Direct Oral Anticoagulants in Nephrotic Syndrome: Our Experience and Literature Review

Abstract

Nephrotic syndrome (NS) is one of the common presentations of kidney diseases both in children and adults. NS patients, particularly those with membranous nephropathy, have increased risk of thromboembolic events. Heparin and vitamin K antagonists (VKAs) continue to be commonly used as prophylactic and therapeutic agents, given the experience of use of these agents in NS and nonrenal indications of anticoagulation. The use of direct oral anticoagulants (DOACs) in NS is reported in some case series, conference abstracts, and a few small studies. We report our experience of using DOACs in 11 patients of NS with severe hypoalbuminemia. Out of 11, one patient required change of anticoagulation from DOACs to VKA and the rest of them did well with DOACs. There were no bleeding episodes in our study. We suggest larger studies to be carried out to better understand the use of these agents in NS.

Keywords: *Anticoagulation, DOACs, nephrotic syndrome, thromboembolic events*

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DOI: 10.4103/ijn.ijn_317_22

Received: 21-09-2022
Accepted: 02-11-2022
Online First: 20-09-2023
Published: 10-04-2024

Introduction

Nephrotic syndrome (NS) is one of the common presentations of kidney diseases both in children and adults. The characteristic features include proteinuria (>3.5 g/day) with low serum albumin levels and edema. The commonest etiology of NS in children is minimal change disease (MCD), whereas in adults, the commonest causes include membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), and MCD.[1] The glomerular filtration barrier is a complex structure comprising capillary endothelium, basement membrane, and podocytes. Abnormalities in this barrier lead to altered functioning and loss of many plasma constituents including albumin, anticoagulants, plasma proteins, and others. To keep pace with these losses, liver increases the production of proteins, including the synthesis of procoagulation factors.[2,3] In addition to increased production of coagulation factors, platelet aggregation and decreased fibrinolysis contribute to the procoagulant state in NS. The risk of thromboembolic events in patients with NS is as high as 25%, and this risk is particularly high in patients with MN during the initial 6 months of presentation.[4] These thromboembolic events further contribute to morbidity and mortality in NS. Nephrotic syndrome can sometimes present with thromboembolic events as the initial presentation.[5] As therapeutic interventions to treat NS take some time to show their effect, prophylactic anticoagulation measures to prevent thromboembolic events are employed till hypoalbuminemia (serum albumin <2.4 g/dl in MN and <2 g/dl in other nephrotic states) settles. The anticoagulants suggested in the latest Kidney Disease Improving Global Outcomes glomerulonephritis (KDIGO GN) guidelines are heparin and vitamin K antagonists (VKAs), given the experience of use of these agents in NS and nonrenal indications.[6] The use of direct oral anticoagulants (DOACs) in NS is reported in some case series, conference abstracts, and a few small studies.[7,8] Given the paucity of information regarding the use of DOACs in NS, we report our experience of using DOACs in 11 patients of NS with severe hypoalbuminemia.

Case Series

The mean age of our patients was 46.2 ± 16.7 years, with four (36.3%) females and seven (63.7%) males. Out of 11 patients, eight (72.7%) had MN (seven anti-Phospholipase A_2 Receptor (PLA2R)

How to cite this article: Nissar SM, Kuchay AA, Mir TH, Goud LN, Latief M. Direct Oral Anticoagulants in Nephrotic Syndrome: Our Experience and Literature Review. Indian J Nephrol. 2024;34:169–71. doi: 10.4103/ijn.ijn_317_22

antibody and one neural epidermal growth factor-like protein (NELL 1) positive) and one each had MCD, FSGS, and secondary amyloid A (AA) amyloidosis. Mean proteinuria was 10.20 ± 2.38 g/24 h, mean serum albumin was 1.66 ± 0.37 g/dl, and mean serum creatinine was 0.93 ± 0.14 mg/dl. All our patients had estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Minimum period on anticoagulation was 2 months. There were no bleeding episodes reported in our study. One patient with anti-PLA_2R MN who had presented with unilateral renal vein thrombosis at the diagnosis of NS developed progression of renal vein thrombus while on apixaban, needing switching over to VKA and improved with it. This patient did not respond to tacrolimus/rituximab therapy, but attained remission with cyclical steroid and cyclophosphamide regimen. In rest of the patients, no thromboembolic event was observed while on DOACs. Tables 1 and 2 shows details about the patient parameters and outcome.

Discussion

Management of NS needs comprehensive care that includes targeting the underlying disease, dealing with complications of nephrotic state, and anticoagulation in patients at risk of thromboembolic events. Heparin and VKAs have been widely used so far, but they have their accompanying issues like need of therapeutic monitoring and parenteral route of administration in case of former.[9] DOACs are being increasingly used in patients with non-nephrotic states for prophylaxis and treatment purposes and have shown encouraging results without the need of monitoring and, of course, due to the ease of administration compared to heparin.[10] There are a few series and small studies which have looked at the use of DOACs in NS and most have shown encouraging results.[7,8] Because of exclusion of patients with renal impairment in early trials with DOACs, it took some time for the scientific community in using these drugs in the CKD population. Lately, evidence is accumulating which shows that not only the DOACs are safer in CKD, but also they might offer added benefits to CKD patients by decreasing the inflammatory burden and reducing the risk of vascular calcification due to VKA.[11-13] In one of the first reports on the use of DOAC in NS, rivaroxaban was successfully used in a patient with carotid thromboembolism who was warfarin intolerant.[14] This was followed by a few more reports and a pilot study demonstrating efficacy of DOACs in NS.[15,16] A recent systematic review on anticoagulation in NS suggested that some form of therapeutic monitoring be developed if patients are to be considered for the institution of DOACs, given the yet incompletely understood pharmacokinetic

Table 1: Patient details and outcome

Patient no.	Details	Anticoagulation used	Outcome
1	36 years/female MN (anti-PLA_2R+) did not respond to tacrolimus and rituximab, but responded to cyclical steroid and cyclophosphamide. Currently in remission	Apixaban as prophylaxis and treatment for renal vein thrombosis	No resolution with apixaban, responded to heparin and warfarin
2	19 years/male MCD with severe hypoalbuminemia responded well to steroids	Apixaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
3	40 years/male MN (anti-PLA_2R+) responded to tacrolimus and steroids	Apixaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
4	35 years/female (anti-PLA_2R+) MN responded to tacrolimus and steroids	Apixaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
5	65 years/female with Secondary Amyloid A (AA) amyloidosis being managed with angiotensin receptor blockers, statins, doxycycline	Rivoraxaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
6	42 years/male (NELL 1+MN) received cyclical steroid and cyclophosphamide and achieved remission	Apixaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
7	59 years/male MN achieved remission with cyclical steroid and cyclophosphamide regimen	Apixaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
8	28 years/male (anti-PLA_2R+MN) responded to tacrolimus and steroid therapy	Apixaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
9	68 years/female primary FSGS responded to angiotensin receptor blockers and steroids and dapagliflozin	Apixaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
10	67 years male/relapsed MN after 20 years and responded to a second course of cyclical steroid and cyclophosphamide regimen	Apixaban as prophylaxis	No thromboembolic event till hypoalbuminemia settled
11	50 years male/MN with (NELL 1+) on cyclical steroid and cyclophosphamide regimen	Apixaban as prophylaxis	No thrombotic event at 5 months of follow-up

FSGS=focal segmental glomerulosclerosis, MCD=minimal change disease, MN=membranous nephropathy

Table 2: Biochemical parameters

Patient no.	Age (years)	Serum albumin (g/dl)	Proteinuria (g/24 h)	Creatinine (mg/dl)
1	36	1.1	5.8	0.9
2	19	1.6	9	0.87
3	40	1.8	9.5	1.1
4	35	2.1	9.8	1.02
5	65	1.4	12.5	1.05
6	42	1.3	15	0.67
7	59	2	8	0.95
8	28	2.2	10	0.8
9	68	1.9	11	0.78
10	67	1.2	11.5	1.11
11	50	1.7	10.2	1.03

and pharmacodynamic profile of these agents in NS.[8] A very recent study from Denmark looked at 21 patients of NS on DOACs and observed no thromboembolic events in these patients and very minor bleeding episodes.[7] Similarly, in our study, there were no bleeding episodes, although a patient did develop progression of the thrombus while on apixaban, needing conversion to VKA. Another series of two patients has reported recurrence of thromboembolic event in MN while on DOACs.[17] Therefore, it is suggested that further large and multicenter studies be carried out to study the use of DOACs in NS. Our study is probably the first study from India to report the use of DOACs in NS.

Conclusion

Ours is a small study of use of DOACs in NS, which showed encouraging results, but at the same time adds to the debate that further studies be carried out to better understand the use of DOACs in NS.

Acknowledgement

We are thankful to Mr. Suhail, Mr. Tariq, and Mr. Qayoom for their help in the conduct of this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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