6

C = crescents, CKD = chronic kidney disease, E = endocapillary hypercellularity, eGFR = estimated glomerular filtration rate, IQR = interquartile range, M = mesangial hypercellularity, MAP = mean arterial pressure, S = segmental sclerosis, T = tubular atrophy/interstitial fibrosis.

Table 2

Mean change of eGFR and percentual change of proteinuria and hematuria over the 24-month treatment period.

	Budesonide group		Corticosteroid group		P* value
A. Mean change of eGFR from baseline (mL/min/1.73m^2)					
Period	Mean value (±SD)	Mean change (95% CI)	Mean value (±SD)	Mean change (95%CI)	
3-mo	48.3 ± 20.8	−0.77 (−9.5 to 8)	55.7 ± 33.8	−0.5 (−4 to 3)	.98
6-mo	48.5 ± 20.5	−0.61 (−8.5 to 7.3)	54.7 ± 36.1	−1.5 (−6.9 to 3.8)	.91
12-mo	46.7 ± 21.5	−2.38 (−10.4 to 5.6)	58.4 ± 38.9	2.1 (−4.2 to 8.5)	.34
18-mo	48.7 ± 27.6	−0.33 (−7.3 to 6.7)	54 ± 37.7	−2.22 (−8.8 to 4.4)	.66
24-mo	48.8 ± 26.8	−0.22 (−8.2 to 7.8)	50 ± 36.5	−5.89 (−12.2 to 0.4)	.44
B. Percentual change of proteinuria from baseline (g/d)					
Period	Median value (IQR)	Median change (IQR)	Median value (IQR)	Median change (IQR)	
3-mo	1.05 (0.6; 1.47)	−32% (−58%; 17%)	1.3 (0.8; 1.6)	0% (−23%; 8%)	.01
6-mo	1.1 (0.4; 1.6)	−46% (−66%; 0%)	0.9 (0.8; 1.4)	−1% (−38%; 8%)	.06
12-mo	1.1 (0.5; 1.6)	−43% (−56%; −4%)	1 (0.6; 1.6)	−8% (−41%; 18%)	.12
18-mo	1.05 (0.4; 1.6)	−45% (−70%; 2%)	0.98 (0.5; 1.6)	−22% (−42%; 21%)	.12
24-mo	1 (0.3; 1.5)	−45% (−79%; −22%)	1.3 (0.6; 1.9)	−11% (−39%; 43%)	.009
C. Percentual change of hematuria from baseline (cells/mmc)					
Period	Median value (IQR)	Median change (IQR)	Median value (IQR)	Median change (IQR)	
3-mo	27 (16; 50)	−12.5% (−50%; 32%)	33 (24; 86)	6% (−3%; 66%)	.14
6-mo	20 (12; 44)	−27% (−54%; 0%)	27 (12; 72)	−2% (−38%; 98%)	.16
12-mo	15 (9; 21)	−49% (−65%; −29%)	20 (9; 26)	−27% (−70%; 0%)	.26
18-mo	11 (7; 19)	−65% (−83%; −32%)	16 (4; 20)	−46% (−82%; −1%)	.28
24-mo	10 (5; 18)	−72% (−90%; −45%)	12 (5; 23)	−73% (−85%; 18%)	.22

eGFR = estimated glomerular filtration rate, IQR = interquartile range.
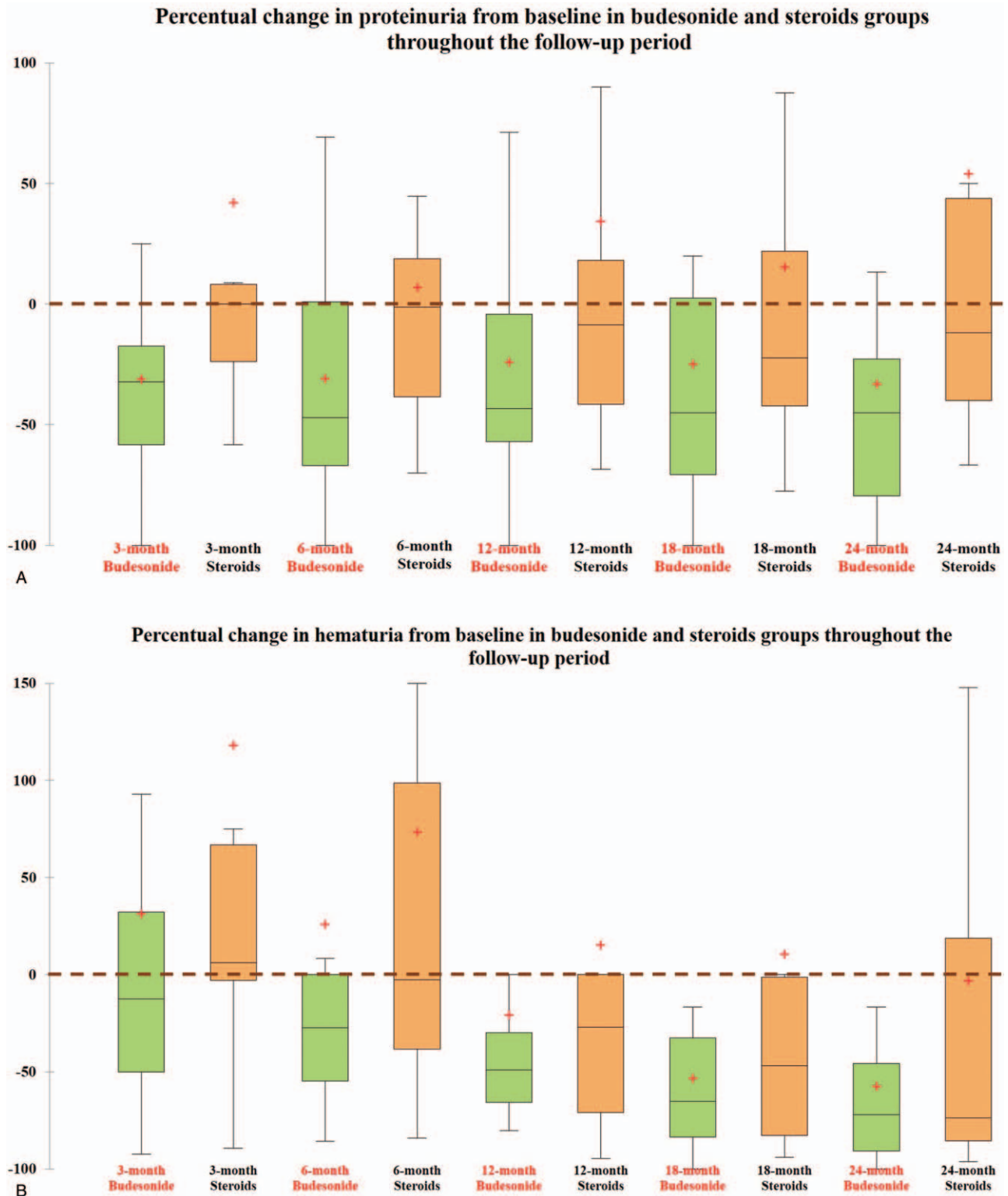* P value expresses between group differences at each time point.

Figure 2. A. Evolution of proteinuria over the follow-up period. B. Evolution of hematuria over the follow-up period.

with subsequent release of inflammatory and fibrotic mediators that will determine, through a mesangial-podocyte-tubular crosstalk, the spread of initial mesangial injury to the entire nephron, ultimately leading to loss of renal function.[2] The pathogenesis of IgAN provides the rationale for locally targeting

the mucosal immune system dysregulation and, most important-ly, targeting the initial pathogenic events, rather than the distant, renal effects of Gd-IgA1 and immune complex deposition.[21] Budesonide is a synthetic corticosteroid that offers the advantage of potent local anti-inflammatory effects combined with a low
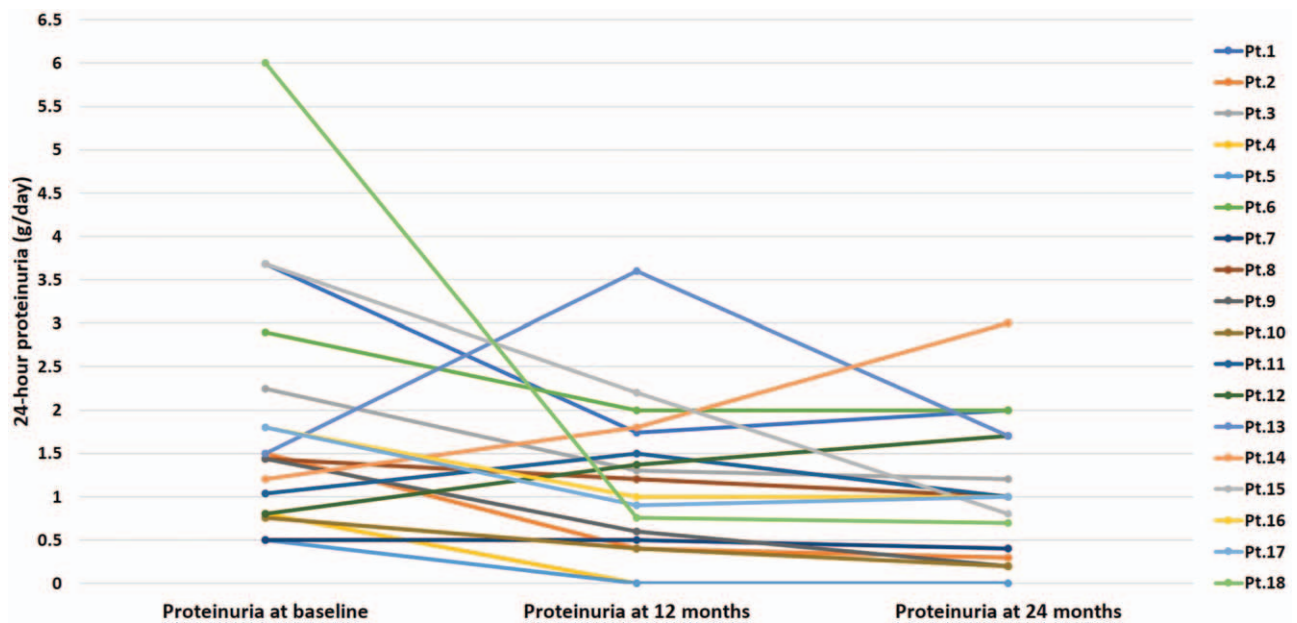
Figure 3. Individual evolution of proteinuria in budesonide-treated patients.

systemic bioavailability.[22] It is available in several formulations for the treatment of mild to moderate forms of Crohn's disease.[22] Budenofalk is a gastro-resistant, pH-modified formulation of budesonide with approximately 70% of active compound being released in the distal ileum and proximal colon, sites with highest density of Peyer's patches.[11,22] After absorption, budesonide undergoes an extensive first-pass metabolism via cytochrome P450 isoenzymes CYP3A4/CYP3A5 in the liver, with only about 10% of active compound finally entering systemic circulation.[11,22] As such, despite a stronger glucocorticoid effect than prednisone, the low systemic bioavailability offers the advantage of a safer profile.[11,22] A new targeted-release formulation of budesonide (Nefecon) was previously developed and tested in patients with IgAN.[21] In a phase 2a trial, a 6-month treatment with budesonide 8 mg/d (Nefecon) determined a 23% reduction in urinary albumin excretion and a 8% increase in eGFR.[8] However, no significant differences between pretreatment and posttreatment Gd-IgA1 levels were identified.[8] In a larger, randomized, placebo-controlled phase 2b trial, a 9-month treatment with budesonide (Nefecon) determined a 24.4% decrease from baseline in urine protein to creatinine ratio associated with a stabilization of renal function, an effect that was sustained throughout a follow-up of another 3 months.[9] Additionally, these effects were paralleled by a significant decline in Gd-IgA1-IgG immune-complex formation.[21] These results support the role of GALT dysregulation in

IgAN pathogenesis and offers the possibility for the first targeted-therapy to be approved in IgAN.[21]

Our study differs in several ways from previous studies. First, we did a propensity-matched comparison of 2 retrospective cohorts of patients treated with budesonide and systemic steroids, respectively. Second, these patients received a different formulation of budesonide (Budenofalk) in 2 sequential treatment periods (12 months with 9 mg/d followed by at least 12 months with a lower dose, 3 mg/d). This is, to our knowledge, the first report of a 24-month treatment period with budesonide in IgAN. We have shown a significant reduction from baseline in proteinuria and hematuria along with a stabilization of renal function. Proteinuria is 1 of the most robust predictors of renal function decline in IgAN[2]. In a meta-analysis evaluating the effect of early change in proteinuria (at 9 months) on clinical outcome (doubling of serum creatinine, end-stage renal disease or death) a 60% lower risk for a 50% reduction in proteinuria (HR per 50% reduction in proteinuria, 0.40; 95% CI, 0.32–0.48) was identified.[23] Additional data support the use of proteinuria reduction as a surrogate end point in trials of IgAN and as a basis for accelerated approval of therapies in this slowly progressive disease.[3] Along with change in proteinuria, GFR slope was recently proposed as a valid surrogate end point for clinical trials in early stages of chronic kidney disease.[24] We report a 45% decline in median proteinuria from baseline that was associated with a GFR decline of -0.22 ml/min over 24 months. This proteinuria reduction is higher than that reported in previous IgAN cohorts treated with other budesonide formulations (23% and 24.4%, respectively).[8,9] Proteinuria reduction was observed as early as 3 months from treatment initiation and was sustained throughout the entire treatment period. Our results are notable given the high-risk of progression population included in the study, with lower baseline eGFR (49±25 mL/min/1.73m^2) and higher proteinuria (median 1.47 g/d) than encountered in the NEFIGAN trial.[9] We characterized the risk of progression by reassessing all of our patients according to the recently proposed risk prediction

Table 3

Budesonide-related adverse events.

Adverse event	Number
Nausea	1
Viral upper respiratory tract infection	1
Oral candidiasis	1
Deep vein thrombosis/pulmonary embolism	1

tool[16] and identified a 5-year risk of progression of 24% (IQR:7-38%). This corresponds to a rate of eGFR decline of approximately 2-3 mL/min/1.73m^2/ year.[16] In our study, budesonide-treated patients had an absolute GFR decline of only -0.22 mL/min/1.73m^2 over the entire 24 months of treatment period. By comparison, the corticosteroid treated patients in previous randomized controlled trials had an eGFR decline of -0.56 mL/min/1.73m^2/year (Manno et al[13]), -1.79 mL/min/1.73m^2/yr (TESTING trial[6]) while the IS arm in the STOP-IgAN trial had an absolute eGFR decline of -1.4 mL/min/1.73m^2/yr[5]. Additionally, the propensity-matched group of corticosteroid-treated patients in our study had a 24-month eGFR decline of -5.89 mL/min/1.73m^2.

These results support the utility of the locally acting glucocorticoid formulation budesonide in the treatment of high-risk patients with IgAN and, indirectly, the role of dysregulated mucosal immunity in IgAN pathogenesis. The limitations of our study include the small number of patients, the retrospective design and lack of Gd-IgA1 and Gd-IgA1-IgG immune complexes assessment. However, the inclusion of a high-risk cohort treated for 24 months in 2 sequential periods and the possibility to compare it with a propensity-matched cohort of corticosteroid treated patients provides additional strengths to our results.

5. Conclusions

In summary, a pH-modified formulation of budesonide with a maximum release of active compound in the distal ileum and proximal colon was effective in the treatment of patients with IgAN at high-risk of progression in terms of reducing proteinuria, hematuria and preserving renal function over 24 months of therapy. Budesonide was well tolerated, with minimal side effects.

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