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Three-Month-Induction Therapy with Prednisone and Mycophenolate Followed by Maintenance Therapy with Mycophenolate Alone for 2 Years: An Effective and Safe Autoimmune Treatment for Triggering Factors Adults with Acute Non-Crescentic Nephritis Associated with Henoch-Schönlein Purpura

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Abstract

Background: Henoch-Schönlein purpura (HSP) is an acute systemic disorder characterized by IgA associated vasculitis. The available data indicate an inherited predisposition to disease with triggering autoimmune phenomena. Hence, we evaluated prospectively the role of a new autoimmune regimen in treatment of its severe nephrotic/nephritic flares associated with non-crescentic nephritis in adult patients. **Patients and methods:** The regimen consisted of an initial induction phase of 3-month Prednisone and Mycophenolate followed by a maintenance phase of Mycophenolate alone for 2 years. **Results:** They were satisfactory with complete remission in 5 of 7 patients and partial in 2. Creatinine clearance was normalized in patients with complete remission and remained stable in the partially-responsive ones. **Conclusion:** Our study has shown the short- and long-term safety and efficacy of such autoimmune regimen directed towards the autoimmune triggering factors in severe forms of non-crescentic HSP.

Keywords

Acute, Henoch-Schönlein Purpura, Treatment, Nephrotic Syndrome, Nephritis, Mycophenolate Mofetil

1. Introduction

Henoch-Schönlein purpura (HSP) is an acute systemic disorder characterized by IgA associated vasculitis. It is the most common systemic vasculitis in children with an incidence of approximately 6 - 22 per 100,000 person-years which is higher than that in adults (3.4 - 14.3 per 100,000 person years) [1]. The disease can affect any organ yet its common presentation is a triad of purpuric skin rash at the lower part of the body, abdominal pains and oligoarthritis of knees and ankles [2]. The disease is usually self-limited and prognosis is favorable. Treatment is usually conservative with analgesics and short-course of corticosteroids which ameliorates its clinical manifestations and shortens its course. Renal disease is usually mild and can manifest as microscopic hematuria due to mild focal proliferative glomerulonephritis associated with mesangial IgA deposits [2]. However, in adults and few children the disease is far from being benign and can present with severe nephritis with/without crescent formation as well as relapsing forms [3]. Large and long-term follow up studies of those patients, with renal disease, had shown that, 14% had developed moderate renal failure, 13% severe one and 11% end-stage kidney disease [4]. Moreover; graft loss after kidney transplantation has been reported [5]. Patients at risk are those with nephrotic-range proteinuria and acute renal failure [6]. In this report; we describe our experience with aggressive therapy for such high-risk subgroup of adult patients.

2. Patients and Methods

During the past 4 years, a total of 7 adult patients with HSP, who presented acute nephritic flare (ANF), were treated and followed up prospectively. Patients were included if they were: 1) adults, 2) manifesting acute nephritic syndrome with rapid increase in serum creatinine (>26 umol/L within 48 hours associated with hematuria and proteinuria) and nephrotic range proteinuria, 3) with the typical triad of purpura, abdominal pain, and arthritis 4) with definite histological diagnosis of, non-crescentic focal mesangioproliferative glomerulonephritis with endocapillary hypercellularity, dominant IgA deposits and C3, made by adequate renal histology during their ANF. Exclusion criteria were for those with; 1) advanced IgA kidney disease (global sclerosis and/or tubulointerstitial disease > 50%), 2) secondary causes of other ANF, and 3) acute non-glomerular kidney injury with clinical, laboratory, serological, radiological and histopathological testing.

2.1. Study Design

Patients who satisfied the inclusion criteria were treated with Prednisone and Mycophenolate mofetil (MMF) for 3 months (induction phase) followed by MMF alone for 21 months (maintenance phase). The initial Prednisone dose was 1 mg/kg/day for 1 month followed by gradual tapering till discontinuation of the drug by end of the 3rd month. MMF dose was 1 g twice daily during induction and maintenance phase. Antihypertensive drugs (calcium channel-blockers, Al-

pha methyl dopa and beta-blockers), in addition to furosemide if fluid overload, were used in the induction phase. Moreover, if no contraindication, ACEI (Ramipril) or ARB (Losartan) was added, in the maintenance phase, as an antihypertensive agent and for their long-term renoprotective role.

2.2. Periodic Assessment

In the induction phase; patients were seen on weekly basis during the first month then every month. In the maintenance phase; follow up was every 2 months. In those visits, patients were assessed clinically for hypertension, fluid overload, 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.

2.3. Definition of Response

Remission was considered complete if creatinine clearance had improved to normal (80 - 120 ml/minute) and protein excretion decreased to <500 mg/day. Partial response was defined as decrease in protein excretion to ≥50% of the initial value without worsening of creatinine clearance. Those who failed to achieve > 50% decrement in protein excretion with/without worsening of creatinine clearance were considered drug-failure.

2.4. Statistical Analysis

SPSS statistical package version 26 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 were normally distributed; they were expressed as Mean ± SD while CrCl and UP were not normally distributed and hence they were expressed as Median (IQR). Comparison of age and duration of follow up between both groups was done using t test. On the other hand; comparison of changes in CrCl and UP at different times (start, 3 months, 12 months and 24 months) was done using Wilcoxon Signed Rank test. Comparison of CrCl and UP between the 2 groups was done using Mann-Whitney U test.

3. Results

A total of 8 patients satisfied the criteria for inclusion in the study. However, 1 patient was excluded due to intolerable abdominal pain/diarrhea induced by MMF. According to their response to treatment; patients were classified into 2 groups. Five patients (71%) had complete remission with treatment and were labelled as the responsive group (R) while 2 patients manifested partial remission and hence were labelled as the partially responsive group (PR). The demographical data of those patients are summarized in Table 1. Two female patients were in the R group yet the 2 PR patients were males. All patients were adults at

Table 1. Demographical profile of the 2 response groups of patients with NS due to HSP.

due to IgA nephropathy subsequent to therapy				
Response groups	No.	Sex	Age*	Duration of follow up*
		(F/M)	(years)	(months)
Responsive	5	2/3	27 ± 3	35 ± 10
Partially responsive	2	0/2	29 ± 2	34 ± 5
Total	7	2/5	28 ± 3	35 ± 8

Abbreviations: NS: nephrotic syndrome, HSP: Henoch-Schönlein purpura, M: males, F: females. *No significant difference between the groups.

35 ± 8 years of age and their duration of follow up was 35 ± 8 months. The 2 parameters were not different in both response groups.

3.1. Response to Therapy

The response to treatment in the 2 groups is summarized in **Table 2**. In the R-group; the initial decline in CrCl had returned to normal by 3rd month and remained stable by 24 months. In the PR one; the initial decline CrCl had marginal improvement yet did not normalize. 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 with decline of UP to ≥50% by the 3rd month that remained stable at ≥1560 mg/day by the 24th month.

3.2. Side Effects of Medications

Periodic laboratory investigations did not show significant changes in the hematological profiles and liver function tests. None of the included patients had diabetes mellitus at inclusion and none had significant glucose intolerance subsequently.

4. Discussion

HSP is associated with deposition of abnormal antibodies (subclass IgA_1 in polymers) in the wall of blood vessels, leading to vasculitis. The disease can be triggered by an upper respiratory tract infection, infections, drugs, chemicals and even insect bites [7]. In those with nephritis due to IgA and HSP an inherited aberrant glycosylation of IgA in the form of galactose-deficient immunoglobulin A1 (Gd-IgA1) has been found in 76% of pediatric and 64% of adult cases [8]. Moreover, IgA-fibronectin aggregates were found in 93.3% in patients with IgA-ANF [9]. These 3 observations indicate an inherited predisposition to disease and their triggering autoimmune phenomena. Since genetics cannot be altered in such patients; treatment of such IgA-ANF should be: 1) directed to decrease the autoimmune triggering factors, and 2) started early in its relapse or disease evolution, and 3) with safe and efficacious long-term immunosuppressive drugs. Those 3 phenomena were evident in the beneficial outcome of our

Table 2. Changes in the 2 response groups of patients with NS due to HSP after therapy.

Response groups	Responsive	Partially responsive	Both groups
	Interval p-value	Interval p-value	Comparison p-value
Changes in creatinine clearance:			
Time 0:	72 (6)	68 (10)	NS
	<0.04	NS	
Time 3 M:	82 (10)	72 (8)	<0.04
	<0.04	NS	
Time 12 M:	92 (18)	77 (14)	<0.001
	NS	NS	
Time 24 M:	92 (12)	76 (16)	<0.001
Final p-value (0 - 24):	<0.04	NS	
Changes in protein output:			
Time 0:	3730 (890)	4020 (380)	NS
	<0.04	NS	
Time 3 M:	460 (140)	1805 (110)	<0.001
	NS	NS	
Time 12 M:	440 (230)	1535 (210)	<0.001
	NS	NS	
Time 24 M:	380 (290)	1650 (180)	<0.001
Final p-value (0 - 24):	<0.04	NS	

Abbreviations: NS: nephrotic syndrome, HSP: Henoch-Schönlein purpura.

new drug-regimen that halted disease progression for ≥24 years. Moreover, the different response to therapy in our 2 patient's groups, and disease severity, further supports the theory of variable phenotypic presentation of genetic disease. In our study; we proposed 2 treatment-phases in management of HSP-ANF: 1) potent drugs in the initial 12 weeks induction-phase, and 2) a safe drug with long-term efficacy in the subsequent maintenance-phase. Previously; multiple drugs have been used in management of non-crescentic HSP-ANF viz. Corticosteroids, Azathioprine, Cyclophosphamide, Cyclosporine A, Dipyridamole, High-dose IV immunoglobulin G (IVIg), ACEIs), ARBs, Danazol, Fish oil [10], of those, only cyclophosphamide has been shown to be effective in a randomized controlled trial [11]. Unfortunately; the long-term infertility of Cyclophosphamide and interstitial fibrosis with Calcineurin-inhibitors limits their long-term use [12] [13]. However, Cyclophosphamide and IVIg can be added in the induction phase of this disease in drug-refractory patients and in its crescentic ANF. There is some evidence to support steroid therapy in the treatment of severe abdominal pain, severe nephritis, and central nervous system involvement [14]. However, the long-term use of corticosteroids is controversial. Frequent re-

lapses, lack of response to steroid, steroid dependency, and steroid side effects may occur in some patients [15]. In our patients we selected Prednisone only in the induction phase to complement MMF for their potent and rapid immunosuppression. On the other hand; MMF was selected as the sole immunosuppressive agent in the maintenance phase due to its potent antiproliferative action [16]. Subsequently, the drug has gained increasing impact in the treatment of non-transplant autoimmune disorders [17]. However, the available evidence to support the use of MMF in HSP is limited to some case study reports in children [18] [19]. Our study has confirmed its efficacy and safety in long-term management of severe nephrotic/nephritic forms of HSP-ANF in adults. In conclusion; treatment of severe forms of non-crescentic IgAN should be directed towards its autoimmune triggering factors with potent, safe and long-term efficacious drugs such as MMF.

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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