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Four-Year Maintenance Therapy with Cyclosporin A for Patients with Steroid-Refractory Idiopathic Minimal Change Disease Allergic to Rituximab

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Abstract

Background: Patients with Steroid-Refractory Idiopathic Minimal change disease (SRIM) have high morbidity and mortality and inherent side effects of immunosuppressive therapy. Except for its cost, R has been shown to be the most practical, safe and effective maintenance therapy for patients with multiple glomerulopathy, including those with SRIM. Being a monoclonal antibody, hypersensitivity reactions are common, and its use is limited in 10% of treated patients. Cyclosporin A (Cy) was a useful alternative, yet it had the potential for chronic interstitial fibrosis in the long term. Hence, a safe management protocol, for its use, was sought. Patients and methods: Over the past 10 years a total of 35 patients were treated with Cyc for SRIM, 11 of whom were children (<14 years). Initially all patients were treated with 100 mg twice daily aiming at an initial trough level 100 - 150 ng/ml. Three months later, the dose was reduced to 50 mg twice daily. Two years later the dose was reduced to 25 mg twice daily for the remaining 2 years. Results: Complete remission of disease (proteinuria <150 mg/day) was achieved 1 month after Cyclo-therapy that was maintained till the end of the study despite dose decrement. Within 1 year, subsequent to Cy-therapy, 4 patients relapsed, yet responded to the reinstitution of Cy. Side effects were tolerable and did not require drug discontinuation, and all patients had normal creatinine clearance at follow-up. In conclusion, 4-year treatment with Cy offers a safe and effective alternative to

R allergic patients with SRIM.

Keywords

Corticosteroids, Cyclosporin A, Rituximab, Nephrotic Syndrome, Minimal Change Disease, Maintenance, Therapy

1. Introduction

Minimal change disease (MCD) is the most common cause of nephrotic syndrome (NS) in children, accounting for > 90% of cases as opposed to 15% in adults [1]. Its incidence and prevalence are 2 - 7 and 10 - 50 cases/100,000 children, while such data are limited in adults since the disease is uncommon [2]. Since MCD is common in children and with 90% response to Corticosteroids (C), kidney biopsy is limited only to those who manifest C-refractoriness (45%) and C-resistance (10%) to avoid the technical difficulties in their biopsy [3]. On the other hand, kidney biopsy is mandatory in adults with NS since MCD represents only 15% of cases, while other C-resistant glomerulopathies are more common, especially membranous ones (40%) [2]. Maltreated MCD is associated with high morbidity and mortality as well as poor quality of life due to its symptomatic anasarca, bacterial infections, venous and arterial thromboembolism as well as the inherent complications of immunosuppressive therapy. Historically, C was its mainstay of therapy, yet nearly 50% of C-responsive patients manifest C-refractoriness viz. frequent relapses and C-dependency [4]. In those patients, previous long-term C-use resulted in acne, hirsutism, peptic disease, infections, psychosis, obesity, growth retardation, hypertension, diabetes mellitus, osteoporosis and adrenal suppression [5]. Moreover, the second-line steroid-sparing immunosuppressants viz. antiproliferative, levamisole, calcineurin inhibitors and mycophenolate mofetil had limited long-term success and were associated with various side effects viz. infertility, interstitial fibrosis and infections [6]. Recently, yearly Rituximab use proved to be the most practical treatment for such forms of MCD [7]. Unfortunately, being a murine monoclonal antibody, hypersensitivity reactions were common. They include type I, cytokine-release, mixed type, and delayed-type IV reactions with a prevalence of 63, 13, 21, and 3% respectively. Of those 10% severe and limited R-use [8]. In an attempt to fill the gap in the treatment of such patients, we conducted the present study to assess the efficacy and safety of a new protocol of Cyclosporin A (Cy) therapy that consisted of an adequate therapeutic dose of only for 3 months (induction-phase) followed by a limited maintenance dose for 4-years only.

2. Patients and Methods

Over the past 10 years, patients were included in the study if they had a) nephrotic syndrome due to biopsy-proven, MCD, b) negative previous kidney and liver

diseases as well as disorders requiring drugs interfering with Cy-blood levels viz. epilepsy, hypertension, and chronic infections, c) negative history, clinical examination, radiological scans as well as laboratory and serological tests for autoimmune diseases, infections, malignancy and drugs-side effect, d) C-refractoriness over > 2 years, e) severe allergy to R-infusions limiting its use, f) adequate follow up for > 5 years.

2.1. Study Design

Initially all patients were stabilized with C at a dose of 1 mg/kg/day. At the same time, Cy was started at a dose of 100 mg twice daily aiming at an initial trough level of 100 - 150 ng/ml for 3 months (induction phase). C-dose was for 3 weeks then reduced gradually till discontinuation by the first 1 month. After the induction phase, Cy-dose was reduced to 50 mg twice daily till the end of 2 years then, was further reduced, to 25 mg twice daily for 2 more years only (induction phase).

2.2. Periodic Assessment

Patients were seen on a monthly basis for the first 3 months then every 2 months. In those visits, patients were assessed clinically for the severity and complications of their NS as well as the side effects of therapy. During those visits, laboratory investigations were done and included complete blood count as well as serum estimates of sugar, renal, liver function tests, lipid profiles and urine routine. Twenty-four-hour urine collections for daily protein excretion (Pr) and creatinine clearance (CrCl) were done at times 0, 3 months, 6 months, 12 months, 18 months, 24 months, 36 months, 48 months and by the end of follow up. In some uncooperative young children spot urine albumin/creatinine ratio (UACR) was used instead. Complete remission of NS was considered if Pr $\leq$ 150 mg/day or UACR $\leq$ 3 mg/mmol.

2.3. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. Since age, duration of previous NS, and duration of follow up were normally distributed, they were expressed as mean ± SD.

3. Results

A total of 35 patients fulfilled the study inclusion criteria. The patient's demographic characteristics and response to Cy-therapy are summarized in Table 1. Eleven patients were children ($\leq$14 years) and 21 (60%) were females. All patients had confirmed NS with C-refractoriness for $\geq$ 2 years and follow up of $\geq$ year after discontinuation of Cy-therapy.

3.1. Response to Therapy

As shown in Table 1, 3 months after the start of Cy, all patients had complete remission of their NS. Such response persisted despite the timed reduction of Cy-

dose (by 3 months, 2 years and 4 years). Within 1 year, subsequent to Cy-discontinuation, 4 patients relapsed, yet responded to a repeat of repeating the Cy-treatment protocol.

Table 1. Demographical data and response to Cyclosporin A in patients with steroid-refractory MCD.

Patients' characteristics:			(n = 35)
Demographical data:			
Gender (F/M)			21/14
Mean age (years)			21 ± 8
Children (age < 14 years)			11
Duration of NS (months)			29 ± 5
Duration of follow up (months)			79 ± 18
Cyclosporin A therapy:			
	Daily dose	Response	
		CR	Relapse
Time 0:	100 mg × 2	0/35	35/35
Time 1 month:	100 mg × 2	35/35	0/35
Time 3 months:	100 mg × 2	35/35	0/35
Time 1 year:	50 mg × 2	35/35	0/35
	50 mg × 2	35/35	0/35
Time 2 years:	50 mg × 2	35/35	0/35
	50 mg × 2	35/35	0/35
Time 4 years:	25 mg × 2	35/35	0/35
	25 mg × 2	35/35	0/35
Time 5 years:	0	35/35	0/35
	0	31/35	4/35

3.2. Side Effects of Therapy

Cy therapy led to a mild darkening of skin color in most hirsutism in most patients as well as mild gum hyperplasia in 2 patients. They were tolerable and decreased significantly after dose decrement. None of the patients manifested decreased creatinine clearance and/or increased proteinuria.

4. Discussion

In our study, we provided a new protocol of Cy-therapy for the treatment of patients

with NS due to SRIM that could not tolerate R for severe infusional reactions. It proved to be an effective treatment that a) induced complete remission in all the 35 patients, b) maintained such remission for 4 years despite dose-decrement, and c) prevented relapse of NS, in 89% of those patients, for 1 year without Cy-use. Moreover, such therapy was a) well-tolerated without patient fallout, and b) safe without inducing biochemical markers of significant and/or permanent kidney disease. Cy selection was based on the current knowledge of the pathogenesis of MCD and the mechanism of action Cy. MCD is a form of autoimmune podocytopathies. Its presumed etiology of primary ones is a T-cell induction of permeability plasma-factors viz. soluble urokinase plasminogen activator receptor (suPAR), cardiotrophin-like cytokine factor-1 (CLCF-1), and CD40 antibodies. They act on negative charges at different adhesion molecules between the podocyte and glomerular basement membrane leading to albumin leak [9]. On the other hand, Cy is a) a potent anti-T cell agent, and b) a stabilizer for the actin cytoskeleton in kidney podocytes; therefore, it is beneficial for treating proteinuric kidney diseases [10]. Cy immunosuppression acts via two pathways, a) the calcineurin/Nuclear factor of activated T cells (NFAT) pathway and, b) the c-Jun N-terminal kinases (JNK) and p38 signaling pathway. The first prevents calcineurin-mediated dephosphorylation, which leads to inhibition of the nuclear translocation of NFAT family members and subsequent gene expression in activated T-cells [11]. The other pathway involves inhibition of the mitogen-activated protein kinase (MAPK) pathway, which has significant roles in cellular activities such as proliferation, stress reactions, apoptosis, and immunological defense via blockage of interleukin-2 (IL-2) gene, promoting the transcription of IL-2 [12] [13]. Moreover, leukin T-B lymphocyte (LT-B) co-operation which is essential for activation of B-lymphocytes is inhibited [14]. Cy-efficacy has been shown in multiple autoimmune disorders viz. solid organ transplantation, rheumatoid arthritis, psoriasis, amyotrophic lateral sclerosis as well as graft vs. host, Behcet, posterior uveitis and glomerular diseases [14]. Unfortunately, chronic interstitial fibrosis limited its long-term maintenance use [15]. In our study, we used adequate therapeutic-doses to induce remission only for 3 months. Subsequently, a smaller dosage was used to maintain remission for a minimum of 4 years. The decrement in Cy-dose was gradual and efficacious. Moreover, it was associated with low Cy-levels, which were essential to avoid the induction of long-term interstitial fibrosis [16]. The choice of such duration was based on our previous experience with R-therapy for MCD [17]. Potent anti-T cell therapy may abolish memory cell leading to tolerance for up to 6 years [18].

5. Conclusion

4-years-treatment with Cy offers a safe and effective alternative to R allergic patients with SRIM.

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Prof/ Kamel El-Reshaid conceived the study, participated in its design, and drafted

the manuscript. Dr. Shaikha Al-Bader and Dr. Hossameldin Tawfik Sallam participated in the study design, follow up of patients and data collection and tabulated the data. Dr John Madda participated in the study design, and was responsible for histological diagnosis, data collection and tabulation of histological data.

Data Availability Statement

The data provided in the current review are available from the references.

Conflicts of Interest

All authors have read and approved the final version of the manuscript. The authors declare no conflicts of interest regarding the publication of this paper.

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