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CASE REPORT

Effect of a triple blockade of the renin-angiotensin-system in recurrent focal segmental glomerulosclerosis after kidney transplantation

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Summary

Recurrent focal segmental glomerulosclerosis (FSGS) after renal transplantation with nephrotic syndrome is a serious problem with a high risk of graft loss. The therapeutic role of renin-angiotensin-system (RAS) blockers in recurrent FSGS is not clear. We present the safety and efficacy of an intensified triple RAS blockade with an ACE-inhibitor, an AT 1 receptor blocker and the direct renin inhibitor aliskiren in a 29-year-old renal transplant recipient with biopsy proven recurrence of FSGS and relapsing severe nephrotic syndrome. We subsequently used full dose ramipril, candesartan and aliskiren under a close monitoring of kidney function and electrolytes and examined the effect on proteinuria, clinical course and tolerability over 12 months. We found a significant and sustained antiproteinuric effect under triple RAS blockade. RAS blockade was generally well tolerated. This can offer a new therapeutic approach in selected hypertensive patients with recurrent FSGS.

Introduction

Recurrent focal segmental glomerulosclerosis (FSGS) is a severe glomerular disease clinically often presenting with nephrotic syndrome [1]. Diagnosis of FSGS is made histologically with focal sclerosis affecting a portion of the glomerular tuft. Glomerular enlargement as well as adhesion of the podocyte to Bowman's capsule can be an early indicator of the sclerotic process which is further characterized by glomerular capillary collapse and a segmental increase in mesangial matrix. Electron microscopy typically shows podocyte enlargement and foot process effacement, whereas immunofluorescence reveals no immune deposits.

Focal segmental glomerulosclerosis recurs in 30% of patients after the first renal transplantation and in up to 80% of patients with a second renal allograft [2,3]. As treatment options, strict blood pressure control and antiproteinuric therapy are major objectives in recurrent FSGS. Aliskiren, the first orally active direct renin inhibitor, has been shown to have antiproteinuric effects [4]. The impact of aliskiren on proteinuria and renal progression in recurrent FSGS is not clear. We present the safety and efficacy of aliskiren added to a dual blockade of the renin-angiotensin-system (RAS) in a nephrotic patient with severe recurrent FSGS.

Case report

A 29-year-old woman developed nephrotic syndrome with proteinuria of 15 g/day, oedema, and renal insufficiency (creatinine of 2.4 mg/dl). Renal biopsy proved primary FSGS with segmental sclerosis and mesangial expansion with hypercellularity. Corticosteroids were administered over several months without remission and progressive renal insufficiency requiring dialysis 1 year after diagnosis. The patient received a kidney transplantation after 10 years on dialysis. Immunosuppressive triple therapy was started with tacrolimus, mycophenolat mofetil (MMF) and corticosteroids. Initially, graft function

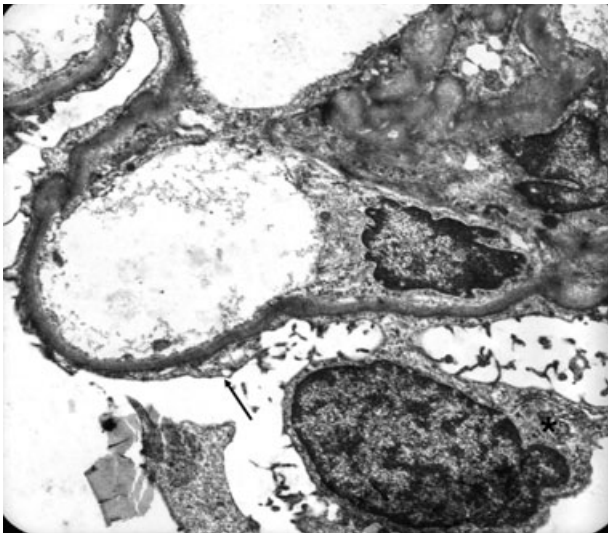

Figure 1 Electronmicroscopical investigations of the renal biopsy of the transplanted kidney with podocyte enlargement (*) and foot process effacement (→) as characteristic finding for focal segmental glomerular sclerosis.

was sufficient (creatinine 1.4 mg/dl) without significant proteinuria. Blood pressure control was achieved (<130/80 mmHg) by the use of ACE-I, calcium channel blocker, betablocker, and diuretics. However, 5 months after transplantation, the patient developed oedema and nephrotic proteinuria (6.2 g/day). A kidney transplant biopsy was performed showing a focal and segmental sclerosis in some glomeruli of the sample accompanied by a focal accentuated interstitial fibrosis. Electronmicroscopical investigation revealed podocyte enlargement and foot process effacement as meaningful characteristic of FSGS (Fig. 1). Immunhistochemically, there was no specific entrapment of IgA, IgG, IgM, c1q or c3c in the areas of a slight increased mesangial matrix. There was no cellular or antibody mediated rejection or tubular atrophy. Based on these histological findings, diagnosis of recurrent FSGS in the kidney transplant was set.

When developing nephrotic proteinuria, antihypertensive medication was enlarged by a dual RAS blockade with ramipril 10 mg/day plus candesartan 24 mg/day and diuretic dosage increased (furosemid 250 mg/day). Immunosuppressive therapy was intensified with increased doses of steroids (initially intravenous pulse 250 mg/day with tapering) besides tacrolimus and MMF (2 g/day). However, the patient continued to have a marked proteinuria of 5.6 g/day. Hence, Rituximab treatment was initiated (375 mg/m^2 body surface). In the peripheral blood, CD 20 positive B cells fell from 5.8% to <0.1%. There was no compelling effect on proteinuria. After 10 months, B-cells had risen to 3% and a second infusion of Rituximab was given after a re-increase of proteinuria up to 7.2 g/day. The antiproteinuric effect of the second Rituximab infusion was time limited. Proteinuria decreased slowly over 8 months after Rituximab down to 4.3 g/day. However, the patient presented again with a further flare of a proteinuria of 11.8 g/day. Plasmaexchange (PE) with a total of four treatments followed by the third Rituximab infusion was initiated. Proteinuria decreased (4.1 g/day) partially, but 1 month later protein excretion increased again up to 5.7 g/day. Antihypertensive medication was intensified with six antihypertensive agents (diuretics, calcium channel blocker, beta blocker, central sympatholytic agents, ACEI and ARB). The dosage of candesartan was increased up to 32 mg/day. Then, triple blockade of the RAS by addition of aliskiren (150 mg/day for 4 weeks) was started. After 4 weeks, dosage of aliskiren was increased to 300 mg/day. After further 4 weeks, candesartan was administered in the maximum dose of

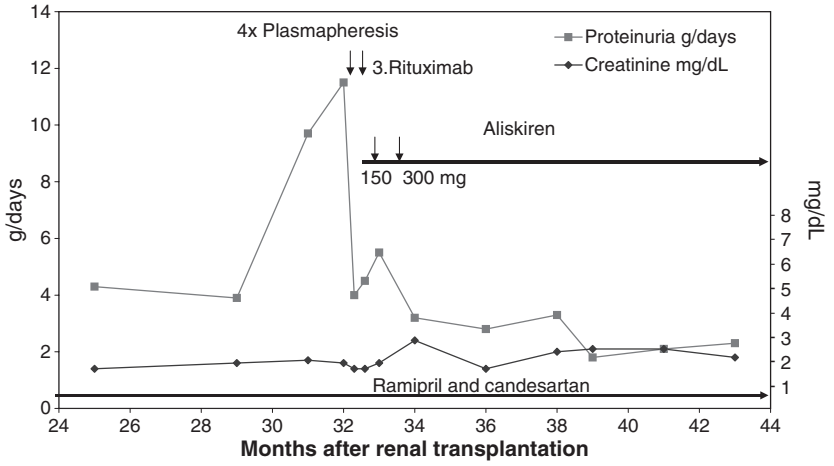

Figure 2 Clinical course of proteinuria (g/day) and serum creatinine (mg/dl) under triple RAS blockade in a patient with recurrent FSGS 10 months up to 43 months after kidney transplantation. The first and second Rituximab infusion (375 mg/m^2) was administered 10 and 21 months after renal transplantation.

64 mg/day. Subsequently, proteinuria decreased for the first time since recurrence of FSGS in the allograft below the nephrotic range. The reduction of proteinuria was significant and sustained. Actually, 42 months after transplantation, proteinuria is 1.8 g/day without oedema. B-cell count in the blood is now 3.5%. Blood pressure levels are less than 125/80 mmHg in casual readings. Aliskiren was generally well tolerated. Gastrointestinal symptoms did not occur. Creatinine was between 1.4 and 1.6 mg/dl [estimated glomerular filtration rate (eGFR) 55 ml/min, Cockroft-Gault formula] when recurrence of FSGS was diagnosed. Creatinine increased up to 2.0 mg/dl (eGFR 42 ml/min) over 11 months under triple RAS blockade. The patient suffered from a post-transplantation anaemia. Under triple RAS blockade, erythropoietin (Darbopoetin 20–40 μg per week) was given achieving stable haemoglobin values of 11 g/dl. White blood cell count and thrombocytes remained stable under triple RAS blockade. The clinical course of proteinuria and creatinine under triple RAS blockade is presented in Fig. 2.

Discussion

It is an important objective for the treatment in patients with recurrent FSGS and nephrotic syndrome to achieve remission of proteinuria as otherwise renal function deteriorates with rapid progress to renal failure requiring dialysis again [5,6]. Treatment strategies comprise immunosuppressive regimen using PE and Rituximab [7,8]. However, the results of these strategies are not consistent [9,10]. In our case, administration of Rituximab led only to a partial and limited remission of proteinuria with an early relapse of nephrotic syndrome. Plasmaexchange achieved only a time limited antiproteinuric effect. The lack of lasting efficacy can be due to the limited applications of PE in our patient. But, the schedule of PE and its therapeutic value in general is still a matter of debate.

A strict blood pressure control and antiproteinuric therapy by the use of ACEI or ARB are associated with a better renal survival in FSGS [11]. A complete remission of proteinuria and also a partial remission with low nadir proteinuria have been shown as important therapeutic targets in FSGS with implications for the renal prognosis [4]. In recurrent FSGS after kidney transplantation, there are single reports about beneficial effects of ACEI on urinary protein excretion [4]. The impact of an intensified combined RAS blockade including a direct renin inhibitor is not clear. We applied a triple blockade of the RAS, starting with the ACEI ramipril, and, adding the ARB candesartan enhancing each dosage until the full therapeutic dose was achieved. To optimize blood pressure control, we added aliskiren to the ongoing dual RAS blockade. The orally active aliskiren inhibits the first step of the renin-angiotensin-aldosteron cascade, reducing plasma renin activity and plasma angiotensin II levels [12]. Aliskiren provides dose-dependent antihypertensive efficacy [13,14]. In our case, under triple RAS blockade, blood pressure values went down to <125/80 mmHg, Proteiunuria decreased to a nadir urinary excretion of 1.8 g/day. The antiproteinuric effect is sustained now for more than 11 months. Triple blocking therapy at 3 different targets of the RAS with coadministration of aliskiren to a full dose ACEI plus ARB achieved some more antiproteinuric response than dual blockade of the RAS. Therefore, the use of aliskiren alone or in combination with other RAS blocking drugs may offer a new therapeutic approach in selected hypertensive patients with recurrent FSGS. A limitation of our case study is that it cannot be excluded that the final outcome might be as a result of the combined effect of the previous therapies or that the disease improved at least in part spontaneously. Potential side effects of a combined RAS blockade, especially with potassium sparing diuretics or nonsteroidal anti-inflammatory drugs have to be taken into account very cautiously. In patients with a glomerular filtration rate of <30 ml/min, kidney function has to be carefully monitored. Possible interactions of the aliskiren degradation via cytochrome p3A4 and the metabolism of cyclosporine A have to be taken into account. As aliskiren is a substrate of the P-glycoprotein (Pgp) transporter, coadministration of a potent Pgp inhibitor such as cyclosporine may increase plasma levels of aliskiren [15]. Over that, blood cell count should be monitored under triple RAS blockade. In our patient, the individual tolerability of the triple RAS blockade was good. There were no episodes of hyperkalemia (>5 mmol/l) or unusual variations of trough plasma calcineurin-inhibitor levels under triple RAS blockade. The increase of serum creatinine levels after addition of aliskiren may be due to reversible hemodynamic effects by the triple RAS blockade.

In summary, this case shows a signifcant antiproteinuric effect of a intensified triple RAS blockade with full dose ACE, ARB, and the direct renin inhibitor aliskiren in a nephrotic patient with recurrent FSGS which can be a new therapeutic option in this disease.

Authorship

VF, HF: designed the clinical research study, carried out the investigations, and assessed the data. KA: performed the kidney transplant biopsy studies and collected the data. HF, VF, UH, KA: analysed the data. All investigators were involved in the writing of the manuscript.

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