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Targeted-release budesonide in immunoglobulin A nephropathy; a mini-review

Shiva Toumaj[1], Shahrzad Alimohammadi[2,3], Maryam Ghasemi[4], Shokouh Shayanpour[5*]

[1]Nickan Research Institute, Isfahan, Iran
[2]Department of Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[3]Doctoral School of Molecular Medicine, University of Debrecen, Debrecen, Hungary
[4]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, USA
[5]Chronic Renal Failure Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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ABSTRACT

Immunoglobulin A nephropathy is the most common kind of primary glomerulonephritis worldwide and one of the main causes of renal failure. Systemic corticosteroid therapy may protect against renal deterioration in IgA nephropathy; however, it is not often advised for long-term treatment due to possible side effects. Recent studies present promising results of the new targeted-release formulation of budesonide that delivers the drug to the distal ileum to reduce side effects for patients with IgA nephropathy. In this paper, we highlighted the potential benefits of budesonide as a treatment option for IgA nephropathy and the need for additional studies to confirm its effectiveness. The lack of alternative treatments to prevent renal deterioration without other systemic side effects motivated us to gather relevant information to fill this gap. In this brief overview, we have reviewed some of the most recently published studies regarding how budesonide protects against IgA nephropathy. Studies reveal that budesonide might significantly decrease proteinuria, hematuria, and creatinine level while maintaining normal renal function. Though, a limited number of trials have been established to date, and further investigations are needed to confirm the benefit of the new targeted-release budesonide in treating IgA nephropathy.

Mini-Review

Implication for health policy/practice/research/medical education:
Preliminary data shows, patients with immunoglobulin A might clinically benefit from budesonide therapy, including the preservation of renal function and a decline in proteinuria and hematuria.

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Introduction

Immunoglobulin A nephropathy (IgAN) is an autoimmune kidney disease and also the most common primary (idiopathic) glomerulonephritis worldwide (1). Immunoglobulin A nephropathy can be diagnosed at any age; however, it is highly probable in the second and third decades of life. The prevalence of IgAN is higher in Asians and Western Europeans. Although both genders are affected equally in Eastern Asians, the male-to-female ratio is 2:1 in North American and Western European populations among adults and children. Most IgAN patients manifest microscopic or gross (single or recurrent) hematuria, with or without mild proteinuria. Patients may less frequently present signs of nephrotic syndrome or acute, rapidly progressing glomerulonephritis and rarely experience acute kidney injury with or without oliguria (2).

The importance of primary management of IgAN includes optimizing supportive treatment, which includes controlling blood pressure to optimal goals, reducing proteinuria by inhibiting the renin-angiotensin system, and providing appropriate lifestyle modifications (3). Only patients with a high risk of developing end-stage kidney disease (ESKD) despite receiving the most supportive care and those with specific types of progressive disease should receive immunosuppressive therapy (4). Immunosuppressants such as corticosteroids improve outcomes in IgAN patients while inducing significant side effects. In IgAN patients, supportive care and oral systemic glucocorticoids have been recommended instead of only supportive care (5).

Recently, budesonide has presented promising results

***Corresponding author**: Shokouh Shayanpour, Email: shayanpour-sh@ajums.ac.ir, dr.shayanpour@yahoo.com

in IgAN treatment (6). The formulation of budesonide is well suited for the targeted treatment of inflammatory illnesses, such as Crohn's disease, which affects the ileum and ascending colon. For treating mild-to-moderate active Crohn's disease (affecting the ileum and/or ascending colon) and also for prolonging symptom control, budesonide has been authorized (7). In oral budesonide treatment, the locally acting budesonide undergoes a significant, primarily hepatic metabolism. It is rapidly absorbed and broken down into two metabolites in the liver, 16alpha-hydroxyprednisolone; and 6β-hydroxy Budesonide, by the cytochrome P450 isoenzyme CYP3A4. About 90% of budesonide taken orally bypasses first-pass metabolism, resulting in a low 10–15% systemic bioavailability (8). In comparison with conventional glucocorticoids, budesonide has a lower systemic action, resulting in a reduced impact on bone mass and adrenal function. Growth failure may occur in individuals receiving long-term budesonide treatment, either due to direct suppression of linear growth or an inability to completely control disease activity (9).

Literature review

In this part, we have thoroughly studied three articles. In this regard, Ismail et al (6), in a retrospective propensity-matched comparative trial, assessed the effectiveness of budesonide (Budenofalk) in treating IgAN. After following 143 patients with IgAN at the Fundeni Clinical Institute's Nephrology Department, they found 18 individuals who got budesonide 9 mg/d during the first 12 months and lowered it to 3 mg/d after 12 months. Eighteen patients with IgAN who received systemic steroids from the same retrospective cohort were propensity matched to these patients. Compared to the corticosteroid therapy group, budesonide therapy was associated with a 24-month decrease in renal function of -0.22 ml/min/1.73 m^2, rather than -5.89 ml/min/min/1.73m^2. At 24 months, the median reduction in proteinuria was 45% in the budesonide group, compared to 11% in the corticosteroid group. In the budesonide group, the median decrease in hematuria at 24 months was 72%, whereas in the corticosteroid group, it was 73%. The side effects of budesonide were not significant.

Furthermore, Smerud et al (10) investigated the efficacy and safety of budesonide. Sixteen patients with IgAN received budesonide 8 mg/d for six months, followed by a 3-month follow-up period. Changes in 24-hour urine albumin excretion, serum creatinine, and estimated glomerular filtration rate (eGFR) were conducted to determine effectiveness. Throughout the treatment period, a median relative reduction in urine albumin excretion was 23%. Two months following the end of the therapy, the median decrease in urine albumin reached a maximum of 40%. During treatment, eGFR increased by around 8% while serum creatinine decreased by 6%. There were no significant corticosteroid-related side effects reported.

In 62 nephrology clinics in ten different European countries, Fellström et al (11) conducted a phase 2b trial that was randomized, double-blind, placebo-controlled, and divided into phases for a 6-month run-in, a 9-month treatment, and a 3-month follow-up. 150 randomly selected patients were treated in the safety set, and 149 patients qualified for the entire analysis set. At nine months of targeted-release formulation of budesonide (16 mg/d plus 8 mg/d), the mean urine protein creatinine ratio (UPCR) had reduced by 24.4% from baseline (mean UPCR had decreased by 27.3% in 48 patients receiving 16 mg/d and by 21.5% in 51 patients receiving 8 mg/d). On the other hand, mean UPCR had increased by 2.7% in 50 patients receiving a placebo. Deep vein thrombosis and unexplained deterioration were two more significant side effects.

Discussion

According to the existing evidence, patients with IgAN might clinically benefit from budesonide therapy, including the preservation of renal function and a decline in proteinuria, hematuria, and creatinine level. Moreover, budesonide is generally well-tolerated and causes fewer side effects. Therefore, budesonide therapy could signify an effective method of treating IgA nephropathy. However, the findings of the present investigations require confirmation by a large-scale, prospective, randomized, controlled clinical trial. Hopefully that the role of budesonide in the treatment of IgA nephropathy will be confirmed with new clinical trials and further studies.

Authors' contribution

Conceptualization: ST.
Investigation: SS.
Resources: ST.
Visualization: ST.
Supervision: SS.
Writing–original draft preparation: ST.
Writing–review and editing: SA, MG.
Project administration: SS.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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