Intravenous Rituximab in Severe Refractory Primary Focal Segmental Glomerulosclerosis

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ABSTRAK

Mengelola glomerulonefritis primer atau bahkan sekunder tetap menjadi tantangan bagi banyak nefrologis. Pada glomerulosklerosis fokal segmental primer (FSGS) dengan proteinuria berat, blokade sistem renin aldosterone dan prednisolon oral dosis tinggi merupakan andalan pengobatan. Obat imunosupresif lainnya seperti Cyclophosphamide, Cyclosporine A dan Mycophenolate Mofetil (MMF) dibenarkan jika remisi lengkap tidak tercapai. Penulis mengilustrasikan kasus pria berusia 21 tahun dengan FSGS primer yang sulit mencapai remisi meskipun menggunakan steroid dosis tinggi dan Cyclophosphamide oral. Pasien juga tidak responsif terhadap kombinasi MMF dan Cyclosporine A (CSA) dan bahkan selama terapi ia mengembangkan steroid dan toksisitas CSA yang signifikan. Pasien dirujuk dengan sindrom nefrotik berat dan cedera ginjal akut yang membutuhkan hemodialisis akut. Meskipun diberikan kembali prednisolon dosis tinggi, total 2,4g Cyclophosphamide intravena, dan MMF, namun gagal mencapai remisi. Kemudian diberikan Rituximab intravena 500mg/minggu untuk 4 dosis dan mampu mencapai remisi selama 1 tahun. Pasien mengalami kekambuhan dan pemberian kedua Rituximab 500mg/mingguan 6 dosis untuk mencapai remisi. Kasus ini menunjukkan kesulitan dalam mengelola FSGS steroid refrakter dan kami menemukan bahwa Rituximab terbukti bermanfaat dalam hal ini untuk menginduksi remisi.

Kata kunci: *refraktori glomerulo-sklerosis, intravena rituximab.*

ABSTRACT

Managing primary or even secondary glomerulonephritis remains a challenge to many nephrologists. In primary focal segmental glomerulosclerosis (FSGS) with heavy proteinuria, renin aldosterone system blockade and high dose of oral prednisolone is the mainstay of treatment. Other immunosuppressive medications like Cyclophosphamide, Cyclosporine A and Mycophenolate Mofetil (MMF) are warranted if a complete remission is not achieved. We illustrate a case of 21 year old gentleman with primary FSGS that was difficult to achieve remission despite on high dose steroid and oral Cyclophosphamide. He was also not responsive to a combination of MMF and Cyclosporine A (CSA) and even throughout the therapy he developed significant steroid and CSA toxicity. He presented to our center with severe nephrotic syndrome and acute kidney injury requiring acute haemodialysis. Despite re-challenged him again on high dose prednisolone, total of 2.4g of intravenous Cyclophosphamide, and MMF, he failed to achieve remission. He was subsequently given intravenous Rituximab

500mg/weekly for 4 doses and able to attained remission for 1 year. He relapsed again and a second course of Rituximab 500mg/weekly for 6 doses were given to attain remission. This case demonstrates the difficulty in managing refractory steroid dependent FSGS and we found that Rituximab is proven beneficial in this case to induce remission.

Key words: *refractory focal segmental glomerulosclerosis, intravenous Rituximab.*

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a kidney disease causing proteinuria due to glomerular sclerosis which may leads to renal dysfunction or end stage renal failure (ESRF). FSGS can be classified as primary where no underlying cause has been found for the development of focal podocytes injury. Whereas, secondary FSGS is considered if the podocytes injury can be explained due to other causes such as obesity, human immune virus infection, IgA nephropathy, vasculitis, lupus nephritis, drugs including heroin and interferon treatment, reflux nephropathy or sickle cell anemia.[1] It is important to distinguish between primary and secondary FSGS as treatment approach is different.[2]

The Kidney Disease Improving Global Outcomes (KDIGO) guideline stated that oral high dose prednisolone is the immunosuppressant of choice for primary FSGS presented with nephrotic range proteinuria.[3] The major prognostic indicator of renal survival is the initial response of the proteinuria to steroid therapy. Thus, remission of proteinuria is the ultimate goal in primary FSGS. A complete remission that is defined as reduction of proteinuria to less than 200 to 300 mg/day, meanwhile partial remission can be defined as 50% or greater reduction in proteinuria to a level that is <3.5 g/day. Any patients relapse while steroid is being tapered, or within two months of stopping steroid therapy, they are considered steroid dependent. Patients with little or no reduction in urine protein excretion after 12 to 16 weeks of treatment are considered steroid resistant.[3]

Most patients with steroid dependent FSGS required long-term low-dose corticosteroid therapy along with either cyclophosphamide (CYC), cyclosporine A (CSA), Mycophenolate Mofetil (MMF) or Rituximab to maintain clinical remission.[4-6] Angiotensin-converting enzyme inhibitor (ACEi) or Angiotensin-II receptor blockers (ARB) is indicated in patients with FSGS but the results on proteinuria is variable.[7,8] Nevertheless, both ACEi and ARB has been proven to retard the progression of chronic kidney disease to end stage kidney disease by reducing proteinuria and maintaining blood pressure.[9,10] However, care must be taken to avoid symptomatic hypotension and increment of creatinine. Fluid overload should be treated with diuretics especially loop diuretics. Combination of loop diuretic with thiazide can be considered in refractory fluid overload. Salt intake to 6 gram/day (2g of sodium) is essential to prevent fluid retention. It is always important to balance the side effects and the benefits of medications given to the patient. Here we illustrate a case of a refractory primary FSGS and the management approach in our centre.

CASE ILLUSTRATION

A 21 year old gentleman presented 3 years ago at a state hospital with nephrotic syndrome. His creatinine was 105 µmol/L (eGFR of 82 ml/min/1.73m^2), serum albumin of 15g/L, urine protein creatinine index (PCI) 0.93g/mmol creatinine. A diagnosis of FSGS; non-otherwise specified (NOS) type was confirmed on renal biopsy and screening tests for secondary causes were all negative. He was initiated on high dose oral prednisolone (1mg/kg/day; 60mg/kg/day). He achieved complete remission after 1 month of high dose oral prednisolone with urine PCI reduced to 0.01g /mmol creatinine, resolution of body edema and preservation of renal function.

Unfortunately, he relapsed while on tapering dose of oral prednisolone to 5mg daily at 6 months of therapy. A second course of oral prednisolone at (1mg/kg/day; 60mg/day) was then restarted. He developed multiple relapses while attempting to taper down the prednisolone. Despite added on

oral cyclophosphamide 125 mg daily (2.5 mg/kg/day) for 2 months his disease remains difficult to control. He was then switched to oral cyclosporine A (CSA) 100 mg twice a day for 9 months. Oral MMF was started following cyclosporine toxicity with worsening of renal profile and gum hypertrophy which later resolved after withdrawal of the drug. He was kept on MMF 1g twice daily with maintaining high dose prednisolone at 60mg daily as every attempt to taper down his oral prednisolone, his urine protein will rose further. His urine PCI was remained at 0.40 g/mmol creatinine after his second relapsed.

He presented to our center with overt nephrotic syndrome and oliguric acute renal failure while he was on prednisolone 60mg/day and MMF 1gm twice daily. His serum albumin was 19 g/L, urine PCI was 2.90 g/mmol creatinine, serum creatinine of 980 μmol/L and urea of 20 mmol/L. An ultrasound of the renal system was normal. Magnetic resonance angiography and magnetic resonance venography showed no evidence of renal artery stenosis or renal vein thrombosis. Renal biopsy was consistent with acute tubular necrosis with underlying focal segmental glomerulosclerosis – non-otherwise specified (NOS) type (**Figure 1**). He was treated with intravenous methylprednisolone 250 mg daily for 3 days followed by 50 mg daily then oral prednisolone 60mg daily.

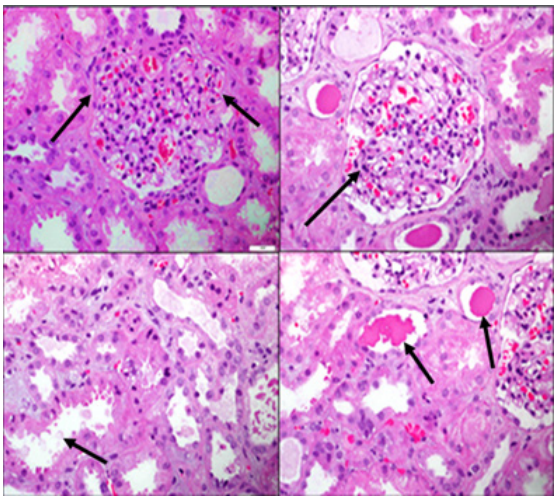

Figure 1. Renal biopsy showed capsular adhesion (upper left) and mesangial expansion and proliferation (upper right). Tubules were dilated and exhibiting cytoplasmic vacuolations and blebbing of apical membrane (bottom left) with eeosinophilic proteinaceous casts within lumen (bottom right).

He required temporary haemodialysis. He was then given intravenous cyclophosphamide (IV CYC) 2 weekly for 5 doses with total cumulative dose of 2.4 gram; subsequently he was then continued with MMF 1 gm twice daily. His urine protein reduced to 1.2 g/day after 5 months and his kidney function was completely recovered. Despite of compliance to his immunosuppressive treatment consist of prednisolone 35mg daily and MMF 1gm twice daily, he never achieved complete remission with urine PCI remains between 0.12 to 0.14 g/ mmol creatinine (**Figure 2**). Calcineurin inhibitor was not started at that time as he was just recovered from acute kidney injury with past history of failure to CSA.

Unfortunately, his high dose steroid therapy caused him to develop steroid induced diabetes mellitus requiring oral antidiabetic medication. Due to refractory FSGS, we decided for 4 doses of intravenous (IV) Rituximab 500mg/weekly. He responded well to the IV Rituximab and in clinical remission (urine PCI less than 0.03 g/mmol creatinine, serum albumin of 37 g/L) for 1 year (**Figure 2**) and subsequently was maintained with MMF 1 g twice daily, oral prednisolone 10mg daily and perindopril 4mg daily then gradually optimized to 8 mg daily. His blood pressure ranging between 110-120 mmHg/70- 80 mmHg.

A year later, he relapsed again with urine PCI increased to 1.70 g/mmol creatinine. Serum albumin dropped from 38 to 19 g/L. His corticosteroid dose was increased again to 60mg/day. MMF dose was maintained at 1gm twice a day and restarted on CSA 50mg twice a day at 1mg/kg/day. He was compliant to his treatment and already had signs of steroid toxicity such as exogenous Cushing's; abdominal striae, and proximal myopathy. Decision was made to give him another prolong course of IV Rituximab comprised of 6 doses of 500 mg/weekly while his oral prednisolone was tapered to prevent further side effects. He responded very well and reduction of his urine protein after the second dose of IV Rituximab (**Figure 2**). We strongly believe that the effect on proteinuria reduction was driven by Rituximab rather than the addition of low dose of CSA itself.

In view of previous history of CSA toxicity (acute kidney injury, gum hypertrophy) at 2 mg/kg/day, his CSA is optimized at a slower pace. Now, he is maintained with oral prednisolone 10mg daily, MMF 1g BD and CSA 100mg twice daily (triple therapy). He is also double anti-proteinuric medications; perindopril 8mg daily, telmisartan 80mg daily and atorvastatin 20 mg at night. His signs of steroid toxicity such as proximal myopathy and abdominal striae have resolved upon tapering down his oral prednisolone and his diabetic control is well manage with dietary control only.

DISCUSSION

Primary FSGS is a glomerular disease with variable clinical course. According to KDIGO guideline, treatment with corticosteroid and other immunosuppressant are only indicated in primary FSGS associated with nephrotic syndrome.[3] Relapse after clinical remission is very common in primary FSGS. It is a challenge for nephrologist in managing refractory FSGS complicated with steroid toxicity as we experienced in this particular case.

Steroid is the mainstay of treatment for primary FSGS. Pulse with high dose of IV methylprednisolone is associated with favorable clinical outcome in active refractory primary FSGS. However, prolonged steroid treatment can cause significant side effects such as diabetes mellitus and exogenous cushing. Thus, for our patient, the ultimate aim was to optimize the steroid sparing immunosuppressant's to render his primary FSGS to remissions and at the same time to taper down his steroid to prevent worsening of his steroid toxicity. Cyclophosphamide (CYC) is an alkylating agent which is recommended as a steroid sparing immunosuppressant for steroid responsive primary FSGS.[11] CYC is administered for 8 to 12 weeks. The combination of CYC with steroid is associated with a longer remission period in steroid dependent primary FSGS. Treatment more than 12 weeks shows no beneficial clinical outcome.[11] Furthermore, bone marrow suppression, hemorrhagic cystitis and gonadal toxicity are well known complications of prolong CYC therapy.

CSA is a calcineurin inhibitor (CNI) which may be beneficial in primary refractory FSGS unresponsive to CYC.[12] It can also serve as first line therapy in primary FSGS where steroid treatment is contraindicated or intolerance to high dose. CSA is associated with 50% reduction in relapse rate and as good as CYC.[13] Remission may take 3–6 months following treatment. Relapses do occur after withdrawal of CSA.[12] However, prolong CSA treatment, perhaps up to one year or longer after remission is achieved associated with low risk of relapse.[14] Side effects of CSA include tremor, hypertrichosis, gum hypertrophy, hypertension, and nephrotoxicity.

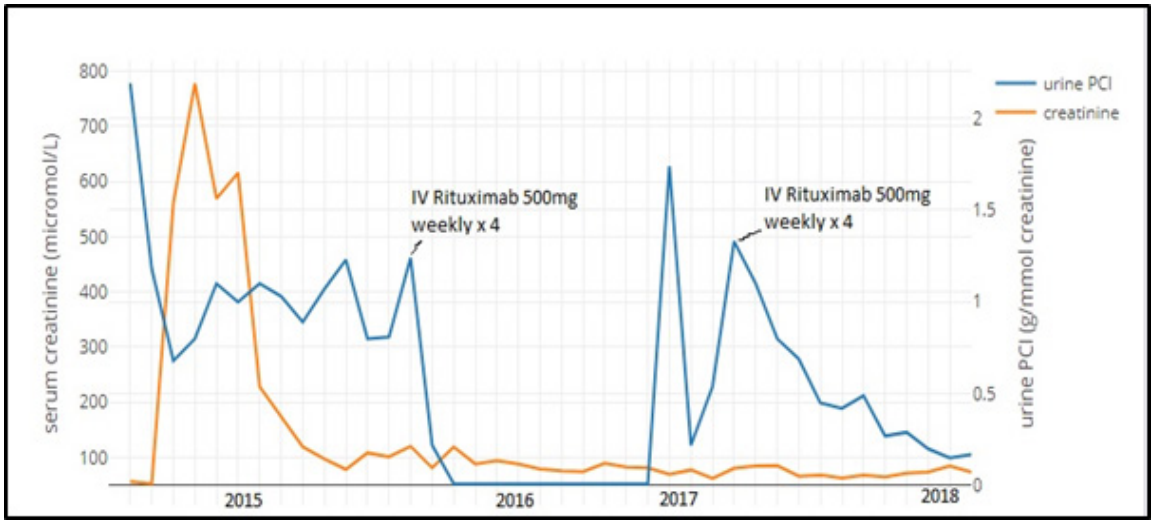

Figure 2. Relationship between serum Creatinine and urine PCI

Risk of nephropathy increases if high-dose CSA (more than 5.5 mg/kg/d) is given, patient has pre-existing chronic renal failure with eGFR less than 60 ml/min per 1.73 m^2 and present of tubule-interstitial fibrosis in renal biopsy.[14] Thus, CNI should be avoided if eGFR is less than 30 mL/min/1.73 m^2. Tacrolimus (TAC) may serve as alternative CNI in cases of CSA-resistant or CSA-dependent FSGS.[15] The cosmetic side effects such as hypertrichosis and gum hypertrophy are not seen with TAC. Thus, it is preferred in patient who cosmetic side effect is a major concern. However, the incidences of other risk factors such as nephropathy, tremor, and diabetes mellitus are the same for both TAC and CSA.[14,15]

MMF acts via inhibition of T cell and B cell. It is an alternative agent in primary FSGS when CNI is contraindicated or refractory and developed complications following CNI therapy.[16] MMF is indicated in patients with partial response to steroid or serves as steroid sparing immunosuppressant in cases of steroid toxicity. In our patients; MMF was started following CSA induced nephropathy. MMF is not inferior to CNI in preventing relapses but only if given at high doses.[16] MMF has relative fewer side effects compare to CNI. Some of the common MMF side effects include gastrointestinal symptoms such as diarrhea, abdominal pain and hyperlipidemia.

As illustrated in our case, he received the conventional therapy as per recommendation in KDIGO guideline. Unfortunately, not only refractory to therapy namely high dose steroid, CYC (oral or IV), combination of prednisolone with CSA as well as MMF, he also developed severe side effects such as nephrotoxicity and gum hypertrophy with CSA and also Cushing's syndrome and diabetes due to the high dose of steroid. Therefore Rituximab was utilized in this case as adjunctive treatment to render him into remission. Rituximab therapy here is reserved after attempts with steroid, CNI, or MMF have failed to induce remission.

Rituximab is a chimeric monoclonal antibody that inhibits CD20-mediated B lymphocytes. Rituximab has protective effect on podocytes. Several reports have demonstrated successful treatment of Rituximab in refractory steroid dependent primary FSGS.[17-19] Therapy for FSGS with IV Rituximab has been reported in some case reports in recurrent nephrotic syndrome after renal transplantation in paediatric population.[17,20] Nevertheless, the potential usefulness of rituximab in adult FSGS has been varies in term of doses, regime and responses.[21] Utilization of Rituximab as a treatment in adult refractory FSGS remains debatable on what will be the optimal dose and how frequent it should be.

Soluble urokinase-type plasminogen activator receptor (suPAR) levels were increased in FSGS as evidence by two large cohorts; the FSGS Clinical Trial (FSGS CT) and the PodoNet European FSGS consortium.[22] suPAR is the cleaved molecule derived from urokinase type plasminogen activator receptor (uPAR) and uPAR is a membrane-bound protein linked to glycosylphosphatidylinositol (GPI) present on podocytes. suPAR may trigger the podocytopathy in the majority of patients with primary FSGS via activation of podocyte αvβ3 integrin. suPAR act as permeability factor that stimulates the podocyte αvβ 3 integrin signaling pathway causing proteinuria. Rituximab inhibit suPAR-podocyte αvβ3 integrin signaling via modulation of sphingomyelin phosphodiesterase acid-like 3b.[23] Unfortunately, in this case we were unable to measure the suPAR as it is not available in our center.

Removal of this circulating factor by plasmapheresis is an option as it can reduce proteinuria and induced clinical remission. However, the efficacy of plasmapheresis in recurrent FSGS is quite variable. The average respond rate ranging 50% to 60%.[24] The respond rate is dependent on the absolute level of the circulating permeability factor. Relapse can occur during rapid tapering of plasmapheresis sessions and usually requires prolonged reinstitution of the plasmapheresis sessions. Hence, individualization of treatment schedule depending on clinical response has been proposed. In this case, we opted to treat him with IV Rituximab and in view of his good response, plasmapheresis was not done. Plasmapheresis perhaps should be considered

if he does relapse again in the future. In those treated with plasmapheresis and responding, treatment should be continued until proteinuria has been reliably suppressed to below 0.5 g/day.

The development of anti-rituximab autoantibodies may be of concern in this case following repeated Rituximab infusion.[25,26] Hence, the presence of anti-rituximab autoantibodies is suspicion for cases of severe infusion reaction and if B cell depletion is not observed following Rituximab therapy. A close relation between B-cell depletion and clinical remission of refractory FSGS has been reported.[25] The typical rituximab regimen is usually given at 2–6 doses (375 mg/m^2/dose), administer once every 1 to 2 weeks.

Rituximab was well tolerated by our patient and allowed us to taper dose of prednisolone to prevent worsening of his steroid toxicity. He achieved full remission after 1st 4 cycles of rituximab with 500mg/week dose. Though he relapsed a year later, a second course of rituximab 500mg/week for 6 weeks also resulted in gradual clinical remission without the need for high dose prednisolone. Currently, his treatment is directed to optimization of his triple immunosuppressive therapy and anti-proteinuric medications while ensuring minimal side effects to induced complete remission as our ultimate target.

CONCLUSION

The management of refractory primary FSGS as illustrated in this case remains a challenge for nephrologists. Steroid in combination with immunosuppressant such as CNI, CYC or MMF may induce partial if not total remission of proteinuria. Rituximab should be considered as an alternative treatment in severe refractory primary FSGS associated with treatment toxicities. This case report supports a generalized effectiveness of rituximab treatment in FSGS. More studies are necessary to characterize further the type of patients who have FSGS that could benefit from rituximab administration. The optimal dosage and frequency of rituximab in this disease remains a challenge. Although mechanistic effects of rituximab on the podocytes were clear and potential permeability factor has been identified, current evidence on the nature of this factor and on the pathogenesis of recurrent FSGS remains inconclusive.

CONFLICT OF INTEREST

No author of this paper has conflict of interest. We receive no financial support for this case report.

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