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The Beneficial Effect of Combination of Mycophenolate with Low-Dose Corticosteroids and Calcineurin-Inhibitor as Well as Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Blocker in Induction and Maintenance of Remission in Corticosteroid- and Rituximab-Resistant Minimal Change Nephrotic Syndrome in Adults

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Abstract

Management of steroid-resistant minimal change disease remains elusive with international guidelines suggesting high-dose corticosteroids and/or Calcineurin inhibitors for months similar to those with refractory idiopathic FSGS. Unfortunately, with such approach, the overall remission rates were 47% - 66%. Moreover, complete remission rates were 32% - 47% and partial remission ones were 19% - 29%. Those limited options of treatment and their poor outcomes led us to conduct the present study to assess the efficacy and safety of a new combined drug-therapy at induction and subsequent maintenance of such disease. The regimen consisted of an initial induction phase of 3-month Prednisone, Calcineurin-inhibitor, Mycophenolate and ACEI/ARB. The latter was followed by a maintenance phase of minimal dose Prednisone and nearly 1/2 the induction dose of Calcineurin inhibitors to decrease their long-term side effects. The results were satisfactory with 14 of the 22 patients, had complete remission. Moreover, 5 patients manifested partial remission and only 3 did not respond. Creatinine clearance was maintained in patients with complete remission yet, was mildly reduced in the partial and non-responsive ones. The safety and efficacy of such new combined drug-therapy provide new tool

and future prospective in management of such relentless disease.

Keywords

ACEI, ARB, Calcineurin Inhibitors, Cyclosporine A, Minimal Change Disease, Mycophenolate, Nephrotic Syndrome, Prednisone, Tacrolimus

1. Introduction

Minimal change disease (MCD) manifests as an acute nephrotic syndrome (NS) and a renal biopsy that shows no glomerular lesions on light microscopy (or only minimal mesangial prominence), negative staining on immunofluorescence microscopy (or low-level staining for C3 and IgM), and foot process effacement but no electron-dense deposits on electron microscopy [1].

In children, MCD is the cause of 90% of cases of idiopathic NS and is usually exquisitely responsive to steroids. Hence; corticosteroid treatment is often initiated without a biopsy, unless clinical and laboratory evidence points to an alternative diagnosis. However, in adults, MCD is the etiology of only 10% - 25% in adults and hence; a kidney biopsy is usually warranted to establish the etiology [2]. Corticosteroids are the mainstay of treatment for adult MCD. Such experience was based on two randomized controlled trials and extensive observational data in adults that confirmed remission in over 80% of cases [3] [4]. However, relapses are common, and some patients become steroid-resistant (SR), steroid-dependent (SD), or frequently relapsing (FR). In recent years; multiple steroid-sparing agents were effective in the initial treatment of SD and FR viz. Calcineurin inhibitors (CNIs). Moreover, in recent years, Rituximab was shown to be an effective maintenance therapy in this patient population with its ease of its yearly administration, lack of nephrotoxicy associated with long-term CNIs-use and infertility with Cyclophosphamide [5]. On the other hand; management of SR MCD remains elusive with international guidelines suggesting high-dose corticosteroids and/or CNIs for months similar to those with refractory idiopathic FSGS [6]. Unfortunately, with such approach, the overall remission rates were 47% - 66%. Moreover, complete remission rates were 32% - 47% and partial remission ones were 19% - 29% [7]. Such limited options of treatment and their poor outcomes led us to conduct our present study to assess the efficacy and safety of a new combined drug-therapy at induction and subsequent maintenance of such relentless disease.

2. Patients and Methods

During the past 4-years; a total of 22 patients with SR MCD were included in this prospective study. Patients were included if they satisfied the following criteria: 1) histological diagnosis of MCD made by adequate renal histology during their initial nephrotic presentation, 2) exclusion of secondary causes of NS after

clinical, laboratory, radiological and appropriate serological testing, 3) NS that had failed 16-weeks treatment with corticosteroid (1 mg/kg/day) with CNIs and Rituximab. Moreover, none of the patients had 1) family history of NS, 2) systemic disease viz. obesity, diabetes mellitus, hypertension, 3) recent viral infections with HIV, CMV, parvovirus B19, EBV, hepatitis B and C, 4) has been exposed to antiviral drugs, anthracyclines, heroin, interferon, anabolic steroids and NSAIDs.

2.1. Study Design

Patients who satisfied the inclusion criteria were treated with 4 drug-combination; 1) Prednisone, 2) Tacrolimus or Cyclosporine A as CNI, 3) Cellcept as a Mycophenolate mofetil (MMF), and 4) Ramipril as an Angiotensin converting enzyme inhibitor (ACEI) or Losartan as an Angiotensin II blocker (ARB). In the induction phase; the dosages of the medications were: 1) Prednisone 1 mg/kg/day for 1 months followed by gradual tapering dose till 5 mg daily by end of the 3rd month, 2) Tacrolimus 0.05 - 0.1 mg/kg/day in 2 divided doses or Cyclosporine A 3 - 5 mg/kg/day in 2 divided doses aiming at a target trough level Tacrolimus 5 - 10 ng/ml or Cyclosporine: 100 - 175 ng/ml and, 3) MMF 1 g twice daily, 4) Ramipril or Losartan doses at tolerable low-normal blood pressure levels. After the initial 3-months induction phase; patients were maintained on all the previous medications except for Prednisone at 5 mg daily. In an attempt to reduce long-term nephrotoxicity of CNI; their dosages were reduced to 1/2 subsequently if remission is maintained after 12 months.

2.2. Specific Drug Selection

Unless limited by intolerable abdominal pain and diarrhea Tacrolimus was the first selection CNI in our patients to avoid cosmetic side effects viz. skin darkness, hirsutism and gum hypertrophy of Cyclosporine A [8]. Ramipril, as an ACEI, was the first choice intraglomerular reducing agent unless limited by intolerable cough or throat pain. If so; Losartan was the alternative.

2.3. Periodic Assessment

Patients were seen on weekly basis during the first month then on monthly basis for 3 months then every 2 months subsequently. In those visits, patients were assessed clinically for edema and side-effects of therapy. Laboratory investigations included complete blood count and serum estimates of sugar, renal, liver and lipid function tests and urine routine. 24-h urine collections for assessment of creatinine clearance (CrCl) and protein excretion (UP) were done on monthly basis in the first year then every 2 months subsequently.

2.4. Definition of Response

Remission was considered complete (CR) if creatinine clearance remained normal and protein excretion decreased to <500 mg/day in adults. Partial response

(PR) was defined as decrease in protein excretion to 50% of the initial value while creatinine clearance remains normal. Non-responders (NR) were defined as those who failed to achieve > 50% decrement in protein excretion within 12 weeks of treatment.

2.5. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. The p-value ≤ 0.05 was used as the cut-off level for significance. Since age and duration of follow up and CrCl were normally distributed; they were expressed as mean ± SD while UP were not normally distributed and hence they were expressed as median (IQR). Comparison of changes in CrCl at different times (start, 3 months, 12 months and 24 months) was done using Paired sample t test while UP by Wilcoxon Signed Rank test. ANOVA was used to test differences among age and duration of follow up. Moreover, ANOVA was used to test the difference among all groups with regards CrCl and Kruskal-Wallis test for UP.

3. Results

A total of 26 patients fulfilled the criteria for inclusion in the study. However, 2 patients were excluded for non-compliance with medications. According to their response to treatment; patients were classified into 3 groups. Group 1 included 14 treatment responsive patients (R), group 2 included 5 who manifested partial response (PR), and group 3 included 3 who did not response to therapy (NR). The demographical data of the included patients are summarized in Table 1. Nine patients were females (41%) and 13 were males (59%). Their age was 24 ± 4 years and their duration of follow up was 35 ± 7 months. There were no statistical differences between the age and duration of follow up in the 3 groups.

3.1. Response to Therapy

The response to treatment in the 3 patients-groups is summarized in Table 2. In the R-group; CrCl declined initially by the first month then returned to base line (time 0) by 12 months and remained stable by 24 months. In the PR one; CrCl declined and persisted at 3 and 12 months yet had returned to base line at 24 months. In the NR one; CrCl declined gradually by 12 months yet subsequently had remained stable till 24 months. UP decreased significantly in the R group by the 3rd month and such changes persisted till 24 months. In PR group; similar time-frame changes were noted though, at 3 months UP remained high at 1560 mg/day. In NR group; mild decrease in UP was noted by 3rd month ($p < 0.04$) that persisted till 24th month.

3.2. Specific Drug Selection

In the R group; 4 patients could not tolerate Tacrolimus for intolerable GI upsets yet were satisfied with Cyclosporine A. Losartan replaced Ramipril in 3 patients; 2 in the R group and 1 in the PR one.

Table 1. Demographical profile of patients with SR MCD in the 3 response groups to combination therapy.

Response groups	No.	Sex	Age*	Duration of follow up*
		(F/M)	(years)	(months)
Responsive	14	6/8	23 + 4	36 + 8
Partially responsive	5	2/3	23 + 4	31 + 4
Non-responsive	3	1/2	24 + 4	34 + 8
Total	22	9/13	24 + 4	35 + 7

Abbreviations: M: males, F: females. *No significant difference between 3 groups.

Table 2. Changes in the 3 response groups of patients with steroid-resistant minimal change disease, after combination therapy.

Response groups	**Responsive**	**Partially responsive**	**Non-responsive**
Interval p-value	Interval p-value	Interval p-value	
Changes in creatinine clearance:			
Time 0:	102 ± 6	94 ± 5	94 ± 6
<0.001	<0.001	NS	
Time 3 M:	92 ± 7	86 ± 5	86 ± 7
NS	<0.001	<0.02	
Time 12 M:	102 ± 5	87 ± 7	73 ± 10
<0.01	NS	<0.008	
Time 24 M:	104 ± 4	93 ± 7	77 ± 7
Final p-value (0 - 24):	NS	NS	0.008
Changes in protein output:			
Time 0:	8870 (2723)	5730 (630)	5820
<0.001	<0.43	NS	
Time 3 M:	370 (258)	1560 (640)	4200
NS	NS	NS	
Time 12 M:	360 (223)	1820 (610)	3900
NS	NS	NS	
Time 24 M:	380 (220)	1900 (600)	4200
Final p-value (0 - 24):	<0.001	<0.043	NS

3.3. Decrement of CNI Maintenance Dosage

Upon trial to decrease CNI dose by the 12th month; most patients remained in remission except for: 1) 2 in the R group and 2 in the PR one that had required 2/3 of their induction dosage, and 2) 1 in the PR group that had required his initial dosage.

3.4. Side Effects of Medications

Periodic laboratory investigations did not show significant changes in the he-

matological profiles and liver function tests. However, most patients had increment in serum potassium that had required strict dietary restrictions.

4. Discussion

The pathophysiology of MCD is not well understood. In the 1970s, Shalhoub proposed that the cause of lipoid nephrosis (a pseudonym for MCD) is a T-cell secreted circulating factor that alters the negative charge on glomerular basement membrane [9]. Although this circulating factor has not been identified; recent studies highlighted a role of immune dysregulation in MCD. In humans; T-regulatory (Treg) cells, attenuated the immune responses by suppressing T-effector cells [10]. Moreover, augmentation of Treg cell function had led to decreased proteinuria in a rat model of the idiopathic NS [11]. However, suppression of such permeability factor/s was limited to steroid-responsive MCD. Previous steroid-sparing protocols in SD and FR MCD viz. CNI and even Rituximab fell short of achieving remission in SR ones indicating multiple pathogenic mechanisms for such disease or reflecting unsampled primary FSGS in such podocytopathy [7]. Hence in our study; we used specific drug-combination regimen to target its multiple possible pathogenic mechanisms of cytopathies. The latter includes; 1) suppressing permeability factor/s formation, 2) hemodynamic abnormalities, 3) protecting podocytes, and lastly 4) prevention of subsequent inflammation and fibrosis [7]. Corticosteroids and CNI were used to suppress permeability factor/s, ACEI and ARB to control hemodynamic abnormalities and MMF for subsequent inflammation and fibrosis [12] [13]. Our patients did not benefit from previous corticosteroid/CNI therapy yet benefited after addition of MMF. Moreover, a previous study, suggested that MMF is inferior to Cyclosporine A in sustaining remission in children with SR NS [14]. However, in ours, MMF-addition led to induction of early and sustained remission with lower dosages of corticosteroids and CNI. The latter management is essential to avoid replacement of NS with serious side-effects of corticosteroids and nephrotoxicity of CNI [5]. The favorable addition of MMF in induction of disease remission may have been a class effect and/or synergetic effect [15]. MMF is a potent suppressor of both B and T cells via stimulation of CD3/CD28 that inhibits T cell IL-17, IFN-γ and TNF-α production but not IL-2 production [16]. Hence, its combination with CNI, that blocks the latter is useful [17]. Moreover, the combination of MMF and CNI may reduce the long-term nephron and hepatotoxicity of CNI [18]. In our study, we did not subject our patients to repeat kidney biopsy to assess their subsequent histopathological changes. The latter is, scientifically, useful to disclose the natural history of treated kidneys and long-term side effects of our therapy. At this stage; we were satisfied with the favorable clinical and biochemical outcomes and safety of our drug-combination. Many observational studies have shown that reduction of proteinuria and stable kidney function are associated with improved kidney outcomes [7] [19]. Even in partially responsive ones and non-responders; the 24-month kidney survival was accept-

able indicating the value of long-term suppression of intraglomerular pressure with ACEI/ARB and MMF. In conclusion; we recommend trial of our drug-combination in patients with SR MCD when other therapeutic options fail and hope for larger studies to confirm their efficacy and safety.

Statement of Ethics

The case was reported according to World Medical Association Declaration of Helsinki. There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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