Preliminary experience with tacrolimus in managing Henoch-Schönlein purpura featuring extrarenal symptoms refractory to conventional therapy

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Short Report

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Abstract

Background

Henoch-Schönlein purpura (HSP) is the commonest vasculitis of childhood, affecting multiple organ systems. The extrarenal manifestations are prominent in some HSP cases, for which no standard treatment is available. It is interesting to examine the value of tacrolimus in such cases.

Findings

Seventeen children received tacrolimus to manage their refractory extrarenal symptoms of HSP in an open-label prospective study. Tacrolimus was administered at daily dose of 0.05–0.15 mg/kg. Tacrolimus was effective in all cases after treatment for 7–21 days. Tacrolimus treatment resulted in complete resolution of extrarenal symptoms in 15 cases, and partial resolution in the remaining 2 cases. During follow-up, skin purpura reoccurred in 2 cases, abdominal pain and loss of follow-up in 1 case each. Drug-related adverse reaction was not observed in any case. Abnormal renal function test was identified in 7 patients by urinary screening tests before tacrolimus therapy, 4 of them received renal biopsy. Only one patient showed evidence of renal impairment during follow-up.

Conclusions

Tacrolimus works quickly without drug-related adverse reaction in managing the HSP patients featuring recurrent extrarenal symptoms. Our preliminary experience suggests good clinical efficacy and safety of tacrolimus in such off-label use.

Introduction

Henoch-Schönlein purpura (HSP) is the commonest vasculitis of childhood. Pathological examination reveals IgA1 deposition in blood vessel walls. Purpuric rashes, gastrointestinal symptoms, swollen and painful joints, and renal involvement are common clinical symptoms of HSP. The extrarenal symptoms such as skin purpura, gastrointestinal symptoms, swollen and painful joints are generally self-limited, for which only symptomatic treatment is required. However, in some cases, the extrarenal symptoms are refractory, such as persistent or recurrent purpuric rashes, swollen and painful joints, and abdominal symptoms. Recurrence of extrarenal symptoms is not only a high-risk factor for renal involvement [1], but also makes the child and his/her family nervous and anxious, and so affects their quality of life [2]. Currently, steroids, gamma globulin, blood purification, various immunosuppressive agents, and biological products are usually tried in clinical practice with inconsistent results.

Tacrolimus (Fk506) is a calcineurin inhibitor [3], showing good compliance when administered orally. It is widely used in the treatment of pediatric patients with renal disease with good clinical outcome. This prospective, observational study aimed to examine the efficacy and safety of tacrolimus in managing HSP patients featuring extrarenal symptoms refractory to conventional therapy.

Methods

The study protocol and informed consent form were approved by the institutional review board of the First Affiliated Hospital of Xiamen University. A child was enrolled if all the following criteria were satisfied. (1) The diagnostic

criteria of HSP proposed by European League Against Rheumatism (EULAR) and European Society for Paediatric Nephrology (ESPN) in 2005 [4]. (2) Fail to respond to the evidence-based conventional HSP treatments as recommended by Immunology Study Group, Society of Pediatrics, Chinese Medical Association (CMA) in 2013 [5], evidenced by presence of persistent or recurrent skin purpura, gastrointestinal or articular symptoms, no family history of diabetes mellitus, and with normal glucose tolerance. (3) Informed consent was obtained from the family of the child about the off-label use of tacrolimus. (4) No history of kidney disease. (5) The purpura caused by other diseases was excluded.

Tacrolimus was administered orally every 12 hours. The total daily dose was 0.05–0.15 mg/kg [6]. Steroids were still used in all cases. Tacrolimus treatment was stopped one week after resolution of extrarenal symptoms (but not in case of purpura nephritis when longer duration of tacrolimus treatment is required), or no response after treatment for 2 weeks.

Trough serum concentration of tacrolimus was determined by enzyme-linked immunosorbent assay after 3 dosing days (reference range 5–10 µg/L). The time to extrarenal symptom resolution was recorded until the endpoint (i.e., 60 days after tacrolimus treatment). Urinalysis and urine protein quantification were repeated biweekly in follow-up period to evaluate drug-related adverse reactions and symptom recurrence.

Results

All the enrolled children (n = 17) were inpatients treated in the Department of Pediatrics, the First Affiliated Hospital of Xiamen University during the period from July 2015 to October 2018, including 10 boys and 7 girls (4.25–14 years old). The extrarenal symptoms were present for 28 to 90 cumulative days before initiation of tacrolimus treatment.

Tacrolimus treatment was effective in all the 17 patients, including complete resolution of extrarenal symptoms in 15 cases, partial resolution in the remaining 2 cases (evidenced by recurrent but less severe skin purpura alone) (Table 1). Tacrolimus treatment worked quickly, which was proved by resolution of gastrointestinal and articular symptoms within 1–4 days, resolution of skin purpura within 2–10 days. The treatment specific for extrarenal symptoms lasted 10–21 days. Renal involvement was found in 2 children during tacrolimus treatment, which was characteristic of nephrotic syndrome (Lee IIIb). Tacrolimus was still used to treat HSP nephritis in one of the two children. Persistent proteinuria and microscopic hematuria were found in 2 cases (Lee IIa). Repeated quantification of urine protein did not meet the criteria of nephrotic syndrome. Tacrolimus was stopped after resolution of extrarenal symptoms. During follow-up, skin purpura reoccurred in 2 cases, one associated with abdominal pain (one episode of skin purpura) and another loss to follow-up (two episodes of skin purpura), respectively.

Therapeutic drug monitoring was available in 13 of the 17 patients 3 days after oral administration of tacrolimus. Serum tacrolimus concentration was higher than 5 ng/ml in 7 cases, lower than 5 ng/ml in 6 cases. The extrarenal symptoms resolved completely in 6 of the 7 children with higher tacrolimus concentration (> 5 ng/ml). Skin rashes relapsed in one of the 6 patients with lower tacrolimus concentration (< 5 ng/ml). Tacrolimus-related adverse reaction was not found in any of these patients. One patient developed non-convulsive seizure during treatment associated with normal serum tacrolimus concentration. Brain magnetic resonance imaging showed low density signal in bilateral hippocampal region, which was considered neurological involvement of HSP. HSP was complicated with pancreatitis in one child (serum tacrolimus concentration < 5 ng/ml). It was considered as a complication of HSP. Serum levels of amylase and lipase were normalized by symptomatic therapy. Imaging study suggested ease of pancreatic edema and relief of abdominal pain. The extrarenal symptoms did not occur again after rechallenge with

oral tacrolimus. Another patient developed orchitis and recurrent skin rashes on treatment but lost to follow-up after discharge.

Renal involvement was identified in 7 of the 17 children before tacrolimus treatment, evidenced by various degrees of hematuria and/or proteinuria. Four patients received renal biopsy for pathological examination (Lee IIa in one case, Lee IIb in another case, and Lee IIIb in the remaining 2 cases). One child developed hematuria alone during follow-up, but renal biopsy was not available.

Discussion

HSP is the commonest vasculitis of childhood, affecting the small blood vessels, with annual incidence of 10–20/100,000 [7]. HSP is primarily mediated by IgA1 (abnormal glycosylation in the hinge region) deposition in the walls of blood vessels and glomerular mesangium. Therefore, it was renamed as IgA vasculitis (IgAV) at International Chapel Hill Consensus Conference in 2012 [8]. For the HSP patients with prominent refractory extrarenal symptoms, no optimal therapy is available at present time. Steroids, gamma globulin, and blood purification are usually used in clinical practice, but associated with higher incidence of steroids-related side effects, and emergence of resistance to steroids and gamma globulin. Blood purification is invasive and expensive, which is not applicable for the treatment of non-life-threatening HSP. In recent years, several immunosuppressants and biological products such as methotrexate, azathioprine, dapsone, colchicine, and rituximab, have also been reported with some successes [9–13].

Tacrolimus is a potent immunosuppressive agent widely used in pediatric kidney diseases. It works primarily by interfering with calcium-dependent signaling pathway and inhibiting the transcription of T cell activation-related gene and subsequent protein synthesis. Tacrolimus can also inhibit cytokine production and IL-2R expression. It is a dual inhibitor of both cellular and humoral immunity. Bhimma [14] et al found that in 20 children with steroid-resistant focal segmental glomerulosclerosis (FSGS), 85% achieved complete or partial resolution after tacrolimus plus low dose steroids combination therapy for 12 months. The relapse rate was only 10% after average follow-up period of 27.5 months. The adverse reactions such as vomiting, anemia, and diarrhea at early stage of oral drug therapy are self-limited, suggesting good treatment safety and efficacy. In a study of steroid-resistant nephrotic syndrome (SRNS), Loeffler [15] found 16 patients switched to tacrolimus due to resistance/dependence ($n = 15$) and intolerable side effects from other therapies ($n = 1$). Tacrolimus showed a complete remission rate of 81% and a partial remission rate of 13%. The overall response rate was 94%. Tacrolimus is much better than other immunosuppressants (mycophenolate mofetil, cyclophosphamide, and cyclosporine A) in FSGS or SRNS in terms of efficacy and safety profiles.

To our knowledge, tacrolimus has not been reported in treatment of recurrent HSP. It is supposed that the effect of tacrolimus found in our study may be associated with its inhibition of T cell proliferation, and so influencing T-cell dependent B cell differentiation and maturation, which reduces the synthesis and secretion of IgA1. On the other hand, tacrolimus can indirectly block alternative complement pathway, which reduces the formation of immune complex IgA-IgG-C3. Tacrolimus acts through these two pathways to relieve the lesions of small blood vessels [16].

Our study showed that tacrolimus was significantly effective in managing all the 17 HSP patients featuring refractory extrarenal symptoms. The extrarenal symptoms resolved in 15 cases during treatment. The remaining 2 patients achieved partial resolution. Tacrolimus treatment is safe in all cases without any drug-related adverse reaction. This study is observational in design and preliminary experience of our clinical practice. More issues and topics such as duration, dosage, time points for evaluation, reduction of renal involvement, and long-term complications, should be further examined and clarified in clinical practice, and optimally confirmed in randomized controlled clinical trials.

In summary, the results of this study suggest that for the HSP patients with refractory extrarenal symptoms who fail to respond to conventional therapy, tacrolimus can be considered as a worthwhile treatment option for its quick effect, good outcome, and safety profile.

Abbreviations

CMA: Chinese Medical Association; ESPN: European Society for Paediatric Nephrology; EULAR: European League Against Rheumatism; FSGS: focal segmental glomerulosclerosis; HSP: Henoch-Schönlein purpura; IgAV: IgA vasculitis; SRNS: steroid-resistant nephrotic syndrome

Declarations

Compliance with ethical standards

The study protocol and informed consent form were approved by the institutional review board of the First Affiliated Hospital of Xiamen University. Legal guardian of the participants provided informed consent before study.

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Authors' contributions

The study was designed by CY and BH. All authors (CY, BH, YY and LZ) were responsible for data collection. All authors had reviewed study data, revised the manuscript and approved the final version for publication.

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Consent for publication

All authors approved the publication of this manuscript.

Conflict of interest

All authors declare no conflict of interest.

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Tables

Table 1 Baseline data and tacrolimus treatment details of 17 pediatric cases of Henoch-Schönlein purpura with extrarenal symptoms refractory to conventional therapy

Case No.	Age (yrs)	Sex	Cumulative days of extrarenal symptoms before treatment				Recurrent symptom (total episodes)	Steroid use (days)	Cumulative dose of gamma globulin (mg/kg)	Tacrolimus treatment		Time from treatment to symptom resolution (days)					Urinalysis				Episodes during follow-up	Kidney pathology
			GI rash	Skin	Angioedema	Joint				Days	Serum level (ng/mL)	GI	Skin rash	Angioedema	Joint	Pre-treatment		Follow-up				
																Occult blood	Protein	Occult blood	24h protein (g)			
1	10.7	M	12	16	0	8	4	20	1200	14	8.6	3	2	0	1	+	Neg	+	0.75	1	ND	
2	6.8	M	14	35	0	1	>5	14	No	16	6.7	2	10	0	1	+++	++	+++	5.18	0	Lee IIIb	
3	5.7	M	25	28	3	9	3	22	No	14	5.1	3	3	1	3	Neg	Neg	Neg	<0.15	0	NA	
4	10.0	F	2	41	0	4	3	37	No	18	ND	2	5	0	1	Neg	Neg	Neg	<0.15	0	NA	
5	6.2	F	10	29	0	3	3	26	No	17	2.9	1	2	0	2	Neg	Neg	Neg	<0.15	0	NA	
6	10.5	F	18	40	0	2	4	38	2000	16	6.2	3	9	0	2	Neg	Neg	Neg	<0.15	2	NA	
7	11.1	F	0	>90	0	0	Persistent	>60	No	Persistent	3.3	0	2	0	0	++	+++	++	4.23	0	Lee IIIb	
8	10.4	M	10	37	0	4	3	20	No	19	ND	1	2	0	1	Neg	Neg	Neg	<0.15	0	NA	
9	9.5	M	19	39	0	0	4	56	1200	17	ND	1	4	0	1	+	++	++	0.99	0	Lee IIa	
10 ^a	7.4	M	7	21	0	0	3	21	2000	10	7.0	1	3	0	0	Neg	Neg	+	<0.15	0	NA	
11	7.8	M	24	24	0	0	4	24	800	21	6.7	2	3	0	0	Neg	Neg	Neg	<0.15	0	NA	
12	14.0	F	0	14	00	0	3	14	No	14	5.2	0	Recurrent	0	0	Neg	Neg	Neg	<0.15	0	NA	
13 ^b	9.0	M	10	>90	0	0	3	14	1200	10	4.4	4	3	0	0	+/++	+/-	++	0.34	0	Lee IIb	
14	13.1	F	0	>60	0	0	2	21	No	12	3.2	0	2	0	0	+	+	Neg	<0.15	0	NA	
15	11.4	F	7	19	2	0	3	25	No	14	3.1	1	2	0	0	+	+/-	+	Neg	1	NA	
16	4.3	M	13	24	0	7	4	46	2000	20	ND	2	1	0	1	Neg	Neg	Neg	Neg	0	NA	
17 ^c	6.0	M	14	20	0	3	3	15	No	8	2.5	2	Recurrent	0	2	Neg	Neg	NA	NA	NA	NA	

^a Developed non-convulsive seizure during tacrolimus treatment associated with normal serum tacrolimus concentration, brain magnetic resonance imaging revealed low density signal in bilateral hippocampal regions, which was considered neurological involvement of Henoch-Schönlein purpura.

^b Complicated with pancreatitis, which was considered secondary to the primary disease. Tacrolimus was discontinued temporarily and resumed after cure of pancreatitis. The total duration of tacrolimus treatment was 10 days.

^c Complicated with orchitis, associated with recurrent abdominal pain, and lost to follow-up after discharge.

F female, *GI* gastrointestinal, *M* male, *NA* not available, *ND* not determined, *Neg* negative