Acta Derm Venereol 2003; 83: 433–437

Taylor & Francis
healthsciences

CLINICAL REPORT

Adjunctive High-dose Intravenous Immunoglobulin Treatment for Resistant Atopic Dermatitis: Efficacy and Effects on Intracellular Cytokine Levels and CD4 Counts

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Although atopic dermatitis generally responds to topical therapy, small numbers of patients have severe resistant disease despite second-line therapies. High-dose intravenous immunoglobulin has been suggested to be of benefit in a small number of reports. We have conducted an open, single-centre study of adjunctive high-dose intravenous immunoglobulin (Flebogamma® 5%). Six patients received treatment at 2 g kg^{-1} month^{-1} for 6 cycles, with a 3-month follow-up period. Skin scores, lymphocyte phenotypes and intracellular cytokine analysis were performed. Four of six patients had major improvements in skin scores and the overall reduction was significant ($p = 0.035$). CD4+ T-cell numbers fell following high-dose intravenous immunoglobulin infusions, recovering by the next cycle. T-cell CD69 expression decreased to 60% of baseline values. Reductions in the proinflammatory cytokines IFN-γ and TNF-α were non-significant. Adjunctive high-dose intravenous immunoglobulin may be a useful therapeutic approach in adults with severe treatment-resistant atopic dermatitis, but it will require further assessment in randomized controlled trials to establish this. ***Key words: atopic dermatitis; intravenous immunoglobulin; intracellular cytokines.***

(Accepted July 24, 2003.)

Acta Derm Venereol 2003; 83: 433–437.

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A small proportion of patients with atopic dermatitis (AD) have severe therapy-resistant disease, which results in recurrent hospital admissions, disruption of personal and family life and significant morbidity. There are now seven reports of the use of high-dose intravenous immunoglobulin (HdIVIg) for severe AD (1–7).

IVIg is a blood product prepared from the pooled plasma of between 1,000 and 15,000 donors per batch by cold ethanol fractionation, which undergoes additional viral inactivation procedures. The immunomodulatory mechanisms of IVIg are mediated via the Fc portion of IgG interacting with Fc receptors and complement, the antigen-binding variable regions $F(ab')_2$, or by substances other than antibody in the IVIg preparations (8–13).

We have conducted an open study of HdIVIg in severe therapy-resistant AD.

METHODS

Study subjects were ≥18 years at consent, with severe, stable AD which was not adequately controlled by topical steroids and oral prednisolone. Patients with variations in the modified Eczema Area and Severity Index (mEASI) score of greater than or equal to 20% in the 12 weeks preceding the study were excluded.

Eight patients with severe AD were considered and six entered the study. Two were excluded: the first improved following the diagnosis of wheat allergy and the introduction of avoidance measures, and the second was found to have cardiac hypertrophy and significant hypertension. Patient details are described in Table I.

Six patients received adjunctive monthly (HdIVIg) Flebogamma® 5% treatment at 2 g kg^{-1} month^{-1} for 6 cycles with a 3-month follow-up period, given over 2 to 5 consecutive days depending on tolerance. Patients were maintained on second-line agents, as HdIVIg given adjunctively is more effective than monotherapy in other skin diseases (14) and because of the published lack of efficacy of monotherapy in adults with AD (4, 7). Skin scores and lymphocyte phenotypes were analysed before and after HdIVIg in all patients and sequential intracellular cytokine analysis was performed in four patients.

The study aimed to assess efficacy and safety of HdIVIg in addition to observing effects on post-stimulation intracellular interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α) levels and the activation marker CD69. Diagnosis of AD was made using the criteria described by Hanifin & Rajka (15). Severity was based on Rajka & Langeland's criteria (16), with "severe" defined as a score of ≥8. Venous blood samples were taken pre- and post-dose.

Efficacy was assessed using the modified Eczema Area and Severity Index (mEASI) (16). mEASI scores were determined at each visit. The mEASI is a variant of the Eczema Area and Severity Index (EASI) developed by Hanifin and co-workers (17) and includes itch because this is a primary symptom of AD (15). Intracellular cytokines were determined using a whole-blood flow-cytometric method during IVIg therapy (18, 19).

 ISSN 0001-5555
DOI: 10.1080/00015550310020549

Table I. *Demographic and treatment details of 6 male patients with atopic dermatis who completed 6 cycles of adjunctive HdIVIg. Age given is age at time of consent.*

Age and baseline mEASI score	Additional therapy	Previous therapy	% Change in mEASI from baseline after 6/12 HdIVIg	Response time for HdIVIg and duration	% Change in CD4 count following HdIVIg	Concurrent conditions
44 years (mEASI 75)	Pred 7.5 mg d^{-1} and Aza 100 mg d^{-1} (Pred reduced to 5 mg d^{-1} in month 3)	Steroids, Aza, Csa, PUVA, Chinese herbs	52% lower	2 months to response lasting 2 months	21% lower	Asthma, hay fever, low bone density
18 years (mEASI 58)	Hxc 200 mg d^{-1}	Steroids, PUVA, Chinese herbs	7% lower	N/A	47% lower	Treated hepatic sarcoma, asthma, hay fever, rhinitis
45 years (mEASI 67.5)	Pred 15 mg d^{-1} Aza 150 mg d^{-1}	Steroids, Csa, Aza, PUVA, UVB	24% higher	N/A	32% lower	Asthma, hay fever, rhinitis, low bone density
32 years (mEASI 70.5)	Aza 150 mg d^{-1}	Steroids, Csa, Chinese herbs	97% lower	2–3 months to response lasting >3 months	41% lower	Hay fever
26 years (mEASI 72)	Aza 100 mg d^{-1}	Steroids, Csa Phototherapy	98% lower	3 months to response lasting >3 months	14% lower	Hay fever, rhinitis, cellulitis, low bone density
53 years (mEASI 28.5)	Pred 15 mg d^{-1} (Pred reduced to 12.5 mg d^{-1} in month 5)	Steroids, Csa	95% lower	2–3 months to response lasting >3 months	16% lower	Asthma, hay fever, migraine, low bone density

Pred – Prednisolone, Aza – Azathioprine, Hxc – Hydroxychloroquine, Csa – Cyclosporin A, PUVA – Psoralen UVA phototherapy, N/A – not available.

Statistical analysis of skin scores and CD4 T cell counts was performed using Student's *t*-test.

RESULTS

Four out of six patients had major improvements in their skin scores, one demonstrated little change and one worsened slightly. Improvements in mEASI scores were apparent in responders from 2–3 months, but continued to improve over the 6-month treatment period (Table I). Overall reductions in mean skin scores from month 1 to month 7 were significant ($p=0.035$) using a paired *t*-test (Fig. 1). Improvements in itch using the mEASI score mirrored those in the other parameters and HdIVIg did not appear to have a selective effect on itch.

Treatment was well tolerated. Side effects were generally mild with two of six patients experiencing headache and one hypertension. These side effects were managed using paracetamol and adjustment of infusion rates.

Lymphocyte phenotypes showed a decrease in CD4 T cells following HdIVIg infusions ($p=0.009$), which recovered by the next cycle one month later (Table I). Four of the six patients were analysed for the activation marker (CD69) and intracellular cytokine expression throughout treatment. A trend towards decreased CD69 expression was observed following ex-vivo activation in both CD4+ and CD8+ T cells during the 6 months of HdIVIg therapy to approximately 60% of baseline values. Changes in intracellular TNF-α and IFN-γ levels following ex-vivo activation were non-significant ($n=4$).

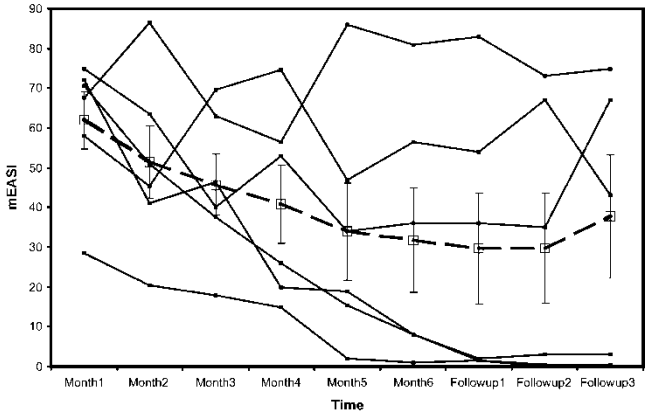

Fig. 1. Patient skin scores measured monthly using the modified Eczema Area and Severity Index (mEASI) score every month and are shown as solid lines. The highest possible mEASI score is 90. The mean skin score and standard error of the mean of each time point are shown on the broken line. A p value of 0.035 was obtained comparing the average skin scores at the beginning of therapy with those at the seven month time point. It can be seen that three of the responders were still in remission at the end of the three month follow-up period.

DISCUSSION

HdIVIg has been suggested to be of benefit in patients with AD in a small number of reports (1–7). There are now 10 children and 30 adults in the literature with AD who have been treated with HdIVIg; 17 of these had adjunctive HdIVIg (Table II). A further study using variable lower dose IVIg with short follow-up is not included in this analysis (20).

Summarizing this small number of patients, 9 out of 10 children improved on monotherapy. The child who failed to respond suffered from Wiskott-Aldrich syndrome. Seventeen of the adult patients were treated with adjunctive therapy and 10 improved (59%); however, of the 7 who did not respond, adjunctive treatment amounted to less than 7 mg of prednisolone per day. None of the adults treated with monotherapy responded. The only randomized study of 9 patients used a single cycle of HdIVIg monotherapy – the authors concluding that the results did not support the use of HdIVIg in AD. However, they did note a significant reduction in skin scores at 60 days (7).

In the current study, four out of six patients with severe therapy-resistant AD responded to adjunctive HdIVIg. The reductions in skin scores were significant ($p=0.035$). It was not possible to identify which patients were most likely to respond from features in their history, physical examination or blood tests.

In view of the time commitment (for both patients and staff) and financial implications of this form of treatment it is important to consider pharmacoeconomics. Prices vary between IVIg products, but at £25 g^{-1} a 70 kg man receiving 2 g kg^{-1} $month^{-1}$ would have a drug bill of £42,000 $year^{-1}$ ($63,000) before any inpatient costs are added. This must be compared to the estimated cost of a quality assessed life year based on dialysis patients of £40,000 ($60,000) in the light of a potentially long-lasting benefit from HdIVIg. Patients being considered for a therapeutic trial of HdIVIg therefore need careful selection. When all reports of HdIVIg for dermatological indications are analysed, the success of monotherapy versus adjunctive therapy is approximately 40% versus 80%, respectively, in spite of a likely reporting bias for successful outcomes (14). In the small number of reports of the use of HdIVIg in AD, the benefit of adjunctive therapy is obvious only in the adults (59% success adjunctively at 2–4 months compared with 0% as monotherapy), while in children under 6 years of age 90% responded to monotherapy.

Drug costs may be reduced by closely monitoring disease indices and increasing the interval between cycles when remission has been achieved. This addresses the question of duration of immunomodulation rather than dose required to immunomodulate (1). Dose reduction may be possible where a lowering in steroid dose has led to weight loss and therefore lower

Table II. *Summary of previous and current studies of HdIVIg in atopic dermatitis.*

No. of patients	Demographics	Dose and frequency	IVIg preparation	Additional treatment	Outcome*	Response time	Duration of remission	Reference
2M, 2F	2–6 years	0.4 g kg^{-1} for 5 days	N/A	Monotherapy	All improved	4–7 days	6 months	(3)
3M, 2F	7–12 months	2 g kg^{-1} month for 3 cycles	Bayer Biological Co.	Monotherapy	All improved	3 months	>6 months	(6)
1M (WAS)	8 months	1 g kg^{-1} for 1 cycle	N/A	Monotherapy	No improvement	N/A	N/A	(5)
10 patients (1 with HIGE)	7–64 years	2 g kg^{-1} month for 7 cycles	Venoglobulin-I®	Pred <7 mg d^{-1} in 5 Monotherapy in 4 (9 completed study)	Non-significant improvement	N/A	N/A	(4)
3M	19–45 years	2 g kg^{-1} month for 11 cycles	Sandoglobulin® & Alphaglobin®	Adjunctive, Pred, Hxc	All improved	2–4 months with maximal benefit at 11 months	1 long-lasting and 2 having IVIg 8 weekly	(1)
3 patients	31–40 years	2 g kg^{-1} month for 6 cycles	N/A	Pred	All improved	N/A	Short-lived	(2)
9 patients	21–38 years	2 g kg^{-1} for 1 cycle	Sandoglobulin®	Monotherapy (Topical only)	Non-significant improvement	N/A	N/A	(7)
6M	18–53 years	2 g kg^{-1} month for 6 cycles	Flebogamma®	Adjunctive, Aza, Pred or Hxc	4 of 6 improved	2–4 months	2 of 4 more than 3 months	Current study

*Although improvement in skin scores was noted in 6 of 9 patients (2 unchanged, worse in 1), this was non-significant overall and these patients have all been classed as non-responders. WAS: Wiskott Aldrich Syndrome, HIGE: Hyper IgE Syndrome, Pred: Prednisolone, Aza: Azathioprine, Hxc: Hydroxychloroquine, Csa: Cyclosporine-A, PUVA: Psoralen UVA phototherapy, N/A: Not available.

the overall dose of IVIg required. Inpatient costs can be reduced by using day case facilities and by making use of an existing IVIg home therapy training programme in the hospital, as is the case for primary antibody deficiencies. Home therapy has been successfully used in patients with chronic neurological disease (21).

Adjunctive HdIVIg may offer a useful therapeutic approach in the small group of adults with severe treatment-resistant AD. Appropriately designed double-blind placebo-controlled trials of at least 4 months adjunctive HdIVIg are required to decide if this form of treatment has a place in the management of this subset of patients with AD.

ACKNOWLEDGEMENTS

We acknowledge Dr Jenny Hughes for her careful reading of the manuscript. Instituto Grifols S.A. Barcelona, Spain sponsored the clinical trial, in which Sarah Broadhurst and Kerry Rawlings, Clinical Research Department, Grifols UK Ltd assisted.

Stephen Jolles is supported by the Leukaemia Research Foundation, American Histiocytosis Association and Peel Medical Research Trust.

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