

Journal of Nephrospathology



Advances in IgA nephropathy management, from pathological insights to personalized treatment

Mitra Shavakhi^{1*}, Agha Wajdan Baqir²

¹Nickan Research Institute, Isfahan, Iran

²Department of Pathology, University of Mississippi Medical Center, Jackson, Mississippi, United States

ARTICLE INFO

Article type:
Min-Review

Article history:
Received: 26 April 2023
Accepted: 21 June 2023
Published online: 14 August 2023

Keywords:
IgA nephropathy, Targeted-release
budesonide, Corticosteroid, Oxford
classification, MEST-C score

ABSTRACT

IgA nephropathy is a common glomerulonephritis with variable clinical outcomes. The optimal treatment for this condition remains uncertain, and corticosteroid therapy is reserved for patients unresponsive to supportive treatment. The histopathologic examination has a significant role in the diagnosis and prognosis of IgA nephropathy, but its role in the initiation of corticosteroid therapy is still under debate. Recently, targeted release formulation (TRF)-budesonide has emerged as a promising treatment due to its localized delivery to the gut and low systemic adverse effects. This brief review aims to assess recent advancements in IgA nephropathy management, focusing on applying Oxford classification in guiding corticosteroid therapy.

Implication for health policy/practice/research/medical education:

Targeted release formulation-budesonide is a novel formulation of budesonide-corticosteroid for IgA nephropathy treatment. By incorporating histopathological features, the MEST-C score provides clinicians with valuable information for identifying patients likely to benefit from corticosteroid therapy.

Please cite this paper as: Shavakhi M, Baqir AW. Advances in IgA nephropathy management, from pathological insights to personalized treatment. J Nephrospathol. 2023;x(x):e21480. DOI: 10.34172/jnp.2023.21480.

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common type of primary glomerulopathy worldwide. It is a significant leading cause of chronic kidney disease and end-stage renal failure. The geographic distribution of IgAN varies significantly, with a higher prevalence in East Asian countries (1,2). IgAN is more common in males, with a male-to-female ratio of 3:1 in the Europeans (2).

Clinical manifestations range from asymptomatic disease to episodes of macroscopic hematuria and/or proteinuria, while in some cases, this disease presents as rapidly progressive glomerulonephritis (3).

Histopathologic evaluation of the kidney biopsy specimen is essential for the diagnosis of IgAN. Immunoglobulin A deposits in the mesangium of the glomeruli are a defining characteristic of IgAN. Researchers have proposed multiple mechanisms to explain the deposition of IgA within this particular area (4).

The pathogenesis of IgAN involves multiple hits;

an increased level of circulating pathogenic poorly O-galactosylated IgA1, production of IgG and IgA autoantibodies, which target this galactose-deficient IgA1 (Gd-IgA1), and the formation of IgA1-immune complex. This complex deposits in the glomerular mesangium and triggers kidney injury (5,6). Moreover, evidence suggests that the deregulation of the mucosal immune system plays a crucial role in the pathophysiology of IgAN (7). The ideal treatment for IgAN remains uncertain. However, the 2021 guideline of KIDGO (Kidney Disease: Improving Global Outcomes) recommends supportive care, control of hypertension, and antiproteinuric therapy such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, corticosteroids, immunosuppressive agents, and other non-pharmacological approaches. It recommends corticosteroid therapy for patients with persistent proteinuria (>1 g/d) and glomerular filtration rate (eGFR) >50 mL/min/1.73 m² despite 6-month optimized renin-angiotensin-system (RAS) blockade (8).

*Corresponding author: Mitra Shavakhi,
Email: mitrashavakhi@gmail.com

Corticosteroids may reduce the long-term risk of progression to end-stage renal disease but require considerations regarding patient selection, optimal dosage, formulation, and duration of treatment. Recent trends focus on personalized medicine based on individualized risk prediction by clinical and pathological tools (9). Targeted release formulation (TRF)-budesonide is a novel therapeutic option, designed to target the gastrointestinal immune system. It delivers to the distal ileum with a high density of Peyer's patches and restricts the release of IgA with aberrant glycosylation from the intestinal wall of patients with IgAN. It is a potent corticosteroid with TARGIT™ drug delivery technology which enables local drug delivery to the distal ileum (10). TRF-budesonide undergoes "first-pass" hepatic metabolism into the inactive conjugates, minimizing systemic steroid exposure with a bioavailability of less than 10% (11).

Literature review

This brief review will provide an overview of recent advances in IgA nephropathy management, with a specific focus on the practical application of the MEST-C score for corticosteroid therapy.

Since the introduction of Nefecon®, several studies have assessed the safety and efficacy of this novel drug. The NEFIGAN trial, a phase 2b randomized, placebo-controlled, double-blind trial conducted at 62 nephrology clinics across 10 European countries, is a study that enrolled 207 patients with IgA nephropathy in the run-in phase, over a treatment period of 9 months and a 3-month follow-up. They compared TRF-budesonide in two doses (16 mg/d versus 8 mg/d) against a placebo. They showed a significant decrease in the mean urine protein to creatinine ratio from baseline by 27% for 16 mg/d of TRF-budesonide and 21.5% for 8 mg/d of this drug. Moreover, TRF-budesonide stabilized kidney function (eGFR) while placebo-treated patients experienced a decline in glomerular filtration rate. Budesonide's effect was dose- and time-dependent. TRF-budesonide served as an adjunct to optimized RAS blockade and supports the administration of it as a supplemental treatment. It was safe and well-tolerated, with only two serious adverse effects reported, including deep vein thrombosis and unexplained deterioration of renal function. Some patients experienced solicited corticosteroid-related adverse events and discontinued the treatment (12). The positive findings of the NEFIGAN study led to the NefIgArd study, a phase three trial, conducted to verify the effectiveness, safety profile, and tolerability of Nefecon 16 mg/d in patients diagnosed with primary IgAN who were at risk of progression to kidney failure despite administration of RAS blockades. This multinational trial is currently underway, spanning 112 clinical sites across Europe, North

America, South America, and Asia Pacific region. The study enrolled 199 patients with a nine-month medication and a three-month follow-up period, in addition to optimized and stable RAS blockade therapy. After nine months of treatment, the urine protein creatinine ratio and urine albumin-creatinine ratio reduced by 27% and 31% respectively in comparison with the placebo, while during the treatment by this drug, renal function decline was attenuated. In part B, patients are monitored for a further 12 months while treatment with optimized RAS blockade continues. Participants tolerated the 9-month course treatment well, experiencing a low rate of adverse events. It did not increase the risk of severe infection, fracture, or osteonecrosis (13).

By contrast, previous trials, including the TESTING trial and STOP-IgAN trial observed significant adverse events such as death, infections, and impaired glucose tolerance with additional immunosuppression (14). The low bioavailability of Nefecon may justify its low rate of serious adverse effects. The NefIgArd study did not test prolonged administration; hence the optimal duration of therapy is still unclear. One limitation of the NefIgArd study was that they did not perform a contemporary renal biopsy, therefore the renal pathology status was indeterminate. We recommend randomized controlled trials (RCTs) to include histopathologic parameters with a follow-up biopsy to evaluate the effect of corticosteroid therapy on renal lesions. The Oxford classification of IgAN was officially published in 2009 as a histopathologic tool and has been updated based on new investigations. Five features to be evaluated include mesangial proliferation (M), endocapillary proliferation (E), segmental sclerosis (S), tubular atrophy and interstitial fibrosis (T), and crescent (C) score. MEST-C scores allow risk stratification at an early point and predict renal outcomes independently of clinical parameters (3). We encourage the application of the Oxford classification (MEST-C scores) for precision therapy of patients who might benefit from Nefecon. Several studies validated the Oxford classification. A study by Moriyama et al validated the revised Oxford classification considering treatment with corticosteroids/immunosuppressants. They demonstrated corticosteroids/immunosuppressants enhanced long-term renal prognosis, especially in patients with the presence of segmental sclerosis (S1), endocapillary proliferation (E1), and crescent lesions up to 25% of glomeruli (C1). Based on their finding, corticosteroid therapy can resolve C1 lesions, which are presumed to be an indicator of disease progression. The T score posed an independent risk factor for the progression to end-stage renal disease (15).

Another study by Itami et al developed a novel grading scale based on Oxford classification as steroid responder score (SRS) and steroid non-responder score (SNRS).

They assigned the cumulative sum of M1, S1, E1, and C1+2 scores to represent the SRS and it ranges between 0-4.

In contrast, the T1+2 scores were deemed unresponsive to steroid therapy, ranging from 0-1. The T score emerged as the best indicator of the renal prognosis. Their findings revealed that steroid therapy was more beneficial in high SRS/ low SNRS patients (16). Recently a post hoc analysis of the European VALIGA cohort validated the application of this novel Oxford scale for steroid therapy. Their findings were similar to the Itami cohort (17).

This innovative scale for assessing steroid therapy in IgA nephropathy patients is advantageous due to its comprehensive nature, as it considers the cumulative sum of multiple histological features rather than relying on a single parameter. It helps in determining the feasibility of the Oxford classification system for guiding a personalized and targeted approach to corticosteroid therapy.

Conclusion

TRF-budesonide is a promising new drug for IgA nephropathy treatment that received accelerated approval from the US Food and Drug Administration (FDA) as the first therapy for IgA nephropathy patients at high risk of disease progression. The MEST-C score is a valuable histopathologic tool that can aid in determining the appropriate candidates for corticosteroid therapy, thus minimizing overtreatment and avoiding potential side effects. Well-designed RCTs are required to determine the benefits of TRF-budesonide in selected patients based on the MEST-C score.

Authors' contribution

Conceptualization: MSh.

Methodology: MSh.

Validation: MSh.

Formal analysis: MSh.

Investigation: MSh.

Resources: MSh.

Data curation: MSh.

Visualization: MSh.

Supervision: AWB.

Project administration: MSh.

Writing-original draft: MSh.

Writing-review and editing: AWB.

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.

Funding/Support

None.

References

1. Schena FP, Nistor I, editors. Epidemiology of IgA nephropathy: a global perspective. *Seminars in nephrology*; 2018: Elsevier. doi: 10.1016/j.semnephrol.2018.05.013.
2. Magistroni R, D'Agati VD, Appel GB, Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. *Kidney Int.* 2015;88:974-89. doi: 10.1038/ki.2015.252.
3. Gutiérrez E, Carvaca-Fontán F, Luzardo L, Morales E, Alonso M, Praga M. A personalized update on IgA nephropathy: a new vision and new future challenges. *Nephron.* 2020;144:555-71. doi: 10.1159/000509997
4. Perše M, Večerić-Haler Ž. The Role of IgA in the Pathogenesis of IgA Nephropathy. *Int J Mol Sci.* 2019 Dec 9;2:6199. doi: 10.3390/ijms20246199.
5. Habas E, Ali E, Farfar K, Errayes M, Alfitori J, Habas E, et al. IgA nephropathy pathogenesis and therapy: Review & updates. *Medicine.* 2022;101:e31219. doi: 10.1097/MD.00000000000031219
6. Scionti K, Molyneux K, Selvaskandan H, Barratt J, Cheung CK. New Insights into the Pathogenesis and Treatment Strategies in IgA Nephropathy. *Glomerular Dis.* 2022;2:15-29. doi:10.1159/000519973
7. Chang S, Li XK. The Role of Immune Modulation in Pathogenesis of IgA Nephropathy. *Front Med (Lausanne).* 2020 Mar 24;7:92. doi: 10.3389/fmed.2020.00092.
8. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int.* 2021;100:S1-S276. doi: 10.1016/j.kint.2021.05.021
9. Glassock RJ. IgA Nephropathy: "The Times They Are a-Changin'". *Glomerular Diseases.* 2022;2:4-14. doi: 10.1159/000515199
10. Vecchio LD, Rimoldi C, Pozzi C. Nefecon (targeted-release formulation-budesonide) for the treatment of IgA nephropathy. *Future Rare Dis.* 2021;1:FRD18. doi: 10.2217/frd-2021-0013
11. Edsbacker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. *Clin Pharmacokinet.* 2004;43:803-21. doi: 10.2165/00003088-200443120-00003.
12. Fellström BC, Barratt J, Cook H, Coppo R, Feehally J, de Fijter JW, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *The Lancet.* 2017;389:2117-27. doi:10.1016/S0140-6736(17)30550-0
13. Barratt J, Lafayette R, Kristensen J, Stone A, Cattran D, Floege J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney Int.* 2023;103:391-402. doi:10.1016/j.kint.2022.09.017
14. 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;10:2493. doi: 10.3390/jcm10112493
15. Moriyama T, Karasawa K, Miyabe Y, Akiyama K, Ogura S, Takabe T, et al. Validation of the revised Oxford classification for IgA nephropathy considering treatment with corticosteroids/immunosuppressors. *Sci Rep.* 2020;10:11151. doi: 10.1038/s41598-020-68087-y.
16. Itami S, Moriyama T, Miyabe Y, Karasawa K, Nitta K. A Novel Scoring System Based on Oxford Classification Indicating Steroid Therapy Use for IgA Nephropathy. *Kidney Int Rep.* 2021 Oct 14;7:99-107. doi: 10.1016/j.ekir.2021.10.007.
17. Cambier A, Troyanov S, Tesar V, Coppo R; Validation Study of Oxford Classification (VALIGA) Group. Indication for corticosteroids in IgA nephropathy: validation in the European VALIGA cohort of a treatment score based on the Oxford classification. *Nephrol Dial Transplant.* 2022 May 25;37:1195-1197. doi: 10.1093/ndt/gfac025.

Copyright © 2023 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.