IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 01 Ver. I (January. 2018), PP 05-09
www.iosrjournals.org

Multi-Drug Therapy Followed By Rituximab in Children with Refractory Nephrotic Syndrome Contributors

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Abstract
Introduction: *Over the last few years, rituximab (RTX) has emerged as a second- line therapy and has shown a 40-48% response rate in steroid resistant and up to 80% remission rate in steroid dependent nephrotic syndrome. The better outcome of RTX therapy in dependent nephrotic syndrome compared to resistant nephrotic syndrome is possibly due to excessive loss of RTX in the urine during active state of proteinuria.*
Objective*: To assess the therapeutic response of RTX during non-proteinuric state in children with steroid and CNIs/MMF resistance nephrotic syndrome following induction of remission by a combined therapy of Prednisolone, CNIs and MMF.*
Materials and Methodology: *In this study we analysed the data of steroid and CNIs/MMF –resistance idiopathic nephrotic children, aged 1-14 years from January 2014 to January 2016. The clinical decision was to treat those patients with a combined therapy (Prednisolone+CNI+MMF) to achieve remission, followed by treatment with RTX at a dose of 375 mg/m^2 body surface area per week for two to four weeks. Five children those who responded to triple regimen were treated with two to four doses of RTX and were followed up for minimum six months following RTX therapy. Post RTX therapy, CNI and prednisolone dose was tapered.*
Results and Discussion: *The characteristics of the five patients and follow-up data were documented Patient 1 and 2 were twin brothers. At six months follow-up, four patients achieved complete remission (80%) and three patients (60%) were completely off medications without any serious adverse effects.*
Conclusion: *Ourstudy showed improved RTX efficacy during non-proteinuric state of refractory nephrotic syndrome. However, as intense immunosuppression may cause serious adverse event further study for evaluatinglong-term efficacy and safety of multidrug therapy are needed.*
Keywords*: Rituximab, Steroid resistant Nephrotic Syndrome, second line therapy.*

Date of Submission: 19-12-2017 Date of acceptance: 06-01-2018

I. Introduction

Idiopathic nephrotic syndrome (INS) is a primary renal disorder defined by the three signs of proteinuria, hypoalbuminemia, and oedema. Histopathological categories of INS include minimal change disease, focal segmental glomerulosclerosis (FSGS), and diffuse mesangial proliferation. [1] Based on the response to steroid treatment, two types of INS can be characterized: steroid sensitive nephrotic syndrome (SSNS), in which the proteinuria resolves, and steroid-resistant nephrotic syndrome (SRNS), in which the proteinuria does not resolve. [1] Most patients with minimal change disease respond well to steroid treatment and, currently, renal biopsy is not routinely performed in patients with SSNS. Minimal change disease hence, has become synonymous with SSNS. [1] However non minimal change Nephrotic syndrome makes up most of the SRNS group which is refractory to multiple drug therapies. Despite advancement in understanding the pathophysiology of nephrotic syndrome in children, there is no general consensus on treatment of SRNS. Several studies have shown that the prognosis of NS depends on the therapeutic response rather than histopathological finding. [2]Over the last few years, rituximab (RTX) has emerged as a second- line therapy and has shown a 40-48% response rate in treatment-resistant and up to 80% remission rate in steroid dependent nephrotic syndrome. [3] The better outcome of RTX therapy in dependent nephrotic syndrome compared to resistant nephrotic syndrome is possibly due to excessive loss of RTX in the urine during active state of proteinuria. Recent study shows the serum half-life of RTX during a phase of active non-selective proteinuria was less than 1 day compared to 20 days in patients with no protein loss. [4]

I. Aim And Objective

The objective of the study was to assess the therapeutic response of RTX during non-proteinuric sate in children with steroid and CNIs/MMF resistance idiopathic nephrotic syndrome following induction of remission by a combined therapy of Prednisolone, CNIs and MMF.

II. Materials And Methods

Study setting:

In this study we analyzed the data of steroid and CNIs/MMF –resistance idiopathic nephrotic children, aged 1-14 years from January 2014 to January 2016 who attended the outpatient department and who were admitted in the inpatient department of SVPPGIP , tertiary care teaching hospital of Cuttack, Odisha.

Study design

The clinical decision was to treat those patients with a combined therapy (Prednisolone+CNI+MMF) to achieve remission, followed by treatment with RTX at a dose of 375 mg/m^2 body surface area per week for two to four weeks. Five children those who responded to triple regimen were treated with two to four doses of RTX and were followed up for minimum six months following RTX therapy. Post RTX therapy, CNI and prednisolone dose was tapered.

Inclusion Criteria:

All children aged 1-14 years who had resistant nephrotic syndrome treated with Steroid and CNI and MMF to induce remission.

Exclusion Criteria:

1. Secondary NS
2. Children who failed to meet the above criteria and those lost to follow up.

III. Methods

Consent was taken and risk and benefits were explained to the patient and patient's parents wherever applicable. Standard rituximab regimen was used with monitoring of vitals by trained nursing and medical staff. Ultrasound guided renal biopsy was conducted in all enrolled patients with standard protocol after obtaining written consent from the parents or guardian. Drug doses and treatment was followed as per the Indian Society of Pediatric Nephrology (ISPN) guidelines. Follow up was done of the patients included in the study and data presented in tabular form.

IV. Results

Characteristics of thefive patients and their response to RTX therapy.

Patient Characteristics	**1**	**2**	**3**	**4**	**5**
Age at Disease onset(years)	1.6	1.8	1.5	2.7	3.2
Age at Study Enrolment (years)	12.8	12.8	3.8	4.8	8
Sex	M	M	F	F	M
Histopathological lesion	FSGS	FSGS	MCD	IgMN	FSGS
Duration of multidrug therapy until remission (weeks)	10	6	8	8	6
Previous therapy	Levamisole CYP MMF Tac	Levamisole CYP MMF Tac	CYP CyA	CyA Tac MMF	Levamisole CyA MMF
Doses of RTX	4	4	2	2	2
Relapses during follow up (Post RTX therapy)	2 with SBP	Nil	1 with SBP	Nil	1 with LRTI
Therapy at 6 months	Prednisolone + Tacrolimus	No meds	Prednisolone	No meds	No meds
Duration of remission following RTX therapy	3 months	14 months	7 moths	9 months	4 months
Status at 6 months follow up	Partial remission	Remission	Remission	Remission	Remission

patients were enrolled in the study out of which patient 1 and 2 were twin brothers. 2 patients had been diagnosed as nephrotic syndrome after the age of 2 years. 3 out of the 5 participants were males. 3 out of the 5 patients showed focal segmental glomerulosclerosis. Patient 1 and 2 were given four courses of rituximab while the others received 2 courses. 3 out of the 5 required no medication at the end of 6 months. Following RTX therapy, 2 patients had no relapses in the 6 months, whereas 2 patients relapsed with SBP and 1 with LRTI. The duration of remission was maximum of 14months and minimum of 3 months following RTX therapy. 4 out of 5 patients achieved remission after 6 months follow up post RTX therapy.

V. Discussion

The characteristics of the five patients and follow-up data are described in the **Table 1**. Patient 1 and 2 were twin brothers. At six months follow-up four patients achieved complete remission (80%) and three patients (60%) were completely off medications without any serious adverse effects. 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 or SDNS. Bagga et al firstly reported that rituximab was effective for the refractory SRNS. [5] Five children with refractory SRNS induced complete remission in 3 patients and partial remission in two. Other reports showed that rituximab is an effective therapy for some Idiopathic Nephrotic Syndrome children with refractory SRNS.[6,7]Rituximab is a promising treatment for complicated FRNS/SDNS in children. A multi-center trial reported by Ruggenti et al showed that one or two doses of rituximab followed by withdrawal of immunosuppression on disease in 10 children and 20 adults with complicated FRNS/SDNS found all patients in remission after 1 year.[8] Furthermore, an open-labelled, randomized, controlled trial showed that rituximab plus lower doses of prednisone and calcineurin inhibitors were no inferior to standard dose of these agent in maintaining short-term remission in children with steroid-and calcineurin inhibitor-dependent nephrotic syndrome. [9]Iijima et al reported a multicenter, double-blind, randomized, placebo-controlled trial of rituximab therapy for childhood-onset complicated FRNS/SDNS. The results showed that the time to treatment failure were significantly longer. The relapse rate was significantly lower in rituximab than in the placebo group with no deaths and only mild side effects. [10] Another multicentric trial by Gulati et al showed Thirty-three patients with SRNS (24 initial, 9 late resistance) and 24 with SDNS, with mean ages of 12.7 ± 9.1 and 11.7 ± 2.9 years, respectively where six months after rituximab therapy, 9 (27.2%) patients with SRNS showed complete remission, 7 (21.2%) had partial remission, and 17 (51.5%) had no response. At 21.5 ± 11.5 months, remission was sustained in 15 (complete: 7, partial: 8) patients. Of 24 patients with SDNS, remission was sustained in 20 (83.3%) at 12 months and in 17 (71%) at follow-up of 16.8 ± 5.9 months. The mean difference in relapses before and 12 months after treatment with rituximab was 3.9 episodes/patient per year.[11]These findings indicated that rituximab was safe and effective, at least for 1 year in the treatment of childhood-onset, refractory nephrotic syndrome. In our study, the response to therapy and remission in one of the twins indicated the efficacy of this regimen in familial NS. However a genetic test to determine underlying mutation could not being done due financial constraint. Serum half-life of RTX can be extremely short, partly due to excessive urinary losses in therapy-resistant nephrotic syndrome with non-selective proteinuria as seen in a case study by Counsilman CE et al.[12] Other case studies showed significant amount of Rituximab is lost from the circulation by excretion into the urine with a close correlation of the excretion of Rituximab to the excretion of IgG molecules suggesting selectivity of proteinuria as the determining factor of Rituximab excretion.[13]In the series by Leclerc and Macher, 22 patients with steroid-sensitive, but steroid-dependent nephrotic syndrome were treated with rituximab. Rituximab reduced B cell count down to an undetectable level in all patients. A second treatment was necessary in 18 patients in order to maintain B cell depletion for up to 18 months. B cell depletion lasted 4.9 to 26 months (mean 17.2 months). At last follow-up, 9 patients were in remission without oral steroid or calcineurin inhibitor, although B cell count had recovered for 2.9 to 17 months (mean 9.5 months).

A remission under ongoing B cell depletion was observed in 10 other patients in the absence of oral steroid or calcineurin inhibitor. Rituximab failed in 2 patients and 1 refused any additional treatment, despite B cell recovery and relapse. Toxicity of rituximab was limited to reversible cytokine shock in 2 patients and reversible neutropenia in 1 patient. No severe infection was observed. [14] Another concern for further research is the number of doses of rituximab ideal for steroid resistant NS and in our study 2 to 4 doses were given according to availability and affordability. One multicentric study by Kamei K et al using 1 dose of rituximab at standard dosing regimen yielded results where all patients (n = 12) were able to discontinue steroids at a median of 74 days after treatment. The frequency of relapses per 6 months was significantly reduced and the steroid-free period per 6 months was significantly increased after treatment compared with those before treatment. The condition in nine of the patients (75%) relapsed at a median of 129 days after treatment, and seven patients were given additional rituximab due to steroid dependency. Most of the relapses developed simultaneously with recovery of B-cells. However, three patients (25%) did not have a relapse with B-cell recovery and the disease was kept in remission for more than 1 year. None of the patients developed life-threatening adverse events. [15] Other studies with more than 1 dosing included Fervenza et al who conducted an open-label pilot trial of rituximab treatment in 15 severely nephrotic patients with proteinuria refractory to angiotensin-converting enzyme inhibition and/or receptor blockade but with adequately controlled blood pressure. Rituximab was given 2 weeks apart and, at 6 months, patients who remained proteinuric but had recovered B-cell counts were given a second course of treatment. Proteinuria was significantly decreased by about half at 12 months. Of the 14 patients who completed follow-up, full remission was achieved in two and partial remission in six patients based upon the degree of proteinuria. Side effects were minor; however, no relationship could be found between the

response and number of B cells in the blood, CD20 cells in the kidney biopsy, degree of tubulointerstitial fibrosis, starting proteinuria or creatinine values. [16] One study by Guigonis V et al like our study used 2 to 4 infusions of rituximab where safety and efficacy of RTX was assessed in a multicentre series of 22 patients aged 6.3–22 years with severe steroid-dependent nephrotic syndrome or steroid-resistant but cyclosporine-sensitive idiopathic nephrotic syndrome. Patients were treated with two to four infusions of RTX. Seven patients were nephrotic at the time of RTX treatment. Peripheral B cells were depleted in all subjects. Remission was induced in three of the seven proteinuric patients. One or more immunosuppressive (IS) treatments could be withdrawn in 19 patients (85%), with no relapse of proteinuria and without increasing other IS drugs. RTX was effective in all patients when administered during a proteinuria-free period in association with other IS agents. When relapses occurred, they were always associated with an increase in CD19 cell count. Adverse effects were observed in 45% of cases, but most of them were mild and transient. The study suggested that RTX could be an effective treatment for severe steroid-dependent nephrotic syndrome. [17]Rituximab, a chimeric anti-CD20 monoclonal antibody originally licensed for lymphoma, is emerging as a novel steroid-sparing agent for idiopathic nephrotic syndrome in children. The potential use of anti-CD20 monoclonal antibodies in idiopathic nephrotic syndrome has contributed to shifting the view of podocytopathies from T cell–mediated to more complex immune-mediated disorders that can benefit from targeting B cells and other mediators of the early immune response. Clinical data on the use of rituximab also have implications on disease management and classification. [18] More studies are needed to understand the pharmaco-kinetics of rituximab but newer clinical trials for resistant nephrotic syndrome show increase losses in proteinuric patients. [11, 16]

VI. Conclusion

Ourstudy showed improved RTX efficacy during non-proteinuric state of refractory nephrotic syndrome. However, as intense immunosuppression may cause serious adverse event further study for evaluating long-term efficacy and safety of multidrug therapy are needed.

Acknowledgement

Our sincere thanks goes out to the laboratory and nursing staff for their hours of monitoring and patient care during the procedures and treatment without which this study wouldn't have taken place.

Conflict of Interest: None

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*1Dr. Saroj Kumar Satpathy. "Multi-Drug Therapy Followed By Rituximab in Children with Refractory Nephrotic Syndrome Contributors ." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) , vol. 17, no. 01, 2018, pp. 05–09.