Entomology and Applied Science Letters
Volume 8, Issue 2, Page No: 85-90

Available Online at: www.easletters.com

ISSN No: 2349-2864

Literature Review: The Efficacy of Glucocorticoids in IgA Nephropathy Patients

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ABSTRACT

Primary most common cause of IgA nephropathy represents glomerulopathy worldwide. While initially thought this disease course was benign and self-limited, a few studies have appeared that it cause renal disease development and continued to end-stage renal disease in nearly one-third of the affected patients. IgA nephropathy is commonly actuated by autoimmune antigens targeting the glomerular mesangium, leading to IgA accumulation. This literature review investigates the efficacy and safety of corticosteroids therapy in IgA nephropathy and provides an updated review of the disease mechanism and pathophysiology. We used the PubMed database, searching for relevant articles on the topic. The following Mesh words were used: IgA nephropathy, corticosteroids, management, adverse effects. Several immunosuppressive therapies were used in addition to standard management for IgA nephropathy. Corticosteroids seem to provide more beneficial effects than other agents, and some studies addressed this efficacy when corticosteroids are added to other immunosuppressive agents. Nonetheless, serious adverse events were reported in the steroids groups, such as serious infection, gastrointestinal symptoms and bleeding, diabetes mellitus, and impaired glucose intolerance. These serious adverse events cannot be ignored and must be encountered seriously in future clinical trials.

Keywords: IgA nephropathy, Nephrotic syndrome, Glomerulonephritis, Corticosteroids, End-stage renal disease.

HOW TO CITE THIS ARTICLE: Aljebrin YJ, Rashed AAB, Alahmed MA, Alsamadani JH, Mahamat FMA, Alrsheedi ASE, et al. Literature Review: The Efficacy of Glucocorticoids in IgA Nephropathy Patients. Entomol Appl Sci Lett. 2021;8(2):85-90. https://doi.org/10.51847/mSqg8ILxvW

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Received: 31/03/2021
Accepted: 19/06/2021

INTRODUCTION

Dr. J. Berger was the first scientist who recognized IgA nephropathy (IgAN) in 1968, which was manifest by diffuse deposits of mesangial IgA on immunofluorescence microscopy. Initially, the malady was believed to be the uncommon and benign cause of rehashed hematuria. Be that as it may, it has since gotten to be clear that IgAN is neither rare nor benign [1]

and is the frequent cause of primary glomerulonephritis around the world [1, 2]. IgAN in up to 15-20% of patients within 10 years from the malady onset which leads to end-stage renal disease (ESRD) and 30-40% within 20 years [2]. Several risk factors have been demonstrated association with IgAN progression, including persistent proteinuria and specific findings on renal biopsy; these findings may help select adequate therapy for IgAN patients [1]. IgAN is a slowly progressive disease that takes years to reach the final stage of clinical usually look into clinical trials [1]. While the main attention is for primary IgAN, secondary IgAN can be induced by other disorders listed in **Table 1**. The commonest disorder among these is Schönlein–Henoch purpura [3].

IgAN affects the body at any age, and the onset is commonly influencing the 2nd and the 3rd decades of life. There is a male: female proportion extending from less than 2:1 in Japan to as high as 6:1 in northern Europe and the United States. Furthermore, Whites and Asian populaces are more inclined to IgA nephropathy compared with black individuals, which remains unexplained. The epidemiological data of IgAN is few to this moment and considered variable among different populations. The recorded incidence in France and one each within The Netherlands, Germany, and Italy changed from 15 to 40 new cases per 1 million population yearly. On the contrary, one study within the United States posted an increment from five cases (from 1975 to 1979) to 12 cases (from 1990 to 1994) every year for each million populace. Moreover, the predominance shows up to be higher in Asia, Australia, Finland, and Southern Europe, representing 20-40%. Nonetheless, the predominance rates are much lesser in the United States, United Kingdom, and Canada [3].

IgAN patients out to be closely monitored by a nephrologist and treated appropriately. Within the last decade, epidemiological, clinical, serological, and histological prove have demonstrated that dynamic IgAN is related to proteinuria, hypertension, kidney function disability, the gravity of glomerulosclerosis, and tubulointerstitial fibrosis in renal pathology, and gene polymorphism. Moreover, initial markers of dynamic IgAN incorporate hefty proteinuria (>1g/day), high blood pressure, altered kidney function (increased serum creatinine by >10% inside three months), glomerular sclerosis, crescent arrangement, fibrosis, and vascular sclerosis. IgAN, in the case clear out untreated, can worsen into renal failure in a short-term period [4].

Table 1. Diseases-induced Secondary IgA Nephropathy

Liver disease: Hepatitis C, Cryptogenic or Primary biliary, Alcohol, Chronic Schistosomiasis
Intestinal disorders: Celiac disease, Chronic ulcerative colitis, Chroh'n disease
Skin disorders: Dermatitis herpetiformis; Psoriasis
Lung/Bronchus diseases: Cystic fibrosis, Sarcoidosis, Bronchiolitis obliteration, Idiopathic primary hemosiderosis
Malignancies: Mycosis fungoides, Carcinoma of the pancreas, larynx, and lung
Infection: Leprosy, Human immunodeficiency virus
Immunologic and other systemic disorder: Rheumatoid arthritis, Behcet's disease, Psoriatic arthritis, Ankylosing spondylitis, Sjögren's syndrome, Familial immune thrombocytopenia, Good-pasture's syndrome, Cryoimmunoglobulinemia, Systemic lupus erythematosus,
IgA Nephropathy with Coincidence disease: Diabetic nephropathy, Wegner's granulomatosis, Membranous nephropathy, ANCA-associated vasculitis

Abbreviations: ANCA; Anti-neutrophil Cytoplasmic Antibodies

IgAN pathogenesis

IgAN is induced by the IgA1 glycans galactosylation and sialylation, accounting for almost 90% of IgA cases. In patients with IgAN, IgA1 molecules contain an anomalous structure of their O-glycans, described by abbreviated glycans composed of N-acetylgalactosamine either with or without sialic acid. The anomalous IgA1 glycosylation is identified as an autoantigen that produces the integration of glycan-specific autoantibodies [5]. Consequently, the union of antibodies to antigens produces circulating immune complexes, which concentrate within the mesangium and impact the actuation of mesangial cells, creation of extracellular matrix, and discharge of proinflammatory cytokines and chemokines [5, 6]. The latter can initiate and propagate glomerular inflammation and damage [5, 6]. The complement system can be actuated via the alternative (the lectin) pathway, which also plays an important role in IgAN pathogenesis [5].

RESULTS AND DISCUSSION

Therapeutic approach for IgAN

IgAN management has been and continues to be debatable among nephrologists. Despite advanced comprehension of the underlying IgAN pathogenesis, there is currently no definite treatment that can specifically prevent the production of galactose-deficient IgA1 or its corresponding autoantibodies that are central to the disease process, IgA1-immune complex formation, or their glomerular mesangium deposition [7]. The Worldwide of contemporary Kidney Disease-Improving Outcomes (KDIGO) Clinical Hone Guidelines and recommended longer-term angiotensin-converting protein inhibitors (ACEi) for Glomerulonephritis or Angiotensin-receptor blockers (ARBs) as treatment when proteinuria is >0.5-1g/day, with dosage up-titration concurring to the blood pressure. Since the early 1980s, a few therapeutic approaches have been suggested, more than in other nephropathies: tonsillectomy, diminished antigenic stack diet, diphenylhydantoin, disodium cromoglycate, danazol, eicosapentaenoic acid, ACEi, ARBs, endothelin receptor antagonists, high dose intravenous immunoglobulins, plasmapheresis, cancer-preventing agent, vitamin E, omega-3-fatty acids, warfarin, dipyridamole, cyclosporin, azathioprine, cyclophosphamide, mycophenolate mofetil, corticosteroids, mizoribine, rituximab, heparin, and budesonide, statins [8].

Patients with the constant proteinuria >1g/day and >50 ml/min of glomerular filtration rate (GFR) despite 3-6 months of maximum management optimization (including ACEi or ARBs), they suggest a 6-month program of corticosteroid treatment [8-10]. Overall, immunosuppressant therapy is believed to provide more beneficial effects in IgAN with moderate and high risk [9]. Nevertheless, recent KDIGO recommendations provide no clear guide for immunosuppression in IgAN patients with GFR between 30 and 50ml/min due to recent RCTs that have rarely recruited this high-risk population [10]. Interestingly, glucocorticoids receptor (GCR) expression played an important role in steroid therapy response, where patients with high GCR expression were likely to reach complete remission and less likely to progress to ESRD than with lower GCR expression. Early studies from Italy and Japan demonstrated beneficial therapeutic effects of steroid therapy on kidney function preservation [11].

Evidence-based medicine

In two retrospective studies, low-dose corticosteroids (prednisolone 30mg/day for 3 months) combined with oral cyclophosphamide provide more significant beneficial effect than supportive measures in IgAN patients with reduced renal function [12]; The second study [13] demonstrated also greater efficacy of steroid therapy compared to non-steroid therapy in advanced IgAN patients, in the forms of reduced proteinuria and maintain creatinine level [12, 13]. Moderate proteinuria and dynamic glomerular lesion are postliminary studies that indicate effectiveness especially for IgAN patients, such as cellular and fibrocellular crescent and mesangial cell propagation [13]. Additionally, Kobayashi *et al*. had demonstrated in their study that steroid treatment is viable in IgAN patients with mild renal damage and proteinuria (~2/day) [13] Even in post-renal transplanted patients secondary to IgAN, although there are no current guidelines to prevent recurrent IgAN after renal transplantation, Messina *et al*. had completed a retrospective single-center study on 29 patients with biopsy-proven de novo and recurrent IgAN after renal transplantation. This study showed that pulse steroid therapy for 6 months was correlated with enhanced kidney function compared with patients who received standard supportive therapy [14]. Furthermore, a few randomized clinical trials (RCT) had illustrated the useful impact of corticosteroids monotherapy or additionally to the standard therapy for IgAN patients. For example, in Manno *et al*. RCT, 97 IgAN patients with nephrotic proteinuria were randomized to get a 6-month course of oral prednisolone plus ramipril (combination treatment) or ramipril alone (monotherapy group).

The combination treatment gives an advantageous impact compared with ramipril monotherapy in preventing the risk of renal malady progression in proteinuric IgAN patients in the long-term follow-up. The chance of renal disease progression was essentially decreased by 87% within the combination treatment. On the contrary, the chance of reaching the combined results (renal disease progression and rate of renal function decline) was overwhelmingly increased with each g/24 h increment in a pattern of urinary proteinuria excretion and each

mg/dl increment in standard serum creatinine. Even after multivariate investigation, the risk of reaching the results was 91% lower within the combination group than within the monotherapy group. The risk expanded significantly more than three times for each g/24h increment in pattern urinary protein excretion [15].

In addition, Ponzzi *et al*. had conducted an RCT, correlating the adequacy of treatment of the steroid oral prednisone 0.5 mg/kg on alternate days for 6 months and ((intravenous methylprednisolone 1g per day for 3 sequential days at the beginning of 1, 3, and 5, months) with standard steady treatment alone. This trial concluded that steroid treatment for a 6-month protected against the primary result (deterioration in renal function) with no clear antagonistic events amid follow-up. Moreover, the steroid useful impact was specifically related to the rate of increment in urinary protein excretion [16]. Besides, in a multicenter, randomized, (prednisolone, azathioprine, heparin-warfarin, and dipyridamole) controlled trial that included 78 children with IgAN were chosen to receive two years of combination treatment or control treatment (heparin-warfarin and dipyridamole). After auxiliary examination, the combination treatment essentially ameliorated acute phase nephritis activity and improved the long-term result of severe childhood IgAN. Also, proteinuria was decreased by 87% from pattern within the combination group compared with only a 21% reduction in the control group. The proportion of patients with overwhelming proteinuria was essentially low at the combination group at the end of the initial two years of treatment in addition to 100% likelihood of renal survival rate in patients without proteinuria at the entire long-term follow-up period [17].

Steroids efficacy and safety considerations

In two systematic reviews, corticosteroids demonstrated a significant reduction in proteinuria and progression into ESRD [18, 19]. In addition, long-term steroid therapy has higher efficacy than short-term therapy and standard therapy in reducing ESRD risks, urinary protein excretion, and urinary protein excretion [18]. Corticosteroids were also found to significantly improve clinical remission rates and the risk of ESRD compared to supportive management alone [20]. Another meta-analysis also demonstrated superior efficacy of corticosteroid compared to standard therapy, particularly impairment of renal function occurs in patients with hypertension or older people [21]. Lin *et al*. had conducted a meta-analysis and compared the efficacy of corticosteroids withs other immunosuppressants therapy in IgAN patients. Similarly, steroids treatment has statistically significant impacts in preventing the decline in renal function, even though this result was not altered by steroids type [22].

Nonetheless, corticosteroids use was linked with several high-risk adverse events [19-21]. For instance, diabetes mellitus or impaired glucose intolerance, high blood pressure, gastrointestinal bleeding, cushingoid features, insomnia, headache, increased weight, and significant infection [19-21]. The frequency of gastrointestinal symptoms, such as gastrointestinal bleeding, enhanced appetite, and dyspepsia, represent vital antagonistic impacts, and these effects increased by 105% within the steroid group [22]. Furthermore, a recent study showed that 18/369 (4.9%) patients had a serious or deadly infection. The TESTING and STOP trials detailed death, in which 2 cases of the steroid group in TESTING and 1 within the placebo group died, while within the STOP trial, 1 case of the steroid group died in an accident, and no deaths were detailed in the placebo group [22]. Subsequently, the adverse incidence in response to corticosteroids must be taken genuinely, and patients experiencing such trials must be closely observed.

CONCLUSION

Although IgA nephropathy's pathogenic mechanism is well understood nowadays, there is no substantiate treatment to prevent advancement to end-stage renal disease. Almost one-third of affected patients eventually developed the end-stage renal disease, mainly after 20 years. Hence, several immunosuppressants have been studied to encounter this complication, of which corticosteroids appear to provide a significant reduction in renal disease progression and proteinuria. However, some trials have reported serious adverse events secondary to steroid use, for which treated patients must be closely monitored. Further randomized, multicenter

clinical trials are warranted to establish the exact rate of adverse events.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Samuels JA, Strippoli GF, Craig JC, Schena FP, Molony DA. Immunosuppressive agents for treating IgA nephropathy. Cochrane Database Syst Rev. 2003;(4):CD003965. doi:10.1002/14651858.CD003965. Update in: Cochrane Database Syst Rev. 2015;8:CD003965.
2. Zheng J, Gong X, Wu Z. Immunosuppressive agents in the treatment of IgA nephropathy: A meta-analysis of clinical randomized controlled literature. Niger J Clin Pract. 2020;23(4):437-49. doi:10.4103/njcp.njcp_112_18.
3. Donadio JV, Grande JP. IgA nephropathy. N Engl J Med. 2002;347(10):738-48. doi:10.1056/NEJMra020109.
4. Wang W, Chen N. Treatment of progressive IgA nephropathy: an update. Contrib Nephrol. 2013;181:75-83. doi:10.1159/000348460.
5. Locatelli F, Del Vecchio L, Ponticelli C. Should we really STOP treating patients with IgA nephropathy with steroids? Physiol Int. 2018;105(2):101-9.
6. Coppo R. Corticosteroids in IgA Nephropathy: Lessons from Recent Studies. J Am Soc Nephrol. 2017;28(1):25-33.
7. Cheung CK, Rajasekaran A, Barratt J, Rizk DV. An Update on the Current State of Management and Clinical Trials for IgA Nephropathy. J Clin Med. 2021;10(11):2493.
8. Pozzi C. Treatment of IgA nephropathy. J Nephrol. 2016;29(1):21-5.
9. Zhang Z, Yang Y, Jiang SM, Li WG. Efficacy and safety of immunosuppressive treatment in IgA nephropathy: a meta-analysis of randomized controlled trials. BMC Nephrol. 2019;20(1):1-2. doi:10.1186/s12882-019-1519-3
10. Tesar V, Troyanov S, Bellur S, Verhave JC, Cook HT, Feehally J, et al. Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study. J Am Soc Nephrol. 2015;26(9):2248-58.
11. Kee YK, Nam BY, Jhee JH, Park JT, Lim BJ, Yoo TH, et al. The Association of Glomerular Glucocorticoid Receptor Expression with Responsiveness to Corticosteroid Treatment in IgA Nephropathy. Am J Nephrol. 2019;50(3):187-95. doi:10.1159/000502327.
12. Ma F, Yang X, Zhou M, Bai M, Zhao L, Li L, et al. Treatment for IgA nephropathy with stage 3 or 4 chronic kidney disease: low-dose corticosteroids combined with oral cyclophosphamide. J Nephrol. 2020;33(6):1241-50.
13. Moriyama T, Honda K, Nitta K, Yumura W, Nihei H. The effectiveness of steroid therapy for patients with advanced IgA nephropathy and impaired renal function. Clin Exp Nephrol. 2004;8(3):237-42.
14. Messina M, Di Vico MC, Ariaudo C, Mazzucco G, Fop F, Segoloni GP, et al. Treatment protocol with pulse and oral steroids for IgA Nephropathy after kidney transplantation. J Nephrol. 2016;29(4):575-83.
15. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. Nephrol Dial Transplant. 2009;24(12):3694-701. doi:10.1093/ndt/gfp356
16. Pozzi C, Bolasco PG, Fogazzi GB, Andrulli S, Altieri P, Ponticelli C, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet. 1999;353(9156):883-7. doi:10.1016/s0140-6736(98)03563-6.
17. Kamei K, Nakanishi K, Ito S, Saito M, Sako M, Ishikura K, et al. Long-Term Results of a Randomized Controlled Trial in Childhood IgA Nephropathy. Clin J Am Soc Nephrol. 2011;6(6):1301-7.
18. Zhou YH, Tang LG, Guo SL, Jin ZC, Wu MJ, Zang JJ, et al. Steroids in the Treatment of IgA Nephropathy to the Improvement of Renal Survival: A Systematic Review and Meta-Analysis. Plos One. 2011;6(4):e18788. doi:10.1371/journal.pone.0018788

19. Lv J, Xu D, Perkovic V, Ma X, Johnson DW, Woodward M, et al. Corticosteroid Therapy in IgA Nephropathy. J Am Soc Nephrol. 2012;23(6):1108-16.
20. Han S, Yao T, Lu Y, Chen M, Xu Y, Wang Y. Efficacy and Safety of Immunosuppressive Monotherapy Agents for IgA Nephropathy: A Network Meta-Analysis. Front Pharmacol. 2021;11:539545. doi:10.3389/fphar.2020.539545.
21. Qian G, Zhang X, Xu W, Zou H, Li Y. Efficacy and safety of glucocorticoids for patients with IgA nephropathy: a meta-analysis. Int Urol Nephrol. 2019;51(5):859-68.
22. Lin Y, Jia J, Guo Y, He D, Zhang Y, Wang F, et al. Corticosteroid for IgA Nephropathy: Are They Really Therapeutic?. Am J Nephrol. 2018;47(6):385-94.