Refractory Minimal Change Disease and Focal Segmental Glomerular Sclerosis Treated With Anakinra

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Received 3 September 2021; revised 17 October 2021; accepted 18 October 2021

Kidney International Reports (2021) -

INTRODUCTION

idiopathic nephrotic syndrome (NS) is the most common cause of proteinuria in children and young adults. Minimal lesion with fusion of slit-diaphragm is the pathologic substrate in most cases, whereas focal segmental glomerular sclerosis (FSGS) often corresponds to drug-unresponsive forms that are at higher risk to develop progressive kidney failure. With the exception of rare genetic forms sustained by inherited modifications in podocyte genes, mechanisms for NS are largely unknown, but efficacy of immunosuppressive therapies suggests that immune abnormalities are implicated in disease pathogenesis. Oral steroids represent the first-line treatment and are successful in 85% of cases. Some patients require chronic steroid therapy to prevent remission (steroid dependent), whereas others require the association with calcineurin inhibitors, mycophenolate mofetil (MMF) or rituximab, to reach remission (steroid resistant). A minor percent of patients with nephrosis (approximately 5%) are resistant to any approach. Considering the toxicity of the above-mentioned drugs and the high risk of progression in patients with resistance to every combination, alternative interventions are urgently needed. Moreover, the prognosis of these patients is further worsened by the high risk of recurrence of the disease after kidney transplantation and the high morbidity of long period of dialysis owing to graft failure. Classical therapeutic approach focused on both innate and adaptive immunities points to the abrogation of T and B cell response. We recently revealed that complement split product C3a binds to its receptor (C3a receptor [C3aR]) in podocytes leading to the production of IL-1β and, through an autocrine loop, signaling with interleukin-1 receptor (IL-1R)1 to promote podocyte cytoskeleton rearrangement and podocyte loss. Importantly, treatment with IL-1R1 antagonist Anakinra reduced albuminuria in the murine model of FSGS induced by adriamycin. Here, we describe the safety/efficacy profile of anti-IL1 receptor Anakinra (Kineret; Amgen, Thousand Oaks, CA) in 3 consecutive patients with severe form of NS, characterized by frequent relapses that were resistant to the combined administration of common therapies. No other patients have been treated with Anakinra so far in our center.

CASE PRESENTATION

Case 1

Case 1 is that of a 22-year-old White woman with multidrug-dependent minimal lesion with fusion of slit-diaphragm since she was 11 years old diagnosed based on kidney biopsy findings when she was 15 years old. Despite the chronic therapy with tacrolimus (target trough levels: 4–6 ng/dl) and/or MMF (1200 mg/mq daily) as steroid-sparing agents, she had severe relapses of NS during her lifetime (approximately one every 6 months) which were treated with oral steroid at the dose of 40 mg/m² or single doses of anti-CD20
antibody (overall, 6 infusions of rituximab and 5 infusions of the fully humanized anti-CD20 antibody ofatumumab). She received the last infusion of rituximab in November 2019. After 6 months, in April 2020, she presented with a new relapse of NS. At that point, the patient stopped MMF and started Anakinra (subcutaneous, 2 mg/kg/d for the first week and then 4 mg/kg/d). After 15 months of therapy with Anakinra, she had no more relapses of NS (compared with the average of 2 relapses per year in the 3 previous years), despite MMF interruption (Supplementary Figure S1).

Case 2
A 26-year-old White woman had FSGS diagnosed based on kidney biopsy findings after presenting with NS and kidney failure. Immunofluorescence result was positive for mesangial IgM and focal C3 deposition. At the time of biopsy, serum creatinine level was 1.6 mg/dl, proteinuria was 20.4 g/d, and serum albumin level was 0.9 g/dl. She was treated with methylprednisolone, 1 g rituximab, and tacrolimus with partial remission of proteinuria (2–4 g/d). Three months after rituximab therapy, she presented with relapse of NS and acute kidney failure requiring 5 hemodialysis treatments, and calcineurin inhibitor was switched to MMF (1200 mg/mq daily) and oral steroids were maintained. Owing to the persistence of NS and worsening of kidney function, 3 doses of immunoglobulin i.v. were required to manage persistent edema.

Given the CKD and the lack of improvement/worsening of proteinuria, the patient started Anakinra (subcutaneously, 2 mg/kg/d for the first week and then 4 mg/kg/d), removing MMF. After 16 months of Anakinra therapy, serum creatinine level is 2.4 mg/dl, proteinuria is 4.2 g/d, and serum albumin level is 1.8 g/dl (Figure 1).

Case 3
A 16-year-old North-African boy had FSGS recurrence at 25 days after kidney transplant based on kidney biopsy findings. Immunofluorescence result was positive per focal C3 glomerular deposition. He presented NS when he was 8 years old, and he started renal replacement treatment since he was 11 years old. To reduce the risk of FSGS recurrence, as per our center protocol, he received plasma exchange treatment (PEX) before kidney transplant. He received standard treatment based on the anti-IL-2 receptor antibodies as induction therapy, maintaining immunosuppression with steroids, tacrolimus (serum target values of 8–10 ng/dl in the first weeks after kidney transplant), and MMF. At 20 days after kidney transplant, recurrence of FSGS presented with proteinuria of 9 g/d and serum albumin level of 2.2 g/dl. After 9 PEX (3/wk), urinary protein excretion declined to 0.4 g/d and serum albumin and creatinine levels returned to normal range. He continued with 1 PEX/wk, but after 2 weeks, urinary protein excretion raised to 14 g/d despite 3 PEX/wk.

Figure 1. Proteinuria and serum creatinine levels in a patient with focal segmental glomerular sclerosis multidrug resistant. h, hour; HD, hemodialysis; IL-1R, interleukin-1 receptor; pCreat, creatinine in patient.
We started administration of Anakinra (subcutaneous, 2 mg/kg/d for the first week and then 4 mg/kg/d) with the goal to reduce the need of PEX per week. After 1 month, protein excretion declined to 4 g/d and PEX was reduced to 2/wk and then to 1/wk. After further 2 months of 1 PEX/week and Anakinra, protein excretion reached the minimal value of 0.4 g/d. Anakinra was maintained for the first 5 months after kidney transplant and stopped after single infusion of rituximab (375 mg/m²). Currently, protein excretion ranges from 0.1 g/d to 1 g/d with normal kidney function (Supplementary Figure S2).

**DISCUSSION**

Here, we presented 2 patients with multidrug-dependent/-resistant NS and 1 case with post-transplant recurrence of FSGS, all had negative results for specific genetic panel of NS (PLCE1, NPHS2, NPHS1, WT1, SMARCAL1, ACTN4, COL4A3, COL4A4, COL4A5, TRIM8, LMX1B, TRPC6, MYO1E, COQ6, CD2AP) and partially responded to the blockade of IL-1β/IL-1R1 signaling with Anakinra. This small case report study, together with our previous animal work, provides a background for larger studies testing the hypothesis that IL-1β or IL-1R1 blockers promote proteinuria remission in glomerular diseases by preventing complement-initiated podocyte cytoskeleton rearrangement.

Recent findings revealed that regulation of C3 convertase in podocyte by decay-accelerating factor (CD55) is deeply implicated in determining proteinuria and glomerular lesions in murine models of glomerulonephritis. In glomerular injury, decay-accelerating factor is cleaved and removed from the podocyte and is associated with C3aR up-regulation. C3 or C3aR deficiency abrogates the disease, confirming complement dependence. Mechanistic studies revealed that C3a/C3aR ligation on podocytes enhance inflammasome activation in the podocytes and the release of active IL-1β that, through an autocrine loop, signals through IL-1R1 leading to actin cytoskeleton rearrangement and podocyte loss. Uncoupling IL-1β/IL-1R1 signaling prevents the disease, providing a causal link.

IL-1β is a highly proinflammatory cytokine involved in local and systemic inflammation, and the availability of specific IL-1β–targeting agents was found to have a pathologic role of IL-1β-mediated inflammation in a growing list of diseases.

Targeting IL-1 began in 1993 with the introduction of Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist, which blocks the activity of both IL-1α and IL-1β. Anakinra currently dominates the field of IL-1 therapeutics owing to its excellent safety record, short half-life, and multiple routes of administration. By specifically blocking IL-1R1, the role of this cytokine has emerged in a large spectrum of inflammatory diseases. Moreover, blocking IL-1β/IL-1R1 signaling, in both experimental and clinical studies, has provided proof of concept for diseases that were not considered to be inflammatory, such as type 2 diabetes.

In the last decade, several studies described the administration of IL-1 inhibitors in subjects with familial Mediterranean fever with associated glomerular AA amyloidosis. Of note, the amount of proteinuria was remarkably reduced after IL-1 inhibitor therapy. The antiproteinuric effects of IL-1 inhibitor therapy in such subjects may be partially explained by the mechanistic insights linking decay-accelerating factor down-regulation to glomerulosclerosis through C3aR-dependent IL-1β production and subsequent IL-1R signaling.

We administered Anakinra in 3 patients with different forms of severe NS.

The first case is a patient with multidrug-resistant/frequently relapsing NS. We added Anakinra to the chronic treatment with calcineurin inhibitor, with the aim to reduce the frequency of relapses and the needing of steroids. The patient has had severe side effects related to the numerous steroid pulses to treat relapses over the years. At 15 months after Anakinra initiation, we recorded no more relapse.

In the second case, we administered Anakinra in a patient with multidrug-resistant nephrotic syndrome owing to FSGS and CKD stage IV. Of note, after the beginning of Anakinra therapy, multiple ongoing immunosuppressive treatments were stopped. At 16 months of follow-up, we report a remarkable improvement of proteinuria and kidney function. We acknowledge that Anakinra did not promote full disease remission, but it was associated with a significant amelioration of disease severity. We investigated possible donors, and we are now ready for the possibility of a pre-emptive kidney transplant by living donor in case kidney function worsens.

In the last case is a patient with early recurrence of FSGS after kidney transplant. The subject first responded to an intensive PEX treatment (3/wk), but

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**Table 1. Teaching points**

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<td>Patients with multidrug-dependent or -resistant nephrotic syndrome are at high risk to develop progressive kidney failure.</td>
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<td>Recent in vitro and in vivo findings revealed that IL-1β/IL-1R1 signaling is involved in progression of disease and blocking the pathway prevents progression of disease.</td>
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<td>Anakinra, by antagonizing IL-1β/IL-1R1 signaling, resulted to be useful by preventing the progression of kidney injury in patients with advanced forms of nephrotic syndrome.</td>
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IL-1R, interleukin-1 receptor.
after shifting to 1 PEX/wk, NS immediately relapsed. Therefore, we started a new course of intensive PEX and introduced Anakinra: with the administration of IL-1RI antagonist, proteinuria remission was maintained with only 1 PEX/wk. We then administered rituximab once the remission phase was achieved: we waited for the absence of proteinuria to prevent the loss of rituximab in the urine. The patient has been in remission since then.

None of the 3 subjects experienced any Anakinra infusion-related reactions, liver function was always in the normal range, and there have been no episodes of infection or other related side effects.

**CONCLUSION**

In conclusion, our data indicate that Anakinra, by antagonizing IL-1β/IL-1R1 signaling, may represent a useful therapeutic option to prevent the progression of kidney injury in advanced forms of NS. With the limitations of a non-controlled study with only 3 cases, these data, together with previous mechanistic animal studies, provide a strong rationale for future clinical trials testing the hypothesis that antagonizing the IL-1β/IL-1R1 signaling safely promotes remission in individuals with severe form of NS (Table 1).

**DISCLOSURE**

The authors declared no competing interests.

**DATA AVAILABILITY STATEMENT**

The data sets generated for this study are available on request to the corresponding author.

**ETHICS STATEMENT**

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements.

**PATIENT CONSENT**

The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

AA and GMG contributed to the conception and design of the work, analysis, and interpretation of data. AM, AT, LMD, GP, EV, FL, and GC contributed to the acquisition of data for the work. PC and GMG revised it critically for important intellectual content. All the authors provide approval for publication of the content.

**SUPPLEMENTARY MATERIAL**

**Supplementary File (PDF)**

**Figure S1.** Proteinuria level in a patient with multidrug-dependent minimal change nephropathy.

**Figure S2.** Proteinuria level in a patient with recurrence of focal segmental glomerular sclerosis after kidney transplant.

**STROBE Statement (PDF)**

**REFERENCES**


