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High dose Rituximab ineffective for Focal Segmental Glomerulosclerosis: a long-term observation study

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Running head: Inefficacy of high dose Rituximab in FSGS

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Background: a beneficial effect of rituximab on Focal Segmental Glomerulosclerosis (FSGS) in pediatric patients or in transplant recipients has been reported in isolated cases. However, the use of Rituximab in adult patients with idiopathic FSGS needs further investigation.

Methods: Eight patients who had biopsy-proven FSGS (63.9 ± 14.0 , range 40-81 yr, 4 women, 4 men) with major risk factors precluding corticosteroids or conventional immunosuppression were treated with high dose of rituximab (8 weekly doses of 375 mg/m^2) and prospectively followed up for at least 2 years (29.1 ± 8.8 mo, range 24 to 42 mo).

Results: Rituximab failed to improve proteinuria in seven out of 8 patients, who had persistent nephrotic proteinuria. In one case, a rapidly deteriorating renal function was also observed. Only one patient showed an improvement of renal function and a remarkable proteinuria reduction. There were no differences in clinical or laboratory characteristics or in the CD20 B lymphocyte count after rituximab between the responder and the 7 non responders patients.

Conclusions: Only a minority (one of eight) in our series of adult patients with FSGS showed positive effects of high doses of rituximab. Future studies are warranted to investigate more promising therapeutic options in the management of FSGS.

Introduction

Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome in children and in adults. More than 60% of patients treated with steroids achieve remission [1]. However, among those achieving remission (either complete or partial), approximately half of them experience relapses [2]. In patients with frequent relapses or steroid dependency, co-morbidities secondary to steroid treatment may be challenging and deeply impacting in prognosis and quality of life [3]. Long-term complications of steroid regimens, such as impaired glucose tolerance, hypertension, osteopenia/osteoporosis, dyslipidemia, and an increased risk of infections and cardiovascular events are common. Steroid-sparing agents such as cyclosporine A, mycophenolate mofetil, azathioprine, tacrolimus, levamisole, cyclophosphamide and chlorambucil have been investigated in FSGS as second- and third-line treatment [4–8], but adverse events and toxicities attributed to these immunosuppressants also limit their long-term use.

Rituximab (RTX) is a chimeric monoclonal antibody directed against CD20 positive B-cells, and is a part of the therapeutic option in diseases like rheumatoid arthritis [9] and ANCA-associated vasculitis [10]. Moreover, RTX is a valuable option in the treatment of several connective tissue diseases [11–13] and immune mediated glomerular diseases as idiopathic membranous nephropathy (IMN) [14,15] and Henoch-Schonlein purpura nephritis [16]. RTX has emerged as an alternative treatment of childhood frequently relapsing, steroid-dependent or steroid-resistant nephrotic syndrome [17–20]. A beneficial effect of rituximab on FSGS in pediatric patients or in transplant recipients has

been shown in isolated reports and few case series [21–23]. However, in adult patients with FSGS with persisting nephrotic syndrome, data on the efficacy of RTX treatment are still elusive [24,25].

Methods:

Consecutive patients meeting the following criteria were prospectively enrolled in our study: (1) biopsy-proven FSGS; (2) nephrotic syndrome; (3) absence of concomitant infections, comorbid conditions, or systemic diseases that could have a pathogenic relationship with the nephrotic syndrome; and (4) presence of major risk factors precluding the use of corticosteroids. For each patient, the following data were extracted from patient records: demographic characteristics, clinical data (elevated blood pressure -BP, body weight, edema), time elapsed since the diagnosis of FSGS by renal biopsy. Any non-specific antiproteinuric treatment before rituximab administration were also recorded. A careful analysis of familial history of renal diseases was performed in every case. The pathologic variant of FSGS (collapsing, tip lesion, cellular variant, perihilar, and FSGS not otherwise specified) was recorded, as well as the percentage of glomeruli showing a global sclerosis. The severity of tubulointerstitial fibrosis was graded as absent (0), mild (+), moderate (++), and severe (+++).

For all patients, the following clinical and laboratory parameters were recorded at baseline (onset of rituximab administration), monthly during the treatment period, and then every 3 to 6 mo after treatment: BP, body weight, complete blood counts, electrolytes, and routine serum biochemistry profile (including total proteins, albumin, a lipid panel, and serum creatinine). Creatinine clearance and proteinuria were measured by 24-h urine collections at each time point. For

all patients, B-cell flow-cytometry was performed after every rituximab treatment. For comparison of variables at baseline and follow-up, Student's t-test was used for normally distributed parameters, and the non-parametric Mann-Whitney test for non-normally distributed parameters. Correlations were calculated and significance determined by Fisher's test. For these analyses, with SPSS (IBM Corporation, NY, USA) software programs was used. $p < 0.05$ was considered significant.

Rituximab Protocol:

Rituximab was given at high dose in 8 weekly infusions of 375 mg/m². This scheme was chosen when analyzing available literature about the use of Rituximab in adult patients with FSGF. In their report, Fernandez-Fresnedo G and co-workers showed that the only three out of eight patients who had a positive response to Rituximab had received more rituximab doses (e.g. eight infusions of 375 mg/m²) than the other five patients, in whom four weekly intravenous infusions of 375 mg/m² of rituximab had been administered [24].

Results:

Eight adult patients who had biopsy-proven primary FSGS received high dose of rituximab (8 weekly doses of 375 mg/m²) and were prospectively enrolled in our study. The main demographic and clinical characteristics of the patients are summarized in Table 1. Patients were 4 women and 4 men, with a mean age of 63.9±14.0 (range 40-81 yrs) and a mean disease duration of 3 ± 3 mo (range 1 to 6 mo). All patient had major risk factors precluding corticosteroid regimens; in details, all the patients had elevated BP, 4 were diabetic (patients #1,4,6,7), 3 were older than 70 yrs (patients#3,6,7), 3 had osteopenia (patients#3,6,7,).

All patients had marked proteinuria at the time of rituximab treatment (mean proteinuria 5.3 ± 1.9 g/24 h; range 3.6 to 8.0 g/24 h), and their mean serum creatinine was 2.6 ± 1.2 mg/dl (range 0.9 to 3.7 mg/dl). Supportive treatments of nephrotic syndrome (including diuretics, statins, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers) given at the time of rituximab administration were maintained during follow-up.

Renal biopsies characteristics are specified in Table 2. The percentage of globally sclerosed glomeruli ranged from 10 to 40%. Interstitial fibrosis was absent in two cases, mild in four, and moderate in two. No correlation between histologic features and response to rituximab treatment was found.

The tolerance to rituximab infusion was good, and no adverse effects were observed during the period of rituximab administration or during the follow-up. The mean duration of follow-up after rituximab therapy was 29.1 ± 8.8 mo (range 24 to 42 mo).

As shown in Figure 1, rituximab failed to resolve nephrotic syndrome in most of the patients. Patients #1,#4,#5 persisted with a massive proteinuria and a roughly stable high serum creatinine. Patients #5 showed a clear worsening of renal function accompanied by a persistent massive proteinuria. Patient #6 and 7 #, who had clearly impaired renal function at baseline (serum creatinine 2.8 and 3.5 mg/dl), showed a marginal non-significant proteinuria decrease after the rituximab course. Patient #8 presented with conserved renal function and her proteinuria remained stable after 24th of follow-up.

Only one patients (patient #3) experienced a sustained improvement. She presented with severe proteinuria and deteriorated renal function at the time of rituximab administration (proteinuria 7 g/24 h and serum creatinine 3.7 mg/dl,

respectively) and showed a clear proteinuria decrease to non-nephrotic values (1.5 g/24 h) accompanied by a slight improvement of renal function (Table 1).

In the whole group of patients, we failed to observe a significant decrease in proteinuria levels (5.3 ± 1.9 g/24 h at baseline to 3.9 ± 1.8 g/24 h at the end of follow-up, and serum creatinine increased from 2.6 ± 1.2 to 3.5 ± 2.5 mg/dl (NS). CD20+ B lymphocytes decreased to undetectable levels after the first course of rituximab in all the patients. Time to recover a normal CD20+ count after rituximab treatment ranged between 9 and 25 mo (12.5 ± 5.6 mo) as shown in Figure 2. No differences in the CD20+ B lymphocyte profile has been observed in the patient with a positive response to rituximab treatment (patients #7).

Discussion

Some case reports and observational studies have created a considerable expectation about the therapeutic possibilities of rituximab in nephrotic syndrome [17,18]. Uncontrolled studies have shown significant proteinuria decrease after rituximab treatment in patients with idiopathic membranous nephropathy [14,26]. Conversely, several case reports in pediatric patients on in transplant suggested that rituximab could be a potentially effective and safe alternative in FSGS [27–29].

The possibility of a beneficial effect of rituximab on primary FSGS was initially suggested by the publication of cases who had recurrent FSGS in renal grafts and had remission of nephrotic syndrome after treatment with rituximab. To date, a very limited number of adult patients with FSGS has been successfully treated RTX [30–34]. Some of these patients were treated with rituximab because of the development of lymphoproliferative disorders [30,32], suggesting a possible

pathogenic relationship between such hematologic disorder and the pathogenesis of proteinuria. Conversely, two other reports, including six patients (four adults, two children) showed a failure of rituximab to improve nephrotic syndrome in renal transplant patients with recurrent FSGS [35,36].

To date, six reports including overall 10 children or adolescents who had primary FSGS in their native kidneys were treated with rituximab [27–29,37,38]. All of them had a positive response, achieving complete or partial remission of nephrotic syndrome, although, in some cases, rituximab was administered when proteinuria was in non-nephrotic values.

Fernandez-Fresnedo and co-workers, who showed a poor efficacy of rituximab in adult patients with severe nephrotic syndrome. In their cohort, 5 of eight patients continued to show massive nephrotic proteinuria, and renal function exhibited a rapid deterioration on follow-up in two of them; however, two other patients, who had a very poor renal prognosis (massive proteinuria accompanied by increasing serum creatinine), showed a partial improvement of renal function accompanied by a remarkable reduction in proteinuria [24]. The remaining patient, who received two rituximab courses, showed a clear proteinuria reduction after every rituximab treatment, but this beneficial effect was only transitory [24].

In our cohort, one of largest of adult patients the longest follow up ever reported, no significant decrease in proteinuria levels paralleled with a substantial increase in serum creatinine was observed. Only one patient had a reduction of about 80% of baseline value of proteinuria.

The reasons why RTX seems to be effective in pediatric patients with primary FSGS or in transplant recipients whereas it fails to induce any improvement in

adult patients with idiopathic FSGF remain unknown. The present cohort had some peculiarities. First, our patients sample included adult cases with definite contraindication to corticosteroids and recent onset of disease. Second, RTX was used as a first line treatment on naïve patients. Third, our patients received very high doses of RTX and the CD20+ B cells profile excluded any possibilities of hematologic resistance or developing of neutralizing anti-chimeric antibodies. This study including one of the largest cohort of adults patients with idiopathic FSGS with the longest follow-up, showed that despite the administration of the high dose of RTX, and no definite benefit in terms of proteinuria or renal function could be observed, and definitely raised the question of ethical justification of treating patients with adult onset FSGS with RTX.

Conversely, our study suffers for some limitations. While reflecting a real word scenario, the presence of several co-morbidities precluding the use corticosteroids (e.g. diabetes, high blood pressure) might have resulted in the substantial heterogeneity in biopsy findings at electronic microscopy. A beneficial role for Rituximab in a restricted cohort homogeneous for widespread foot process effacement at electronic microscopy cannot be ruled out.

Conclusions

Our results do not support the promising effects initially reported with rituximab in adults with FSGS. Among eight adult patients who had nephrotic proteinuria, only one patient showed a sustained positive response, with a reduction of 80% of baseline of proteinuria value. More studies are necessary to further characterize the FSGS patients who could benefit from RTX.

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Table 1: Demographic and clinical characteristics of the patients with FGSG treated with Rituximab.

Table 2: Biopsy characteristics of the patients with FGSG treated with Rituximab.

Figure 1: Evolution of serum creatinine (panel A) and proteinuria (panel B) after rituximab therapy.

Figure 2: Circulating B cells at the time of rituximab administration (day 0) and at different time points thereafter