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Original Research Article

Rituximab efficacy in pediatric patients with refractory nephrotic syndrome

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ABSTRACT

Background: Nephrotic syndrome (NS) in children is a disease of glomerular filtration barrier failure, manifesting with severe proteinuria leading to hypoalbuminemia, hypercholesterolemia, and generalized edema. it could be primary or secondary. In primary NS, also known as idiopathic NS, the histological findings of Primary NS include minimal change disease which mainly respond to steroids (steroid sensitive NS), focal segmental glomerulosclerosis which are usually steroid resistant or membranous nephropathy. Rituximab has been shown to be effective for patients with complicated FRNS/SDNS and refractory SRNS. While the incidence of nephrotic syndrome (NS) is increasing, the morbidity of difficult-to-treat NS is significant.
Methods: This is a retrospective cohort study that took place in King Abdulaziz University Hospital from 2012 to 2016. Patients included: Any patient under 18 years, and diagnosed with steroid resistant and dependent nephrotic syndrome. Patients excluded: Any patient above 18 years, and known to have secondary Nephrotic Syndrome.
Results: Present study consists of 24 children with nephrotic syndrome (NS) were recruited in the study. In the population 8 patients (33.33 %) were diagnosed with SDNS, while the other 16 patients (66.67%) were diagnosed SRNS. Also, patients who were treated with Rituximab we found that (the mean) number of relapses per year before rituximab was about 2.67±1.49 (standard deviation 1.49), while patient who relapsed after rituximab was about 1.09±1.38 (standard deviation 1.38).
Conclusions: Rituximab is a biological agent that started to be widely used in difficult nephrotic syndrome cases. The effectiveness of rituximab is most observed in steroid depended nephrotic syndrome patients since it decreases the frequency of relapses and steroid dependency. However, it has been shown that it is less effective in steroid resistant nephrotic syndrome cases and was associated with significant numbers of relapses.

Keywords: Nephrotic syndrome, Rituximab

INTRODUCTION

Nephrotic syndrome (NS) in children is a disease of glomerular filtration barrier failure, manifesting with severe proteinuria leading to hypoalbuminemia, hypercholesterolemia, and generalized edema. it could be primary or secondary. In primary NS, also known as idiopathic NS, the histological findings of Primary NS include minimal change disease which mainly respond to steroids (steroid sensitive NS), focal segmental glomerulosclerosis which are usually steroid resistant or membranous nephropathy.

Secondary nephrotic syndrome refers to an etiology extrinsic to the kidney. Secondary causes of nephrotic syndrome include (1) autoimmune and vasculitis, such HSP, SLE and ANA (anti-neutrophil cytoplasmic antibody) associated vasculitis; (2) infectious diseases, such as congenital syphilis, malaria, (HIV), and hepatitis B and C; (3) malignancy; (4) environmental and drug exposure, such as heroin and mercury; and (5) systemic diseases such as diabetes mellitus, (5) genetic. Idiopathic nephrotic syndrome is the most common chronic glomerular disease in children. At least 20 % of children with this syndrome show frequent relapses and/or steroid dependence during or after immunosuppressive therapies, a condition defined as complicated frequently relapsing/steroid-dependent nephrotic syndrome (FRNS/SDNS). Approximately 1-3% of children with idiopathic nephrotic syndrome are resistant to steroids and all immunosuppressive agents, a condition defined as refractory steroid-resistant nephrotic syndrome (SRNS); these SRNS children have a high risk of end-stage renal failure. Rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown to be effective for patients with complicated FRNS/SDNS and refractory SRNS. While the incidence of nephrotic syndrome (NS) is increasing, the morbidity of difficult-to-treat NS is significant. Efforts to minimize treatment toxicity of steroids. Studies showed that rituximab has an effective role in the management of nephrotic syndrome, evidenced by a decrease in the use of corticosteroids (steroid-free interval), decrease in number of relapses. A few studies argue that rituximab only delays relapses, but does not result in disease cure.[1] Most studies were done on patients with steroid-dependent nephrotic syndrome; there was one study in our literature review that was done on steroid-resistant NS. Most studies conclude that Rituximab is a generally safe drug with a low-incidence of side-effects.[2,6]

METHODS

This is a retrospective cohort study that took place in King Abdulaziz University Hospital from 2012 to 2016. Patients included: Any patient under 18 years, and diagnosed with steroid resistant and dependent nephrotic syndrome. Patients excluded: Any patient above 18 years, and known to have secondary nephrotic syndrome. SDNS defined as presence of relapses two times or more in either tapering down steroid dosage or within 14 days of stopping steroid, while SRNS defined as no response to steroids in a period of 4 weeks. The study got approved from the ethical board committee from College of Medicine in King Abdulaziz University Hospital. The data included age, gender, nationality, diagnosis, number of relapses 12 months before using Rituximab, number of relapses after using Rituximab from 3-12 months, number of Rituximab doses. In the present study, the statistical Package for Social Sciences (SPSS version 20) was used. statistical analysis was applied to study the primary and secondary objectives:

- Descriptive statistics (Frequency tables, Cross tabulation and Charts)
- The categorical variables between groups were compared using Chi–square test.
- Chi-square, Fisher's Exact Test to find the significant relationship between variables.
- A probability (P) <0.05 was considered significant.

RESULTS

Present study consists of 24 children with nephrotic syndrome (NS) were recruited in the study. There were 15 boys and 9 girls. The mean age of the children at the time of evaluation was 10.63±2.3 years, with an interquartile range of 3 and 18 years. Eleven (45.8%) children were Saudi and the rest (54.2%) were non-Saudi. In the population 8 patients (33.33 %) were diagnosed with SDNS, while the other 16 patients (66.67%) were diagnosed SRNS.

Also, patients who were treated with Rituximab we found that (The mean) number of relapses per year before rituximab was about 2.67±1.49 (standard deviation 1.49), while patient who relapsed after rituximab was about 1.09±1.38 (standard deviation 1.38).

Regarding the developing of proteinuria after treatment with rituximab, we found that (the mean) 0.95 number of patients developed proteinuria 6 month after Rituximab, on the other hand, (the mean) 1.30 number of patients developed proteinuria 12 months after rituximab.

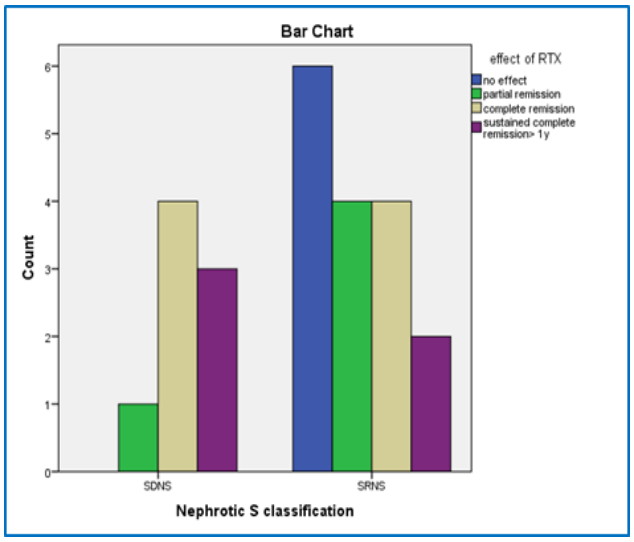

Figure 1: Nephrotic S. classification.

After RTX administration (Figure 1) in patients SDNS the results were either complete, sustained or partial remission with a percentage of 50%, 37.5% and 12.5% respectively. While in SRNS patients the results were either complete, sustained, partial or no effect with a percentage of 25%, 12.5%, 25% and 37.5% respectively.

DISCUSSION

Rituximab is considered to be an option for treating patients with SDNS.

In present cohort study, we found a decline of number of relapses after the administration of Rituximab in patients diagnosed with SDNS with a percentage 40.8%. The results are similar to other studies were conducted from other facilities.[1-3,5] In this study, we demonstrated that Rituximab can be used to decrease the dose of oral steroid in SDNS patients. This finding is consistent with other clinical trials.[2,4,6]

In Niu et al A single dose of Rituximab was given to 19 patients diagnosed with SDNS, 10 patients went in complete remission and did not relapse within 4-50 months without administration of oral steroid or immunosuppressive therapy. While 9 patients relapsed, but kept on lower dosage of treatment. And in Van Horebeek et al a retrospective single-center study was done including patients with an age of 2-18 years and labelled as difficult to treat SDNS. Nine patients with a median age of 4.75 years at the time of diagnosis, and a median age of 16.08 years at administration of Rituximab. The study showed a reduction of relapses with median number of relapses from 1.70 to 0.26 relapse per year, regardless of stopping or decreasing the dose of immunosuppressive therapy.[5] A study by Ravani P et al also showed similar results and reported the median relapse-free time between Rituximab treatments in their study was 18 months.[7] From our data, we noticed that RTX had some effect in steroid-resistant nephrotic syndrome (SRNS), but was associated with many relapses.

Other studies in the literature had varying results. Some found that it has positive effects such as in Sinha A et al where 34 SRNS patients received RTX and results showed that prednisolone was discontinued in 25 (73.5%) patients at 5.4±2.2 months; 18 of 19 patients discontinued concomitant therapy with CNI (Calcineurin inhibitors) and a decrease in frequency of relapses by 71.0%.[8-12] On the other hand, in Magnasco et al 31 SRNS children received RTX and it did not reduce proteinuria at 3 months (change- 12% [95% confidence interval- 73% to 110%]; P=0.77 in analysis of covariance model adjusted for baseline proteinuria).

CONCLUSION

Rituximab is a biological agent that started to be widely used in difficult nephrotic syndrome cases. The effectiveness of rituximab is most observed in steroid depended nephrotic syndrome patients since it decreases the frequency of relapses and steroid dependency. However, it has been shown that it is less effective in steroid resistant nephrotic syndrome cases and was associated with significant numbers of relapses. Our small number of patients might have limited the generalizability of the results. Further studies about the efficacy and safety of rituximab in nephrotic syndrome patients specially those who are resistant to steroid are required with full consideration of a larger sample size. Reaching to a better understanding of the efficacy of this agent and factors associated with treatment success is recommended for optimal disease management and clear guidelines.

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