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Experience with intravenous immunoglobulin in severe childhood atopic dermatitis

To the Editor,

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by dysregulated immune responses, which affects approximately 10–15% of children and persists until adulthood in approximately 6% of the population. Treatment generally relies on a balance between control of the condition and quality of life, and safe long-term treatment. The role of intravenous immunoglobulin (IVIG) in severe atopic dermatitis has been investigated in only a few trials with inconclusive results. We herein present our experience with this drug in four patients with severe AD refractory to standard treatment.

Cases

Here we present our experience on four severe AD cases who were treated with IVIG. The use of IVIG in each of these patients was approved by the local Drug and Therapeutic Committee. Informed consent was obtained from all the patients or their parents.

Patient 1

A 165/12-year-old boy with severe AD had been referred to our unit for further evaluation four years before, when he was 12 years old. He had multiple skin prick test positivity including house dust mite (HDM), egg and milk. He was then started on a series of topical anti-inflammatory medications. Since his respiratory symptoms were refractory to avoidance measures and optimal pharmacological treatment, he commenced sublingual immunotherapy (SLIT) for HDM (ALK, Abello, Madrid, Spain). His skin problems exacerbated during these treatments. Treatment with first and second line drugs, including potent topical steroids and topical calcineurin inhibitors for several months, systemic steroids for three months and cyclosporin 5 mg/kg for 12 months (interrupted due to severe infections) failed to control his disease. At 14 years of age, he was started on IVIG (Octagam®, Octapharma, Stockholm, Sweden) with a dose of 0.5 g/kg given monthly and continued for a total of 16 months (=16 cycles). His AD symptoms started to improve dramatically after the second cycle and completely resolved at the end of the treatment along with a decrease of a total IgE level from 37,400 kU/L (1–200 IU/L) initially, to 2450 and an eosinophil count from 1900/mm^3 to 200/mm^3. His AD remains currently in remission off immunoglobulin therapy for the last seven months (Table 1).

Patient 2

A girl of seven years and three months had a four-year history of persistent AD, which had failed to respond to potent topical corticosteroids, 0.1% topical tacrolimus, daily emollients and oral antihistamine treatments. Laboratory examination revealed a serum total IgE level of 8982 kU/L and a positive Radioallergosorbent test for HDM. The initial Scoring Atopic Dermatitis (SCORAD) index was 71. When she was 6.5 years old, she was started on IVIG with a monthly dose of 1 g/kg in addition to her usual treatments (Octagam®, Octapharma, Stockholm, Sweden) After nine cycles, her AD symptoms improved. The SCORAD index and IgE level decreased to 25 and 3420 kU/L respectively, with a minor decrease in eosinophil count.

Patient 3

A 13-year-old girl who has had AD since five years of age presented with extensive disease involving almost her entire body surface area. The disease remained active despite topical steroid therapy for a year, 0.1% topical tacrolimus for three months, and oral antihistamine treatment as needed. Her skin prick testing was positive for HDM, grass, wheat and cockroach. The initial level of IgE was 18,868 kU/L, and a SCORAD index of 84. Systemic steroid therapy for four months and phototherapy for two months were commenced, however they yielded no improvement. IVIG therapy with a monthly dose of 1 g/kg was initiated (Octagam®, Octapharma, Stockholm, Sweden). After five doses, a satisfactory improvement has been noted, and she is still currently under this mode of treatment. The SCORAD index and the IgE level decreased to 25, and 5489 kU/L respectively, and eosinophil count also declined from 3700/mm^3 to 1200/mm^3.

Patient 4

A 23-year-old young man who has had asthma since five years of age and AD for the last five years presented with the exacerbation of his skin symptoms. He had been

Table 1 Clinical and biochemical features of the four patients described.

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	16 years, five months	Seven years, three months	13	23
Gender	Male	Female	Female	Male
IVIG dose and number of cycles	0.5 g/kg, ×16	1 g/kg, ×9	1 g/kg, ×5	0.5 g/kg, ×8
Prior treatments				
Systemic steroid	—	—	—	+ (For two months prior to IVIG)
Cyclosporine	+ (12 months)	—	—	—
SLIT	+ (Still using)	—	—	+ (Three years. ago, for two months)
Phototx	—	—	+ (For two months)	—
Systemic antibiotic tx	+	+	—	—
Adjunctive treatment				
Systemic steroid	—	—	—	+ (For six months)
Cyclosporine	—	—	—	—
SLIT	+	—	—	—
Phototx	—	—	—	—
Systemic antibiotic tx	—	—	—	+
Laboratory findings				
Eosinophil count at baseline (in mm^3)	1900	2200	3700	1100
Eosinophil count during IVIG tx	—	1800 (after the 8th dose of IVIG tx)	1200 (after the 3rd dose of IVIG tx)	900 (after the 8th dose of IVIG tx)
Eosinophil count after IVIG tx	200			
Total IgE baseline (kU/L)	37,400	8982	18,860	10,740
Total IgE during IVIG tx	17,200 (after the 4th dose of IVIG tx)	3420 (after the 8th dose of IVIG tx)	5489 (after the 3rd dose of IVIG tx)	9400 (after the 8th dose of IVIG tx)
Total IgE after IVIG tx	2450 (18th month of IVIG)			
SCORAD index				
Initial SCORAD index	80	71	84	71
SCORAD index during IVIG tx	18 (At the 16th dose of IVIG)	25 (At the 9th dose of IVIG)	25 (At the 4th dose of IVIG)	58 (At the 5th dose of IVIG)
SCORAD after cessation of IVIG treatment	1	Still using	Still using	Still using

SLIT: Sublingual immunotherapy, Phototx: Phototherapy, Tx: Treatment, SCORAD: Scoring atopic dermatitis, IVIG: Intravenous immunoglobulin (Octagam®, Octapharma, Stockholm, Sweden).

started on SLIT for HDM (ALK, Abello, Madrid, Spain) for his asthma symptoms, which he had to stop after two months due to a systemic reaction. AD was unresponsive to systemic steroid therapy (methyl prednisolone 60 mg) given for two months. Laboratory investigations revealed a total IgE level of 10,700 and a peripheral blood eosinophil count of 1100/mm^3. He was started on IVIG (0.5 g/kg every three weeks, Octagam®, Octapharma, Stockholm, Sweden) as an adjunctive treatment to systemic steroid with a baseline SCORAD index of 71. An upper gastrointestinal endoscopy was performed due to his abdominal pain while he was on IVIG therapy. Histological examination revealed Helicobacter pylori gastritis. Eradication therapy of amoxicillin and clarithromycin in addition to a proton pump inhibitor was given for two weeks. At the second week of this treatment his AD symptoms almost completely resolved, allowing him to discontinue systemic steroid treatment. Upon the return of his symptoms after the cessation of this mode of therapy, we considered starting prophylactic antibiotic treatment. Currently, he has been off steroid therapy for the last one month after an eight-month IVIG treatment. Although his AD symptoms are milder compared to his baseline status, he continues to have AD symptoms with a current SCORAD score of 58 with a total IgE of 9400 kU/L and eosinophil count of 900/mm^3.

High-dose IVIG with a dose of 2 g/kg/month is used as an immunomodulatory agent and it is thought that it provides the clinical improvement of AD by exerting its anti-inflammatory effects.[1] The ability of IVIG to downregulate T-cell function and particularly interleukin-4 production has

made it a candidate for the treatment of AD.[2] IVIG exhibits anti-inflammatory activity in AD by decreasing IFN-γ levels.[3] Additionally, IVIG contains high concentrations of staphylococcal toxin-specific antibodies that inhibit the in vitro activation of T cells by staphylococcal toxins.[4] The current data suggest that IVIG can improve skin scores in childhood AD when used as mono-therapy with a dose of 2 g/kg. On the contrary, mono-therapy with IVIG does not appear to have the same effect in adult patients.[5] However, it may offer an improvement of 50–60% in severe AD when used as an adjunctive treatment.[6] Regarding the use of lower doses of IVIG, a trial evaluating the efficacy of single cycle IVIG in patients with steroid resistant AD revealed conflicting results with some patients displaying reductions in IgE levels at the third week of treatment and a proportion of patients experiencing some improvement in symptoms.[7] However, the follow-up duration was too short and the study population was heterogeneous in that study.

For two of our cases (patients 1 and 4) with a body weight of over 80 kg, we used an IVIG infusion with a dose of 0.5 g/kg at each cycle not to exceed the maximal dose. For the other two cases IVIG infusions were performed with a dose of 1 g/kg/cycle. During IVIG treatment no significant side effects were observed in any of the patients other than few episodes of mild symptoms (chills, nausea, and headache). In all three paediatric patients significant clinical improvements were observed after the first IVIG dose as mono-therapy. On the basis of our particular experience with three children, it is likely that of 0.5–1 g/kg doses of IVIG prove efficacy in the childhood period, whereas our limited experience with only one patient suggests that this lower dose in adults may not be as efficacious as that which we used in children. These findings support the previous notion that children with AD have a better response to IVIG than adults.[8]

Our observations raise the question as to whether the clinical improvements observed parallel to the reductions in total IgE levels indicate a causal relationship, or the changes in both parameters are secondary to separate pathogenetic pathways. In the literature, some immunological parameters including eosinophil counts, ECP, IgE, ICAM-1 and ELAM-1 have been shown to correlate well with the improvement in symptoms.[8] However, it is also reported that clinical improvements in the severity of AD may not accompany alterations in those parameters. A trial on the efficacy of low-dose anti-IgE therapy in patients with AD with high serum IgE revealed that the reduction of free serum IgE was not a good marker of clinical response to treatment.[9] In interpreting all those reports it should be noted that there is a high variability of characteristics of patients and regimens. Therefore, it is not yet possible to draw conclusions from the present studies as to the optimal dose and duration of the IVIG in AD. Future studies should consider this heterogeneity and be designed appropriately to address those issues.

In conclusion, our particular experience with IVIG treatment in severe AD demonstrates that this treatment when used as monotherapy in children is safe and effective in alleviating symptoms as well as lowering IgE levels and eosinophil counts with comparatively lower doses (0.5–1 g/kg/dose). The key questions remaining to be answered before defining the exact role of IVIG in severe AD include: (1) Is it also effective in other AD phenotypes such as those with lower IgE levels?; (2) Is it superior to alternative second line drugs such as cyclosporine?; (3) What is the lowest effective dose, and when should treatment stop? Well-designed prospective randomised controlled trials may help to elucidate these questions as well as the precise mechanism of action of IVIG in severe AD.

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