

Single Case

First Successful Treatment of a Patient with a Primary Immune Complex-Membranoproliferative Glomerulonephritis with Iptacopan: A Case Report

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Keywords

Primary immune complex-associated · Membranoproliferative glomerulonephritis · Iptacopan · Alternative complement pathway · Complement factor B inhibitor

Abstract

Introduction: Nowadays, there is insufficient evidence for the recommendation of management patients with a primary membranoproliferative glomerulonephritis (MPGN). A better understanding of the pathogenesis has led to the reclassification of primary MPGN and distinction into the two main entities of either primary immune complex-MPGN or C3 glomerulopathy. Both entities share overlapping pathophysiological features with complement alternative pathway (AP) dysregulation. Iptacopan is an oral inhibitor of the complement factor B that effectively blocks the complement AP. **Case Presentation:** We report the first successful treatment of a 47-year-old man suffering from a primary immune complex-MPGN with iptacopan. So far established immunosuppressive therapies with prednisone and mycophenolate mofetil failed to control the current flare of the disease, mainly presenting with impaired kidney function and proteinuria within the nephrotic range. However, 3 months after starting the treatment with iptacopan urine protein-creatinine ratio decreased impressively to a level of 100–150 mg/mmol. Thereafter, low-level proteinuria and kidney function remained stable during follow-up. Do date, the treatment with iptacopan is continued as a monotherapy and is well tolerated. **Conclusion:** To the best of our knowledge, this is the first case report which suggests that iptacopan may be an interesting treatment option for primary immune complex-MPGN.

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Introduction

A better understanding of the pathogenesis of primary membranoproliferative glomerulonephritis (MPGN) has subsequently led to a reclassification and distinction into the two main entities of either primary immunoglobulin-mediated (immune complex-) MPGN with combined glomerular IgG and complement factor C3 deposits, or C3 glomerulopathy with predominant or exclusive C3 deposits [1, 2]. Importantly, both entities share overlapping pathophysiological features with complement alternative pathway (AP) dysregulation involved in both glomerular diseases [3].

Despite the expanding knowledge of the pathophysiology of primary immune complex-MPGN, the currently proposed treatment options are limited. The KDIGO 2021 guidelines for the management of glomerular diseases propose to tailor immunosuppressive therapy of primary immune complex-MPGN to the severity of the disease presentation and histology findings [4]. However, apart from the ubiquitous acceptance of the role of blockade of the renin-angiotensin-system in all patients with primary immune complex-MPGN, there is no unique immunosuppressive regimen besides glucocorticosteroids, which is supposed to be superior to others in those who should be aggressively treated [4]. Further, the avoidance of side effects of high-dose glucocorticosteroids should always be considered when treating patients with a primary glomerulonephritis, and steroid-sparing immunosuppressive treatment options should be the preferred.

Iptacopan (Novartis Pharma AG, Switzerland) is an oral, first-in-class, and highly potent inhibitor of complement factor B (FB) that effectively blocks the AP [5]. FB includes a serine protease domain (Bb), which is the proteolytically active component of the AP C3 (C3bBb) and C5 (C3bBb3b) convertases [5]. Consequently, iptacopan-mediated inhibition of FB suppresses C3 convertase activity, blocking the cleavage of C3 and activation of the so-called amplification loop [5]. Further, this results in prevention of downstream generation of the C5 convertase complex as well as the terminal complement cascade with its effectors consequences [5]. The activation of the AP as well as blockade by several complement blockers at different steps of the complement cascade is summarized in Figure 1.

To date, iptacopan has been investigated in two phase 2 studies in patients with paroxysmal nocturnal hemoglobinuria (PNH), either with persistent hemolysis despite ongoing treatment with the complement C5 inhibitor eculizumab (Alexion/AstraZeneca Rare Disease, Boston, MA, USA) [6] or in treatment-naïve PNH patients [7]. Recruitment of PNH patients for two confirmatory phase 3 clinical trials has recently been finalized (*Clinical.Trials.gov*; NCT04558918 and, NCT04820530) (mentioned in [7]). Furthermore, iptacopan was investigated in a phase 2 clinical trial in patients with C3 glomerulopathy [8] and is under investigation in a phase 3 double-blind placebo-controlled clinical trial for the treatment of C3 glomerulopathy (*Clinical.Trials.gov*; NCT04817618) [9]. Moreover, iptacopan is under investigation in a single-arm, open-label, phase 3 study to evaluate the efficacy and safety in patients with complement-mediated atypical hemolytic uremic syndrome (aHUS) naïve to complement inhibitor therapy (*Clinical.Trials.gov*; NCT04889430) [10], and is under investigation in a phase 3 clinical trial for the treatment of IgA nephropathy (*Clinical.Trials.gov*; NCT04578834) [11]. In conclusion, a multicenter, randomized phase 3 study for patients with primary immune complex-MPGN has recently been started (*Clinical.Trials.gov*; NCT05755386) [12]. To the best of our knowledge, we herewith present the first successful treatment of a patient with a primary immune complex-MPGN with iptacopan which has not been published before. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000540013>).

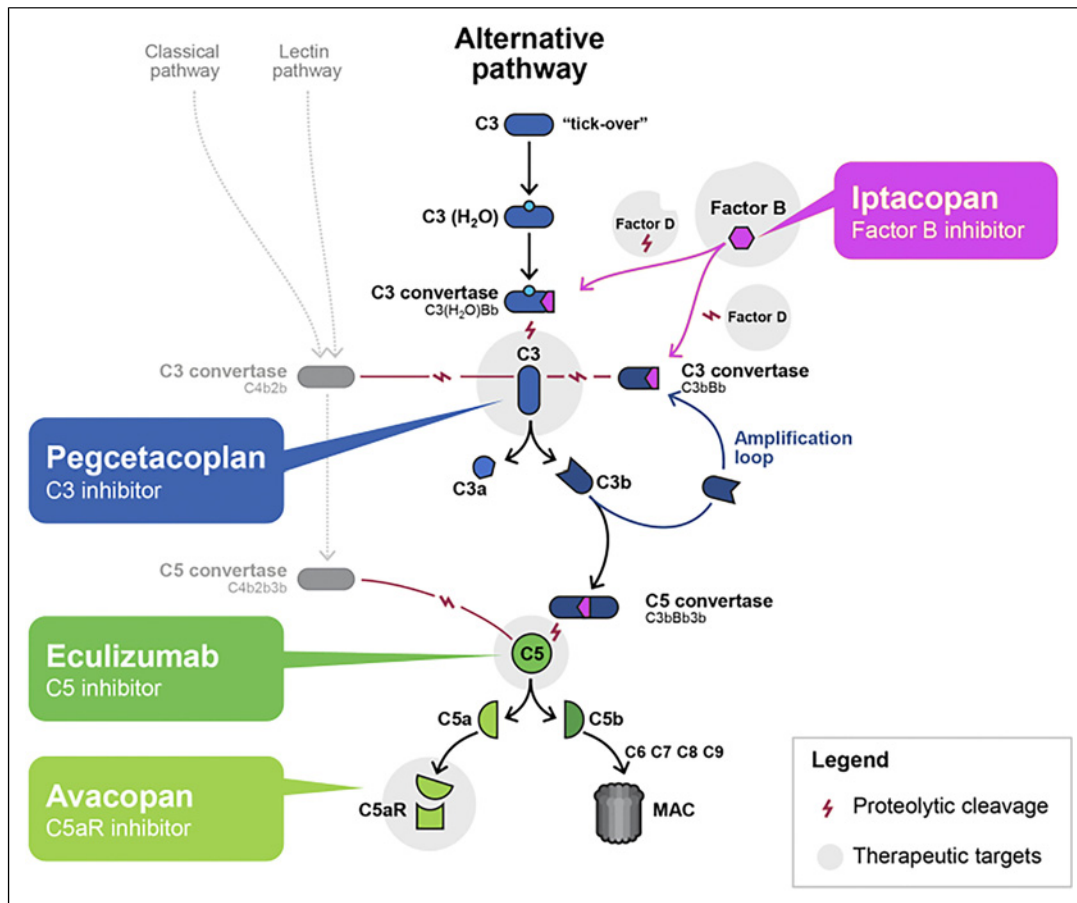


Fig. 1. Targeting of the complement system by different complement inhibitors. Adapted with courtesy of Novartis.

Case Presentation

In April 2017, a 47-year-old male patient with known arterial hypertension and genuine epilepsy but otherwise healthy status and without known risk behavior and negative family history for renal diseases was referred to our outpatient clinic for a diagnostic work-up of a newly diagnosed impaired kidney function with proteinuria and glomerular microhematuria. Approximately 1 month before the initial consultation, renal function impairment was diagnosed for the first time during further examination of uncontrolled blood pressure. At initial consultation, he presented with good general condition and obese nutrition status (BMI 32 kg/m²). Blood pressure was 160/95 mm Hg without relevant lateral difference. Further, he presented with normal pulse of 75/min and unremarkable cardiopulmonary auscultation. In addition, the patient showed mild bilaterally lower leg edema as well as an unremarkable abdominal examination and pulse status. Laboratory tests confirmed impaired kidney function with a serum creatinine level of 172 µmol/L (reference ranges 49–97 µmol/L), corresponding to an eGFR according to the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) of 42 mL/min/1.73 m². Urine protein-creatinine ratio (UPCR) was 171 mg/mmol (reference range <11 mg/mmol) which peaked to 372 mg/mmol at the time of kidney biopsy which

was performed soon after the first presentation (Fig. 2). Urine sediment examination showed repeated glomerular microhematuria. Histology work-up of the kidney biopsy followed standard procedures (of 2 biopsy cores obtained with a 16-gauge needle) including evaluation by light microscopy, immunofluorescence (staining for immunoglobulins, complement factors and light chain components as well as fibrinogen), and electron microscopy. A detailed description of the histologic findings is given in Table 1 and illustrated in Figure 3a–d. Briefly, the histologic pattern best described an immune complex-MPGN.

Consequently, comprehensive laboratory analyses were performed including autoimmune serology (ANA, anti-DNS, anti-C1q, cryoglobulins) and complement screening (factor C3, C4, and CH50 test) which were all within the normal ranges. Concerning screening for complement abnormalities, serum levels of C3 and C4 were measured by nephelometry (Siemens Healthcare) and MicroVue® (Quidel) CH50 test was performed to assess the activity of the classical complement pathway. In addition, the search for infectious diseases (HIV, HCV, HBV) and monoclonal gammopathy was negative (i.e., serum protein electrophoresis which showed a normal distribution pattern of globulins and a negative monoclonal component plus free serum light chains lambda and kappa where not elevated either). Further, we decided not to take blood cultures, as the patient showed no evidence of a bacterial infection either clinically or in the laboratory tests. A subsequent echocardiogram showed no suspicious signs of an endocarditis.

After exclusion of possible secondary forms of immune complex-MPGN, the patient was first treated with a conservative therapy with maximum tolerated renin-angiotensin-system blockade until March 2018 (antihypertensive medication consisted either of candesartan 32 mg in combination with hydrochlorothiazide 25 mg per day or later in the course azilsartan 40 mg in combination with chlorthalidone 25 mg per day). However, during that time UPCR raised to 607 mg/mmol which no longer justified a sole conservative therapy. Thus, a therapy with prednisone 1 mg/kg body weight was started, which was tapered during the following months and stopped in February 2019. During steroid treatment, the patient suffered from serious side effects (i.e., severe inner restlessness, accompanied by insomnia and difficulty concentrating so that he could hardly work, further increasingly hypertensive blood pressure, weight gain, edema, and leg pain), therefore other immunosuppressive regimens were established as the disease was not under control (summarized in Fig. 2). Tacrolimus was started in October 2018 (5 mg BID, trough levels 6.4–7.0 µg/L) but was stopped already after 1 month because of gastrointestinal side effects. Finally, mycophenolate mofetil (MMF) therapy was started at a dosage of 1,000 mg BID in November 2018 (for details, see Fig. 2). Mainly under the monotherapy of MMF, the immune complex-MPGN seemed to be more or less stable during the follow-up of 3 years with slightly improved kidney function with new eGFR baseline of about 50 mL/min/1.73 m² and proteinuria of around 1 g per day. Therefore, in January 2022 the immunosuppressive therapy with MMF was stopped and the patient was followed closely in our outpatient clinic. However, the course of the disease did not remain stable without any immunosuppressive therapy. A first short flare of the disease was diagnosed in April 2022 which lasted until June 2022 with UPCR climbing up to a level of 387 mg/mmol, but fortunately was self-limited without further adaption of therapy. Nevertheless, in December 2022 another severe flare of the disease occurred with heavy proteinuria in the nephrotic range (Fig. 2). Prednisone (again starting with 1 mg/kg body weight) and MMF (1,000 mg BID) therapies were re-started, but MMF had to be stopped in February 2023 for a short period of 10 days because of a severe influenza A virus infection but was continued thereafter. Due to recurring side effects, prednisone therapy was tapered again after 2 weeks of full dose and was stopped in March 2023. At that time UPCR peaked to

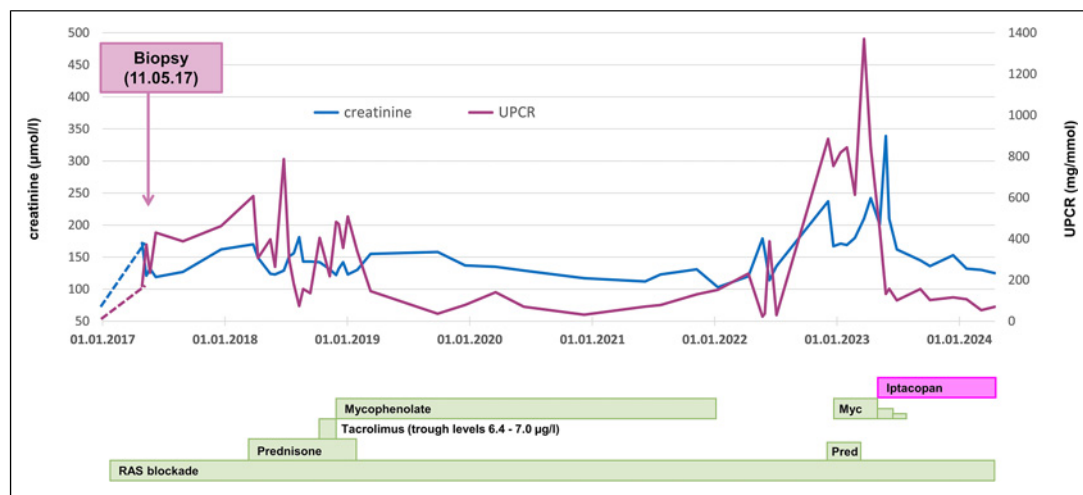


Fig. 2. Course of the successful treatment of a 47-year-old man suffering from a biopsy-confirmed primary immune complex-MPGN with the complement factor B inhibitor iptacopan. For the dosage of medication, refer to the text. MPG, membranoproliferative glomerulonephritis; UPCR, urine protein-creatinine ratio; RAS, renin-angiotensin-system.

1,370 mg/mmol. Presumably, due to the severe influenza A virus infection or flare of the primary renal disease, acute on chronic kidney failure occurred with a raise of creatinine levels more than 200 $\mu\text{mol/L}$ and decrease of eGFR to 30 mL/min/1.73 m^2 . Complement activity screening was repeated measuring serum levels of C3 and C4 (Siemens Healthcare) and by testing the activity of all three pathways with a commercially available enzyme immunoassay (COMPL300, Complement System Screen kit, Wieslab®), showing normal activity within all three pathways.

As so far established immunosuppressive therapies failed to control the primary immune complex-MPGN there was an urgent need for an experimental rescue therapy. Due to promising results in treating patients with C3 glomerulonephritis with iptacopan a request was made to the company (Novartis Pharma AG, Switzerland) to timely obtain iptacopan within a Managed Access Program (MAP), as there was no study launched at this time to test iptacopan for the treatment of primary immune complex-MPGN for which the patient gave written informed consent. Thereafter, iptacopan was started in May 2023 (200 mg BID), and at the same time MMF was reduced to 500 mg BID. MMF was further reduced to 250 mg BID at the end of June 2023, and stopped mid-August 2023, respectively. Four weeks before starting the treatment with iptacopan the patient received meningococcal and pneumococcal vaccination. Three months after starting the treatment with iptacopan UPCR decreased impressively to a level of 100–150 mg/mmol and kidney function return to his baseline level (Fig. 2). Thereafter, proteinuria at a low level and kidney function remained stable during follow-up (Fig. 2). Complete blockade of alternative complement cascade in our case was confirmed and monitored monthly after starting the treatment of iptacopan (COMPL300, Complement System Screen kit, Wieslab®). To date, the treatment with iptacopan is continued and is well tolerated with no adverse side effects and it is worth to mention that the patient is under the monotherapy of iptacopan for nearly 6 months. Furthermore, as the patient suffered from serious side effects of glucocorticosteroids, the steroid-sparing therapy with iptacopan is highly appreciated by himself.

Table 1. Kidney biopsy findings

Light microscopy

Large biopsy from renal medulla and cortex, the latter with up to 27 glomeruli hit, 6 of them are completely obliterated, three others with segmental loop thickening with increased matrix hyalinosis, and partially planar capsular synechiae. The better preserved capillary loops and the remaining glomeruli with lobulated structure. The mesangium broadened with increased matrix and strong cell proliferation. Peripheral capillary loops thickened with double contouring of the basement membranes, sectional cell interposition, and protein thrombi. Capsular spaces free

Tubular apparatus of the cortex in multiple foci, together about 20%, atrophic, surrounded by a widened, fibrosed, and moderately dense predominantly lymphohistiocytic interspersed interstitium. The remaining tubules better preserved. In the proximal sections an increased cytoplasmic protein storage. Three interlobular arteries with typical wall structures. Preglomerular arterioles with segmental wall hyalinosis. In the renal medulla no increased inflammatory infiltrates

Immunofluorescence

Immunofluorescence examinations were performed on cryosections. Diffuse global mixed granular deposits of C1q, C3, C4, C5-9, and IgG, kappa, and lambda light chains. Detection of IgA, IgM, and fibrinogen glomerular negative. Preglomerular vessels with moderate grade deposits of C5-9

Electron microscopy

A glomerulus was examined by electron microscopy. The glomerular capillary loops are with a regular structure. The mesangium and peripheral glomerular basement membranes widened with evidence of numerous mesangial, subepithelial, and intramembranous electron-dense, non-structured deposits. The podocytes with extensive loss (70%) of the foot processes. No fibrils

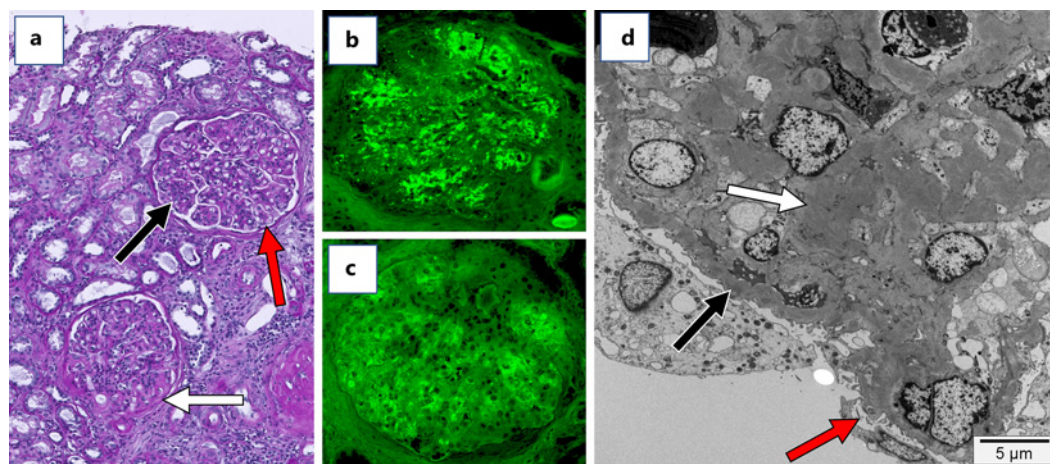


Fig. 3. Histopathological findings. **a** By light microscopy, the glomeruli showed a prominent lobular architecture with increased mesangial and intracapillary cellularity (black arrow). The peripheral glomerular basement membranes focally showed double contours (red arrow). There were also several segmental scleroses (white arrow), PAS-staining, $\times 200$. By immunofluorescence, there was diffuse global granular deposition of C3 (**b**) and IgG (**c**) (immunofluorescence, $\times 400$). **d** By electron microscopy there was intensive remodeling of peripheral glomerular basement membranes with presence of intramembranous, subepithelial and subendothelial deposits (black arrow). There were also mesangial deposits (white arrow). Further, there was extensive loss of foot processes (red arrow) (electron microscopy, $\times 2800$).

Discussion

This case report opens an interesting therapeutic field for the use of complement blockers of the AP for the treatment of primary MPGN, which are in general well tolerated. Thereby, iptacopan has the potential to become the first oral standard-of-care complement inhibitor not only for the treatment of C3 glomerulopathy but also primary immune complex-MPGN as well as other complement dysregulation-associated glomerular diseases. We must keep in mind that nowadays no randomized clinical trial or case series exist for the treatment of primary immune complex-MPGN based on the new classification system. Therefore, there is insufficient high-quality evidence for the recommendation of management patients with primary immune complex-MPGN. As a randomized clinical trial for patients with primary immune complex-MPGN, investigating the efficacy of iptacopan, has just recently been started (*Clinical.Trials.gov*; NCT05755386) [12], it is important to learn in the meanwhile from case reports to gain helpful information of the efficacy and safety of iptacopan. From this point-of-view, the current case report provides important preliminary information about the efficacy and safety of treatment of primary immune complex-MPGN with iptacopan which was highly effective regarding the reduction of proteinuria and prevention of further decline of kidney function and is well tolerated. Furthermore, even under the 6-month monotherapy with iptacopan to date, the disease is in remission with proteinuria at a low level and stable kidney function. Of course, we must note at this point that clinical information obtained from a case report will never reach the same level of evidence as a thoroughly conducted randomized, placebo-controlled clinical trial. Therefore, the results of the ongoing multicenter, randomized phase 3 study are expected with great interest [12].

What about the treatment of primary immune complex-MPGN with other blockers of the complement cascade? By targeting FB, iptacopan suppresses the activation of the amplification loop of the AP as highlighted in Figure 1. It also blocks the amplification of classical and lectin pathway-dependent C5 activation, although it does not impact amplification-independent complement activation via these pathways. This may potentially lead to a lower infection risk in vaccinated patients as compared with other proximal complement inhibitors [13] like, for example, pegcetacoplan (Apellis Pharmaceuticals, Waltham, MA, USA; Fig. 1), which is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of patients with PNH, who remain anemic after at least 3 months of treatment with a complement C5 inhibitor [14]. The first approved complement inhibitor overall was eculizumab, which is a highly effective C5 inhibitor (Fig. 1). Nowadays, eculizumab is the first-line treatment option for patients with complement-mediated aHUS. The benefits of terminal complement blockade with eculizumab have also been tested in a small number of patients with C3 glomerulopathy with variable results [15]. By C5 blocking, eculizumab mainly targets glomerular inflammation evoked through terminal complement effector functions but has only small effects on dysregulation of the proximal complement cascade that seems to be predominantly involved in C3 glomerulopathy [15]. As C3 glomerulopathy and primary immune complex-MPGN are supposed to share overlapping pathophysiological features with AP dysregulation found in both glomerular diseases [3], we decided against a rescue therapy with eculizumab in our case.

Further, the C5a receptor (C5aR) inhibitor avacopan (CLS Vifor, Switzerland; Fig. 1) has been approved by the FDA, EMA and recently the Swissmedic for the treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Activation of AP, which results in terminal C5a production, is a key component of the pathogenesis of ANCA-associated vasculitis [16]. Avacopan selectively suppresses the effects of C5a through C5aR blockade (Fig. 1), including impeding of neutrophil chemoattraction and activation [17]. Therefore,

avacopan mainly acts as an anti-inflammatory agent preventing organ inflammation and damage [17]. Compared to iptacopan, avacopan has only an impact on the lower end of the complement cascade. The safety and efficacy of avacopan was also investigated in a randomized, double blind, placebo-controlled phase 2 study in C3 glomerulonephritis (*Clinical.Trials.gov*; NCT03301467), and the results are expected with great interest. However, due to the same reason as for eculizumab, we did not consider avacopan as a rescue treatment option in our patient.

It is important to highlight that no available complement biomarker accurately predicts response the treatment in primary immune comple-MPGN. The well-known clinical parameters (serum creatinine, eGFR, UPCR) and probably kidney biopsy features (i.e., the extent of inflammation and fibrosis) are to date the most reliable predictors of renal outcome. From this point-of-view, demonstration of suppression of complement activation markers and/or histological features in follow-up biopsies are only relevant if associated with concomitant clinical improvement. Due to the large reduction of proteinuria followed by improvement of kidney function, we so far decided against the performance of a follow-up biopsy in our case report as well as against genetic testing of genes encoding for complement factors.

Conclusion

Our case report suggests that iptacopan may become a promising oral treatment option for primary immune complex-MPGN. However, to address this issue, further studies are warranted.

Acknowledgments

The patient has been provided with iptacopan therapy via Managed Access Program (MAP) of Novartis Pharma AG, Basel, Switzerland. Novartis has conducted a scientific accuracy review of the case during the MAP process but has not influenced the content of the publication.

Statement of Ethics

The research was conducted in accordance with the World Medical Association Declaration of Helsinki (<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>). The patient gave written informed consent for publication of this case report including details of the medical case and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local guidelines.

Conflict of Interest Statement

The authors of this manuscript declare no conflicts of interest as described by *Karger Case Reports in Nephrology and Dialysis*. This study received funding from Novartis Pharma AG, Basel, Switzerland as indicated within the funding section.

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Author Contributions

All authors contributed equally to the literature review and the text of the manuscript. S.A., M.N., M.D., and P.H.M. were responsible for the patient care and treatment. T.M. and H.H. were responsible for the correct interpretation of the biopsy results.

Data Availability Statement

All the data analyzed for this case report are included in this article. Further inquiries can be directed to the corresponding author.

References

- 1 Fakhouri F, Fremeaux-Bacchi V, Noel LH, Cook HT, Pickering MC. C3 glomerulopathy: a new classification. *Nat Rev Nephrol*. 2010;6(8):494–9. <https://doi.org/10.1038/nrneph.2010.85>
- 2 Sethi S, Nester CM, Smith RJ. Membranoproliferative glomerulonephritis and C3 glomerulopathy: resolving the confusion. *Kidney Int*. 2012;81(5):434–41. <https://doi.org/10.1038/ki.2011.399>
- 3 Noris M, Donadelli R, Remuzzi G. Autoimmune abnormalities of the alternative complement pathway in membranoproliferative glomerulonephritis and C3 glomerulopathy. *Pediatr Nephrol*. 2019;34(8):1311–23. <https://doi.org/10.1007/s00467-018-3989-0>
- 4 Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4):753–79. <https://doi.org/10.1016/j.kint.2021.05.015>
- 5 Schubart A, Anderson K, Mainolfi N, Sellner H, Ehara T, Adams CM, et al. Small-molecule factor B inhibitor for the treatment of complement-mediated diseases. *Proc Natl Acad Sci U S A*. 2019;116(16):7926–31. <https://doi.org/10.1073/pnas.1820892116>
- 6 Risitano AM, Roth A, Soret J, Frieri C, de Fontbrune FS, Marano L, et al. Addition of iptacopan, an oral factor B inhibitor, to eculizumab in patients with paroxysmal nocturnal haemoglobinuria and active haemolysis: an open-label, single-arm, phase 2, proof-of-concept trial. *Lancet Haematol*. 2021;8(5):e344–54. [https://doi.org/10.1016/S2352-3026\(21\)00028-4](https://doi.org/10.1016/S2352-3026(21)00028-4)
- 7 Jang JH, Wong L, Ko BS, Yoon SS, Li K, Baltcheva I, et al. Iptacopan monotherapy in patients with paroxysmal nocturnal hemoglobinuria: a 2-cohort open-label proof-of-concept study. *Blood Adv*. 2022;6(15):4450–60. <https://doi.org/10.1182/bloodadvances.2022006960>
- 8 Wong E, Nester C, Caverio T, Karras A, Le Quintrec M, Lightstone L, et al. Efficacy and safety of iptacopan in patients with C3 glomerulopathy. *Kidney Int Rep*. 2023;8(12):2754–64. <https://doi.org/10.1016/j.ekir.2023.09.017>
- 9 Bomback AS, Kavanagh D, Vivarelli M, Meier M, Wang Y, Webb NJA, et al. Alternative complement pathway inhibition with iptacopan for the treatment of C3 glomerulopathy-study design of the APPEAR-C3G trial. *Kidney Int Rep*. 2022;7(10):2150–9. <https://doi.org/10.1016/j.ekir.2022.07.004>
- 10 Kavanagh D, Greenbaum LA, Bagga A, Karki RG, Chen CW, Vasudevan S, et al. Design and rationale of the APPELHUS phase 3 open-label study of factor B inhibitor iptacopan for atypical hemolytic uremic syndrome. *Kidney Int Rep*. 2023;8(7):1332–41. <https://doi.org/10.1016/j.ekir.2023.04.029>
- 11 Rizk DV, Rovin BH, Zhang H, Kashihara N, Maes B, Trimarchi H, et al. Targeting the alternative complement pathway with iptacopan to treat IgA nephropathy: design and rationale of the APPLAUSE-IgAN study. *Kidney Int Rep*. 2023;8(5):968–79. <https://doi.org/10.1016/j.ekir.2023.01.041>
- 12 Vivarelli M, Bomback AS, Meier M, Wang Y, Webb NJA, Veldandi UK, et al. Iptacopan in idiopathic immune complex-mediated membranoproliferative glomerulonephritis: protocol of the APPARENT multicenter, randomized phase 3 study. *Kidney Int Rep*. 2024;9(1):64–72. <https://doi.org/10.1016/j.ekir.2023.10.022>

- 13 Ispasanie E, Muri L, Schubart A, Thorburn C, Zamurovic N, Holbro T, et al. Alternative complement pathway inhibition does not abrogate meningococcal killing by serum of vaccinated individuals. *Front Immunol*. 2021; 12:747594. <https://doi.org/10.3389/fimmu.2021.747594>
- 14 Hillmen P, Szer J, Weitz I, Roth A, Hochsmann B, Panse J, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;384(11):1028–37. <https://doi.org/10.1056/NEJMoa2029073>
- 15 Le Quintrec M, Lapeyraque AL, Lionet A, Sellier-Leclerc AL, Delmas Y, Baudouin V, et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. *Am J Kidney Dis*. 2018;72(1):84–92. <https://doi.org/10.1053/j.ajkd.2017.11.019>
- 16 Schreiber A, Xiao H, Jennette JC, Schneider W, Luft FC, Kettritz R. C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. *J Am Soc Nephrol*. 2009;20(2):289–98. <https://doi.org/10.1681/ASN.2008050497>
- 17 Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384(7):599–609. <https://doi.org/10.1056/NEJMoa2023386>