

Rituximab as a treatment for severe atopic eczema: failure to improve in three consecutive patients

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Summary

Biological therapies may provide the breakthrough in treating moderate to severe atopic eczema (AE) that is unresponsive to standard therapy. Rituximab has been shown to benefit some patients in published case series, and so we treated three consecutive patients with severe AE with rituximab. Despite achieving low/absent peripheral blood CD19+ B-cell numbers following rituximab administration, this was not associated with clinical benefit as there was no major change in pre- and post-treatment Eczema Area and Severity Index (34, 64.4 and 42.2 compared with 33.2, 66 and 56.4, respectively). We would therefore recommend that there is a compelling need for a formal, double-blind, placebo-controlled study to demonstrate efficacy of rituximab as a treatment of moderate to severe AE.

Moderate to severe atopic eczema (AE) failing to respond to topical therapies and phototherapy may be treated with methotrexate, ciclosporin, azathioprine, mycophenolate or short courses of systemic corticosteroids.¹ In patients who are intolerant to these therapies or in whom they are ineffective, biological therapies offer possible alternatives. Such therapies include high-dose intravenous immunoglobulin (IVIg), omalizumab, dupilumab and rituximab. To date, IVIg and dupilumab are the only biological therapies that have been assessed in formal trials,^{2,3} and evidence of efficacy for other biological treatments are based on case reports and series.^{4–7} For this reason, we wish to communicate the failure of rituximab in three consecutive patients with severe AE.

Report

Patient 1 was a 47-year-old man who had been treated with topical corticosteroids, tacrolimus and phototherapy, and then with adequate doses and duration of

azathioprine, ciclosporin, mycophenolate, methotrexate and fumaric acid esters, with little or no benefit. He continued to have severe AE with an Eczema Area and Severity Index (EASI) of > 30 (maximum 72) and serum IgE level of > 5000 kU/L (normal range < 120 kU/L). In 2010, the patient received IVIg 2 g/kg monthly, but after 10 infusions this treatment had to be discontinued because of severe migraines. The recalcitrant AE affected the patient's ability to work, and despite warnings to the contrary, he became maintained on doses of prednisolone 20–25 mg daily. In an attempt to reduce the dose of corticosteroid, he was administered rituximab 375 mg/m² weekly for 4 weeks in August 2012. Initial clinical improvement ensued, and he reduced the dose of prednisolone to 5 mg daily. However, within 2 months his eczema flared, with an EASI of 33.2. Peripheral blood CD19+ B cells were nearly undetectable at $0.002 \times 10^9/L$, while serum IgE was unchanged. The patient insisted on increasing the prednisolone to 25 mg daily. Continued activity of his AE warranted a further course of rituximab, 2 doses of 1 g each, given 2 weeks apart in May 2013. The AE did not improve and CD19+ B cells remained low at $0.009 \times 10^9/L$. Attempts to reduce the prednisolone have failed and the patient has become markedly cushingoid (Tables 1 and 2).

Patient 2 was a 54-year-old woman, whose AE had also failed to respond to potent topical corticosteroids

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Table 1 EASI and DLQI scores pre-treatment and post-treatment with rituximab.

	Patient 1		Patient 2		Patient 3	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
EASI*	30	33.2	64.4	66	42.2	56.4
DLQI†	17	18	19	25	18	21

DLQI, Dermatology Life Quality Index, EASI, Eczema Area and Severity Index. *EASI is an objective assessment of the severity of atopic eczema (scoring erythema, thickness, excoriations and lichenification) and the percentage area affected in four regions of the body.¹¹

†DLQI is a 10-question self-assessment questionnaire, evaluating the patient's perception of different aspects of how their illness affects their daily life.

Table 2 Effect of different therapeutic options.

Treatment	Patient 1	Patient 2	Patient 3
Azathioprine	Ineffective (2 mg/kg/day) and recurrent skin infections	Nausea, vomiting and headache (2.5 mg/kg/day)	Ineffective (2.5 mg/kg/day)
Methotrexate	Ineffective (15 mg/week) and development of recurrent skin infections	Ineffective, deranged liver function tests and alopecia (20 mg/week)	Ineffective (20 mg/week)
Psoralen ultraviolet A	Ineffective and caused burning sensation	Initial improvement, then ineffective	Ineffective
Ultraviolet B	Ineffective	Ineffective	Ineffective
Ciclosporin	Ineffective (4 mg/kg/day) and recurrent skin infections	Initial improvement, then ineffective (3 mg/kg/day)	Ineffective (3.5 mg/kg/day)
Mycophenolate mofetil	Ineffective (3 g/day)	Alopecia, nausea and loose stools (2 g/day)	Ineffective (2.5 g/day)
Fumaric acid esters	Ineffective (60 mg/day) and patient unable to tolerate due to gastrointestinal side effects	—	—
IVIg	Initial improvement then ineffective, with side effects of nausea, vomiting and headache (2 g/kg/month)	Primary care trust refused funding	Primary care trust refused funding
Rituximab	Ineffective, with no improvement during 6 months of follow-up	Ineffective, with no improvement during 6 months of follow-up	Ineffective, with no improvement during 6 months of follow-up
Concurrent therapy	Required at least 20 mg prednisolone daily (more for flares)	Required prednisolone for flares	Required at least 15 mg prednisolone daily (more for flares)

IVIg, intravenous immunoglobulin.

and phototherapy, and adequate duration and doses of azathioprine, mycophenolate, methotrexate and ciclosporin. Patch testing revealed weakly positive reactions to cobalt and chromium. The patient's IgE levels were > 5000 kU/L, with an EASI of 64.4 and Dermatology Life Quality Index (DLQI) of 19 (higher scores indicate greater impairment). In view of the ongoing sub-erythrodermic and short-lived benefit following intensive inpatient treatment, the patient was treated with rituximab given as four doses of 600 mg each at monthly intervals starting in April 2013. There was no improvement in her AE, with EASI of 66 and DLQI of 25 at 2 months after completing rituximab.

Patient 3 was a 50-year-old man, who had previously been treated with adequate duration and doses of azathioprine, ciclosporin, methotrexate, mycophenolate

and phototherapy. The only treatment that had been efficacious was oral, and he had been unable to reduce his prednisolone below a daily dose of 15–20 mg for 6 years. An application for funding IVIg was refused, but funding for rituximab was forthcoming. The patient's EASI and DLQI were 42.2 and 18, respectively, before treatment, and 47.7 and 20 at 1 month after the second of two infusions of rituximab 1 g administered 2 weeks apart. Two months after the rituximab infusions, the eczema had not improved, with an EASI and DLQI of 56.4 and 21, respectively, despite very low levels of CD19+ B cells ($0.001 \times 10^9/L$).

None of our patients reported side effects from the rituximab therapy.

There is a good rationale for using rituximab to treat patients with severe AE. Patients with the extrinsic form

of the disease have peripheral blood eosinophilia and raised IgE levels. The IgE level correlates with disease severity, and B-lymphocyte stimulation is believed to be driven by interleukin (IL)-4, IL-13 [T helper (Th)2], IL-17 (Th17) and IL-22 (Th22). Rituximab induces depletion of CD20+ B cells, resulting in decreased *de novo* generation of both short-lived and long-lived plasma cells. Rituximab also interrupts the interaction between autoreactive Th cells and antigen-presenting B cells. Rituximab leads to significant reduction of CD40 and CD80 expression on B cells,^{8,9} as well as reduction in CD69, inducible T-cell co-stimulator, human leucocyte antigen-DR, and CD40L expression on CD4+ Th cells^{9,10} thus interfering with the costimulatory signalling regulating T-cell–B-cell interactions. Rituximab increases the release of B-cell activating factor and IL-10 from monocyte-derived macrophages, and directly induces CD4 + CD25 + regulatory T cells, identified by increased mRNA expression of Foxp3, glucocorticoid-induced TNFR-related protein, and cytotoxic T-lymphocyte-associated protein 4.

In the first study assessing the efficacy of rituximab in AE, Simon and colleagues¹ treated six patients with two intravenous infusions of rituximab 1000 mg, 2 weeks apart. All patients showed an improvement of their skin symptoms within 4–8 weeks, and there was a significant reduction in the mean EASI from 29.4 to 8.4. A further two patients² with severe AE have been reported, who were given a lower dose of rituximab (two doses of 500 mg each, 2 weeks apart); one patient improved, with SCORAD (SCORing Atopic Dermatitis) score reducing from 99 to 58 at week 10, but the other experienced a worsening of AE with SCORAD score increasing from 63 to 74 at week 10. A third study³ reported the effects of a rather complex cycled therapy of omalizumab and rituximab. Four patients received omalizumab first, while another two patients received rituximab first, and there was no predetermined repeated order of the cycling of these drugs subsequently. In addition, the patients received an induction cycle of rituximab (four IV infusions, with each infusion administered weekly at a dose of 375 mg/m² of body surface area) and then four of the six patients received a maintenance cycle (two infusions of 1 g each, separated by 2 weeks). No objective assessment of disease severity was reported, but some patients did improve and some had prolonged benefit.

In our study, the three patients reported failed to respond to rituximab, which conflicts with the earlier studies suggesting a benefit of rituximab in AE. We would therefore recommend that there is compelling need for a formal, double-blind, placebo-controlled study.

Learning points

- Some case reports have pointed to a beneficial effect of rituximab in AE.
- Rituximab has not been assessed by formal trials.
- Our case series demonstrates failure to achieve a sustained response in three consecutively treated patients with severe AE.

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