

Lack of effect of ustekinumab in treatment of allergic contact dermatitis

Nannie Bangsgaard, Claus Zachariae, Torkil Menné and Lone Skov

Department of Dermato-allergology, University Hospital of Copenhagen, 2900 Hellerup, Denmark

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Summary

Background. Allergic contact dermatitis is a chronic inflammatory T cell mediated disease that can be recalcitrant to existing treatments. Ustekinumab is a monoclonal antibody blocking IL-12 and IL-23, shown to be effective and safe for patients with psoriasis. Despite both IL-12 and IL-23 involvement in contact allergy, the effect of Ustekinumab on allergic contact dermatitis has not been reported.

Objectives. To evaluate the clinical effect of Ustekinumab in patients with allergic contact dermatitis.

Methods. A retrospective, case cohort study of patients with allergic contact dermatitis treated with Ustekinumab in our department.

Results. Five patients had been treated with Ustekinumab for allergic contact dermatitis, with limited effect.

Conclusion. Our observation suggests that, although theoretically plausible, Ustekinumab does not seem to be a valuable therapeutic approach for chronic allergic contact dermatitis.

Key words: allergic contact dermatitis; treatment; ustekinumab.

Ustekinumab is a fully human monoclonal antibody that inhibits interleukin (IL)-12 and IL-23 activity by binding, with high affinity and specificity, to the p40 subunit of IL-12 and IL-23, preventing these cytokines from binding to IL-12 receptor $\beta 1$ on the surface of immune cells (1). Ustekinumab is expected to be effective in the treatment of diseases in which these cytokines play a role. Ustekinumab has, indeed, proven to be effective in the treatment of psoriasis (2, 3), and has a favourable risk–benefit profile and good tolerability; it has therefore been approved by the European Medicines Agency for the treatment of this disease. Ustekinumab has also shown good treatment results in patients with Crohn's disease (4); however, mixed results have been presented for the treatment of another chronic inflammatory autoimmune disease: multiple sclerosis (5).

Allergic contact dermatitis is a common chronic inflammatory disease with a wide clinical spectrum. At the top end of the spectrum are patients with severe long-standing dermatitis, which severely affects their everyday lives. Traditional treatments are not always clinically effective or well tolerated, so alternative treatments for this group of patients are needed. Allergic contact dermatitis is the clinical manifestation of a contact allergy to small molecular weight chemicals in the environment, and is traditionally believed to be a typical Th1 reaction with the involvement of interferon (IFN)- γ , tumour necrosis factor (TNF)- α , and IL-12 (6–8). Recent reports, however, have suggested that IL-23 and IL-17 are also likely to play a role in contact allergy (9, 10). Therefore, ustekinumab could theoretically be effective in the treatment of allergic contact dermatitis, although this has never been reported. The objective of this study was to evaluate treatment with ustekinumab for allergic contact dermatitis.

Correspondence: Nannie Bangsgaard, Department of Dermato-allergology, University Hospital of Copenhagen, Gentofte, Niels Andersens Vej 65, DK-2900 Hellerup, Denmark. Tel: +45 39777161; Fax: +45 39777615. E-mail: Nanban01@geh.regionh.dk

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Materials and Methods

We included all patients with allergic contact dermatitis treated with ustekinumab in the Department of Dermato-allergology, University Hospital of Copenhagen Gentofte. Patient records were systematically reviewed for lines

Table 1. The 5 patients treated with ustekinumab

Patient, age (years)/sex	Duration (years)	Localization	Allergies	DQLI	Therapy just prior to ustekinumab (washout period)	Injection of ustekinumab
1, 59/male	25	Hands, arms	Nickel, thiuram mix, t-butyl phenol formaldehyde resin, 2-bromo-2-nitropropane-1,3-diol, sorbic acid, methyldibromo glutaronitrile, diphenylguanidine, 1,3-cyclohexyl thiothalamide	9	Ciclosporin (3 weeks)	Week 0 + 4
2, 58/female	31	Hands	Formaldehyde, iodopropynyl butylcarbamate, methyldibromo glutaronitrile, sesquiterpene lactone mix	20	Acitretin (4 weeks)	Week 0 + 4
3, 42/male	36	Hands, arms, legs, face	Colophonium, formaldehyde, methyldibromo glutaronitrile, sesquiterpene lactone mix	7	Prednisolone (3 weeks)	Week 0
4, 64/male	7	Hands, arms, back	Colophonium, epoxy resin, formaldehyde, methyldibromo glutaronitrile	14	Ciclosporin (3 weeks)	Week 0
5, 57/male	11	Hands, arms, feet	Iodopropynyl butylcarbamate, methyldibromo glutaronitrile, sesquiterpene lactone mix	12	UVB (4 weeks)	Week 0 + 4

DQLI, Dermatology Quality of Life Index; UVB, ultraviolet-B.

of treatment, other treatments given, treatment effects, and side effects. In all records, there was information on positive treatment effects, as well as lack of response, assessed by the clinician and the patient through photographic documentation. The intended treatment regimen involved treatment at weeks 0 and 4 and follow-up at week 16, with renewed treatment depending on treatment effect. All 5 patients were reviewed at week 16.

Four of the patients weighed less than 90 kg, and received subcutaneous injections of 45 mg of ustekinumab. Patient no. 4 weighed 100 kg, and received an injection of 90 mg of ustekinumab. The patient-specific treatments with ustekinumab are listed in Table 1. No other topical or systemic treatments were given during the treatment with ustekinumab, and systemic treatment was stopped at least 2–3 weeks prior to treatment with ustekinumab (Table 1).

Results

Five patients with allergic contact dermatitis had been treated with ustekinumab in our department. All 5 patients had longstanding chronic allergic contact dermatitis. They were all polysensitized, with positive patch test reactions to more than three contact allergens.

None of the patients had atopic dermatitis. Table 1 shows the patient characteristics. All patients had involvement of the hands. In patient no. 2, the hands were exclusively affected, whereas the other patients also had involvement of the arms, legs and/or face (Table 1). All patients had been treated with a variety of systemic treatments, including prednisolone, azathioprine, ciclosporin, and mycophenolate mofetil, for long periods of time, with limited improvements and with side effects. The severity

of disease was evident, with Dermatology Quality of Life Index scores ranging from 7 to 20 (Table 1).

A significant clinical improvement was noticed only in patient no. 2. The treatment effect was static for the first 2 months; however, the effect was not strong enough to keep the eczema from flaring during the summer months. A third injection with ustekinumab was given, without any effect. In the other 4 patients, no clinical improvement was evident. In 2 of the patients, the treatment was accompanied by adverse reactions; patient no. 1 developed herpes zoster, and patient no. 4 developed a serious flare of eczema with concomitant infection with *Streptococcus pyogenes* and *Staphylococcus aureus* – he was admitted to hospital and treated appropriately.

In patient no. 3, the lack of response was accompanied by a delayed flare of a reaction to a patch test performed 1 week prior to the start of treatment with ustekinumab. The flare was present at the second visit, 4 weeks after the start of treatment (Fig. 1).

None of the patients developed disease severity worse than that prior to treatment with ustekinumab.

Discussion

Allergic contact dermatitis can be severe and debilitating, with a major impact on the quality of life in affected patients. Our patients had undergone various treatment courses, including prednisolone, azathioprine, ciclosporin, and mycophenolate mofetil, but had never reached stable remission; alternative treatment options were therefore warranted.

Allergic contact dermatitis has been ascribed to the development of allergen-specific CD4⁺ Th1-biased and CD8⁺ effector T cells (11), with involvement of the cytokines IL-12, IFN- γ , and TNF- α (6–8); recent studies

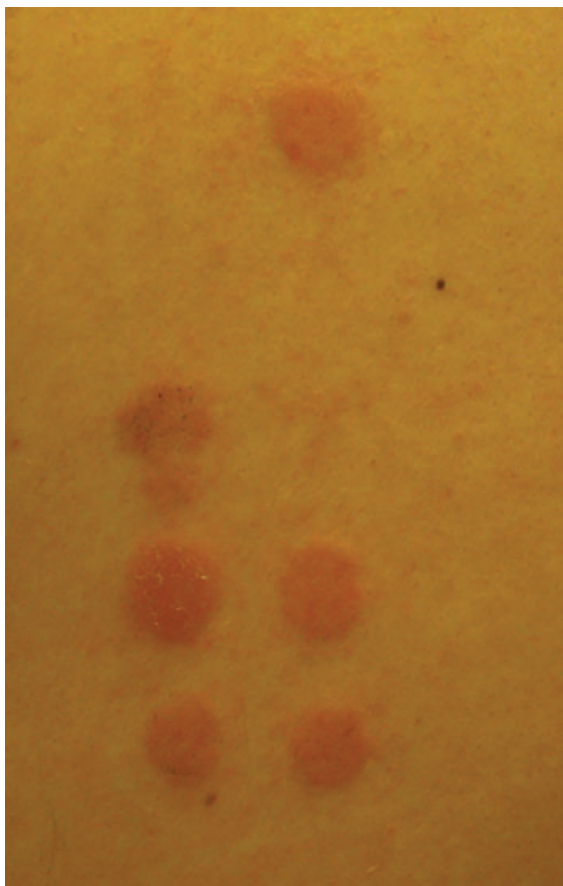


Fig. 1. Delayed flare of patch tests performed prior to ustekinumab treatment in patient no. 3.

have suggested a role for the Th17 cells in the elicitation phase of contact allergy (9, 10). Larsen et al. showed, in a human study, that keratinocytes produced IL-23 in response to nickel stimulation *in vitro*, and IL-17 was

found to be expressed in inflamed skin of nickel-challenged allergic individuals (9). In line with this, Cavani et al. have demonstrated a pathogenic role of IL-17-producing CD4⁺ T cells in allergic contact dermatitis (10). Ustekinumab affects both IL-12 and IL-23, and so, theoretically, the treatment could be effective in treating allergic contact dermatitis. A significant treatment effect was, however, seen in only 1 of our 5 patients, and the effect was not strong enough to keep the eczema from flaring during summer because of a sesquiterpene lactone allergy.

The results should be viewed in light of the limitations of the study: (i) it is a small study, including only 5 patients, and 2 of the patients received one treatment because of side effects; (ii) it is a retrospective study, in which parameters, including washout period, could not be standardized; and (iii) the treatment effect was based on the clinician's assessment as stated in the records, and no objective measure of treatment effect was available.

Some investigators have suggested that allergic contact dermatitis, in developing from an acute to a more chronic form, shifts from a Th1-dominated allergy to a cutaneous cytokine milieu with a Th2 profile (12, 13). A possible explanation for the lack of response in our patients could be the chronic nature of the dermatitis in the patients. In our patients, the allergy and clinical manifestations had persisted for between 7 and 36 years before the onset of treatment with ustekinumab; however, treatment with ustekinumab could not inhibit a flare of a recent patch test in patient no. 3, demonstrating that the treatment was not effective in inhibiting acute eczema.

Up to now, there have been no reports of patients being treated with ustekinumab for allergic contact dermatitis. Our observations suggest that, although its use theoretically plausible, ustekinumab does not seem to be a valuable therapeutic approach for chronic allergic contact dermatitis.

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