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ORIGINAL ARTICLE

Efficacy of rituximab (RTX) versus cyclophosphamide (CTX) in the treatment of steroid dependent minimal change disease (MCD) in adult population of Islamabad, Pakistan.

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ABSTRACT… Objective: To determine the efficacy of rituximab (RTX) versus cyclophosphamide (CTX) in the treatment of steroid dependent MCD in adult population of Islamabad, Pakistan. **Study Design:** Randomized Controlled Trial. **Setting:** Department of General Medicine, PAF Hospital, Islamabad. **Period:** One and Half Year November 2022 to April 2024. **Methods:** A total number of 60 patients' ≥ 18 years of age with steroid dependent MCD were selected for the study and divided in 2 groups of 30 patients each using block randomization. In RTX group, patients were given two doses of injectable RTX in a dose of 1000 mg two weeks apart. While in CTX group, oral CTX was given in a dose of 2–2.5mg/kg/d for 8 weeks. Efficacy was determined in terms of incidence of relapse, steroid withdrawal and making patient drug-free. **Results:** The mean age of patients in this study was 41.11±13.5 years. The results showed that RTX was significantly more effective than CTX in reducing the incidence of relapse (12 Vs 21 patients, p-value=0.02), in steroid withdrawal (27 Vs 16 patients, p-value=0.002) and in making patients drug free compared to CTX (27 Vs 12 patients, p <0.0001). **Conclusion:** RTX is more effective in reducing the relapse of nephrotic syndrome in adults with steroid dependent MCD compared to CTX and helps in making the patient drug free.

Key words: Cyclophosphamide, Minimal Change Disease, Rituximab, Recurrence.

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INTRODUCTION

Minimal change disease (MCD) is one among the main reasons described for nephrotic syndrome and globally accounts for approximately 10-15% of total cases in adults, standing as 3rd largest cause. In contrast to pediatric populations, the etiology of MCD in adults demonstrates greater complexity, as it not just a primary mechanism but a broader spectrum of secondary causes including use of pharmacological agents like non-steroidal anti-inflammatory medications (NSAIDs) and lithium, infectious diseases including viral illnesses, and hematologic abnormalities such as lymphoproliferative disorders.[1,2] The pathological cause is not clear in most of the cases however it is linked with deregulations related to immune system and explained as a disorder of podocytes. Diagnosis of MCD is characterized by nephrotic syndrome with no glomerular abnormalities under light microscopic examination. Hence in adults, a definitive diagnosis requires renal biopsy, as the clinical response to steroids is mostly slow and less predictable.[3]

In contrast to Pediatrics, the risk of progression to end stage renal disease is higher in adults. When initial steroid treatment proves insufficient, there is recommendation for adding immunosuppressive therapies to achieve complete remission (CR). There is, however, no consensus on the treatment strategies for adult onset MCD that can provide a rapid remission over the long term compared to Pediatrics.[3,4]

CS are the most widely used treatment option and found highly effective in MCD and other glomerular diseases. Compared to pediatrics, adult onset MCD has delayed response to glucocorticoids and are also at increased risk of acute kidney injury.[5] Moreover, both children and adults have shown good improvement with high-doses of prednisolone but these high doses of glucocorticoids also result in significant side effects which are more frequent

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when recurrent courses of glucocorticoids are to be used. In MCD, the remission rate with steroids is estimated as 75% in adults but relapse rate is also as high as 40% in the tapering dose over time and after steroid withdrawal.[6,7] In a study conducted by King C et al. , frequent relapses were reported in 25% of the patients while steroid dependency was reported in 30% of adult patients.[8]

In a study conducted in Pakistan, adult MCD typically responded well to steroid treatment, with most patients achieving disease control. However, disease recurrence remained a significant challenge, often requiring alternative immunosuppressive agents. This pattern highlighted the importance of developing consistent therapeutic protocols to enhance treatment efficacy in adult MCD.[9] In view of the above discussion, researchers have focused on the use of lesser doses of glucocorticoids to avoid their serious side effects and opt for other treatment options in MCD.[10]

The use of alternative options is therefore in discussion with more efficacy and tolerable side effects. Calcineurin inhibitors, mycophenolate mofetil and cyclophosphamide (CTX) have been studied for this purpose, however, with their use serious side effects are reported like acute kidney injury, gastrointestinal side effects and infertility, respectively. CTX, an alkylating agent, specifically has been found to provide remission over long term in 50% of the patients with MCD but there are reported serious adverse events with this drug like infertility and cytotoxicity. There are also complaints of frequent relapses with these drugs.[11,12]

Rituximab (RTX), a monoclonal antibody has also been used in paediatric patients with steroid dependent MCD. While some studies in pediatrics have shown that both the reduction and withdrawal of steroids was observed with RTX keeping the relapse rate lower but the incidence of relapse in adult onset MCD is relatively unclear.[13,14]

As discussed above the treatment strategies for adult with steroid dependent MCD are used without any clear recommendations and the use of immunosuppressive agents are uncertain in steroid resistant and frequently relapsing cases. The study was therefore planned to determine the efficacy of RTX versus CTX in the treatment of steroid dependent MCD in terms of incidence of relapse in adult population of Islamabad, Pakistan. The results of this study will help our clinicians to opt for evidence-based treatment plan for these patients.

METHODS

This Randomized controlled trial was conducted at the Department of General Medicine, PAF Hospital, Islamabad, Pakistan from November 2022 to April 2024, over a period of 18 months. Approval of conducting the study was received from the ethical committee of the hospital (4/10/22).

The sample size calculation was performed with a significance level (α\alpha$\alpha) of 5% (two-sided) and a statistical power of 90%. The expected percentages in the two populations were p_1=84.6% (patients becoming drug free in RTX group) and p_2 =37.5% (patients becoming drug free in CTX group). Based on these assumptions, the estimated sample size required for each group was 21 participants.[15]

A total of 60 patients' ≥ 18 years of age with steroid dependent MCD were included in the study through consecutive sampling. Patients were randomized into 2 groups of 30 patients each using block randomization to ensure balanced allocation of participants to each group.

Inclusion Criteria

Patients' ≥ 18 years of age with steroid dependent MCD who had previously received only CS and no other immunosuppressant were included in this study.

Diagnosis was confirmed by renal biopsy with normal light microscopy and fulfilling the criteria of nephrotic syndrome.[16]

Exclusion Criteria

Patients with secondary causes of MCD like cancers or infections, steroid dependence, frequent relapses and patients with focal segmental glomerulosclerosis.

Potential confounding factors included secondary causes of MCD, which were addressed through the

exclusion criteria. Block randomization was used to ensure balanced allocation and minimize potential confounding variables between groups.

In the RTX group, patients were given rituximab as two doses of 1000 mg two weeks apart, while in the CTX group, oral cyclophosphamide was given in a dose of 2-2.5mg/kg/d for 8 weeks. CS were allowed to be continued as subsequent therapy.

Primary outcome was set as overall incidence of relapse (Including disease progression, on-drug relapse and off-drug relapse), steroid withdrawal and patient being drug-free at the last follow up visit at the end of 15 months period.

A relapse during the tapering or within 2 weeks of discontinuation of steroid was declared as steroid dependence. Definition of steroid resistance, partial remission and complete remission was set as per the guidelines. After the initial response ≥2 relapses within 6-month period or ≥ 4 relapses within 12 months were declared as frequent relapses. In the CTX group, any progression of disease after 6 months was taken as non-response to treatment.[16]

Measurement of 24 hours urinary protein was done to quantify proteinuria. All the laboratory measurements were noted down at baseline, at any report of relapse and at final follow up visit.

Statistical analysis was performed using SPSS version 25.0, employing descriptive and inferential statistical methods. Continuous variables were presented as mean and standard deviation or median with interquartile range, depending on their distribution, which was assessed using the Shapiro-Wilk test. Categorical variables were presented in shape of frequencies and percentages. Group comparisons utilized independent t-tests for normally distributed continuous variables and Mann-Whitney U tests for non-normally distributed data. Categorical variables were analyzed using chi-square or Fisher's exact tests. A p-value <0.05 was considered statistically significant.

RESULTS

Age range in this study was 18-68 years with mean age of 41.11±13.5 years and male gender was dominant (55%) in overall study population. Details of clinical characteristics and laboratory investigations in both groups are shown in Table-I.

The achievement of primary outcomes at the final follow-up visit shows better efficacy in RTX group compared to CTX group in shape of less number of patients suffering from relapse, more patients able to have steroid withdrawal, and becoming drug free, as given in Table-II.

TABLE-I

Clinical Characteristics and Laboratory Investigations. n=60

Clinical & Lab. Findings		RTX Group (n=30)	CTX Group (n=30)
Hypertension n (%)		17 (56.55)	16(53.33)
Systolic BP mm HG(Mean±SD)		123±16	121.8±16.35
Diastolic BP mm Hg (Mean±SD)		79.86±9	80.53±9.76
Other Therapies	RAAS I n (%)	13 (43.33)	19 (63.33)
	Statins n (%)	11 (36.66)	16 (53.33)
	Furosemide n (%)	30 (100)	30 (100)
Previous Response on glucocorticoids	Complete Remission n (%)	25 (16.66)	27 (90)
	Partial Remission n (%)	5 (16.66)	3 (10)
Urine protein (g/day)		17.8±4.58	18.56±3.64
Serum Creatinine (mg/dl)		1.21±0.53	1.22±0.48

TABLE-II

Patient's outcome at the final visit n=60

Variables	RTX Group (n=30)	CTX Group (n=30)	Chi-Square Value	P-Value*
Relapse n (%)	12 (40)	21 (70)	5.46	0.02
Steroid withdrawal n (%)	27 (90)	16 (53.33)	9.93	0.002
Drug Free at completion of study n (%)	27 (90)	12 (40)	16.84	<0.0001

* McNemar Chi-Square test

DISCUSSION

The mean age in this study was 41.11±13.5 years. The male gender was in majority compared to females in overall study population (55% Vs 45% respectively). The results of primary outcomes of our study showed that the incidence of relapse was significantly lower in RTX group compared to CTX group (40% Vs 70% respectively, p-value =0.02).

A study by Ruggenenti P et al conducted in 2014 also reported a decreased number of relapses by (from 88 to 22) with RTX administration in one year period (P<0.001).[17] Munyentwali H et al. conducted a retrospective study in Nice, France, and analyzed 17 patients with steroid-dependent, frequently relapsing MCD. Over a mean follow-up period of 26.7 months, their findings demonstrated a significant reduction in annual relapse rates among patients treated with RTX group compared to the non-RTX group (20% versus 57%, respectively).[18] Janardan J in a clinical case report shared that an adult female patient of MCD who was initially non-responsive to steroid and then to CTX responded to two doses of RTX (500mg each) rapidly within 1 month. This remission was sustained over a long term follow up of up to 32 months period.[19] Heybeli et al. conducted a study in 2021 with 76 adult MCD patients and showed superior outcomes with RTX compared to CTX with fewer relapses (6 Vs 11 patients respectively), longer time to relapse (66 Vs 44 months respectively), and no disease progression in the RTX group compared to 3 cases in the CTX group.[15] In a prospective study conducted in India by Ramachandran R, 11 patients with steroid dependent/resistant MCD who were treated with RTX were in complete remission after 12 months.[20] A review by Gauckler P discussing the role of RTX in adult MCD shared that long term follow up proves a relapse free survival with RTX in adults with steroid dependent MCD.[21] In a recent study by Sun Y et al with 21 MCD patients, 90.48% achieved complete remission (median time: 4 weeks). RTX monotherapy showed 88.89% remission (3 weeks), RTX with low-dose glucocorticoids achieved 75% remission (4 weeks), while RTX with adequate-dose glucocorticoids demonstrated optimal results with 100% remission (3.5 weeks).[22]

The results of the study also revealed that significantly more number of patients had steroid withdrawal in RTX group compared to CTX group (90% Vs 53.33%, p-value=0.002). Similarly, significantly more number of patients were able to become drug free in group-A compared to Group-B (90% Vs 40%, p-value <0.0001). Similar results regarding steroid withdrawal were also reported in the studies conducted by Ruggenenti P et al. with statistically significant reduction in steroid dose in all patients including adults over 1 year period.[17] Munyentwali H et al. also reported that out of 11 patients, 9 successfully discontinued both steroids and immunosuppressants.[18] Discontinuation of steroid was also reported by Heybeli et al. in 92.3% patients in the RTX group while in 62.5% in CTX group. At the last follow up visit 84.6% of the patients in RTX group were drug free while this was observed in 37.5% patients in CTX group.[15]

In a study of 16 patients conducted by Bruchfeld A et al., MCD treated with a combination therapy of steroid and RTX, reported a complete remission in 13 patients, hence the tapering off or discontinuation of corticosteroid was possible. After a median of 44 months follow up relapse was reported in 7 patients while 4 patients responded to RTX re-administration.[23]

The findings of our study are aligned with those of previous researches discussed above for the treatment of adult patients with steroid dependent MCD and supports the evidence that RTX reduces the relapse rates and allows the steroid withdrawal. Treatment with RTX was also able to make these patients not only steroid free but also drug free.

The major limitation of this study is small number of patients and short follow up period. Future prospective studies with larger number of patients and longer follow up duration, therefore, will be helpful to suggest more evidence-based treatment strategies.

CONCLUSION

MCD in adults is a frequently relapsing disease despite the treatment strategy employed, including glucocorticoids and immunosuppressive agents. RTX is more effective in reducing the incidence of relapse in adults with steroid dependent MCD

compared to CTX and helps in making these patients drug free. The results of this study are useful and suggest evidence based treatment strategies for adult patients with steroid dependent MCD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Ayesha Salim:** Manuscript writing.
2	**Muhammad Tahir:** Critical review.
3	**Muhammad Zuhair Tahir:** Acquisition, analysis.
4	**Muhammad Zubair Tahir:** Design.
5	**Aamen Sajid:** Conception.
6	**Hifza Shahid:** Interpretation of data.