Delayed-type hypersensitivity to secukinumab with tolerance to ixekizumab

Clinical communications

Delayed-type hypersensitivity to secukinumab with tolerance to ixekizumab.

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Short title: Delayed hypersensitivity to secukinumab.

Financial disclosure: The authors have no financial relationships relevant to this article to disclose.

Funding source: No funding was secured for this study.

Conflict of interest: The authors have no conflicts of interest relevant to this article to disclose.

Clinical Trial Registration: not applicable.

Clinical implications box: 30

Text word count: 1078

References: 11

Figures: 3

Clinical implications box

Secukinumab, an interleukin-17A inhibitor to treat psoriasis and psoriatic arthritis, may cause delayed-type hypersensitivity. Patch tests are useful to define a safe alternative, the latter still including related interleukin-17 inhibitors.

The interleukin-17 inhibitors secukinumab, ixekizumab and brodalumab are recommended in the treatment of psoriatic arthritis (PsA) when patients fail to respond to the first-line Tumour Necrosis Factor (TNF)α-inhibitors, and they are currently preferred over IL-12/23-inhibitors[1]. Secukinumab, an interleukin (IL)-17A inhibitor, exhibits a good safety profile with mainly mild upper respiratory tract infections, nasopharyngitis and candidiasis being highlighted. Herein we report a patient with a severe injection-site reaction to secukinumab, manifesting as a cutaneous delayed-type hypersensitivity (DTH), and we detail the allergy work-up.

A 51-year-old woman, known with PsA, had received treatment with the TNFα-inhibitor Enbrel® (etanercept; Pfizer, Brussels, Belgium) during 12 years, but, as her PsA became progressively worse, this biological had been recently switched to Cosentyx® (secukinumab; Novartis Pharma, Dublin, Ireland). The patient had tolerated the first administration of the latter drug, that is, 2 subcutaneous (s.c.) injections of 150 mg each in the abdominal skin. However, 1 week later, following the second administration of 2 s.c. injections of 150 mg, again in the abdomen, she developed, approximately 24 hours later, strongly pruritic, erythematous skin lesions on both injection sites. During the following days these lesions became strongly vesicular and purplish, and they rapidly extended over the abdomen and the lower part of the breasts, without involving the back (**Figure 1**). A few satellite lesions were present on thighs and arms. At the emergency department she was treated with peroral methylprednisolone (32 mg daily, in descending doses), antihistamines and topical corticosteroids. This made the eruption settle in 3 weeks leaving only residual skin desquamation. Given the PsA, her treating rheumatologist preferred the use of Taltz® (Eli Lilly, Utrecht, The Netherlands), a related IL-17 inhibitor, instead of switching back to the class of TNFα-inhibitors. Therefore, the patient was addressed to our department for an allergy work-up. Cosentyx® contains, besides secukinumab, also excipients: trehalose dihydrate, L-histidine, L-histidine monohydrochloride, L-methionine, polysorbate 80 and

water. Taltz® contains, besides ixekizumab: sodium citrate, citric acid anhydrous, sodium chloride, water and polysorbate 80, the latter being the common excipient between both drugs. Patch tests were performed according to guidelines of the European Society of Contact Dermatitis[2]. Beside a baseline series also Cosentyx® ('as is', obtained from the patient), Taltz® ('as is', obtained as a drug sample from the rheumatologist) and polysorbate 80 5% in petrolatum (pet.) (Chemotechnique, Vellinge, Sweden) were patch-tested on the upper back and on the site of the abdomen where the skin eruption had been present. Readings on days (D)2, 4 and 7 showed a positive reaction to Cosentyx®, on the back and on the abdomen, whereas the patch test with polysorbate 80 5% pet. and Taltz® remained entirely negative on both locations (**Figures 2-3**). Other positive patch tests (nickel, cobalt, budesonide, hydrocortisone-17-butyrate) were not relevant for the dermatosis. Patch tests with the same Cosentyx® drug ('as is') in 10 non-exposed control patients were negative. A prick-test with Taltz® (ixekizumab) remained negative after 15 min, 2, 4 and 7 days. As no other (sterile) sample of Taltz® was available, and given the high cost price of the drug, no additional intradermal test was performed. Given the positive patch test to Cosentyx®, but negative patch test to Taltz®, we allowed the s.c. administration of the latter drug, albeit in a graded fashion. The initial regimen of a loading dose of 160 mg on D0, followed by 80 mg every 4 weeks, was spread over 2 weeks, that is, with one loading dose of 80 mg on D0 and a second dose of 80 mg on D14, followed, on D30, by the regular scheme of 80 mg every 4 weeks. This was well tolerated, but the PsA was eventually still insufficiently controlled, necessitating again a switch to a TNFα-inhibitor (Cimzia®; certolizumab pegol; UCB, Brussels, Belgium).

Only three poorly documented cases of potentially delayed-type hypersensitivity (DTH) reactions from secukinumab have been reported so far[3-5]. The first case concerned a 52-year-old woman with PsA who, after the fourth administration of the drug, developed

erythematous skin papules three days after the injection. A skin biopsy was compatible with a drug eruption, but no skin tests were performed. However, s.c. reintroduction of secukinumab at full dose led to a relapse of dermatitis two days later. Peigottu et al described another female patient who, three days after the fourth dose of secukinumab, developed a widespread, pruritic and papular skin eruption of the trunk, extermities, face and neck[4]. A skin biopsy showed "focal parakeratosis, exocytosis of lymphocytes, rare apoptotic keratinocytes and rare eosinophils". This "rash", however, was not further characterized and an allergy work-up was not performed either. Finally, Wong *et al*. reported a third female patient with axial spondylarthritis, treated with secukinumab since a few months[5]. She presented with a diffuse, maculopapular rash and mild liver dysfunction, attributed to the drug, which improved spontaneously one month after its withdrawal; the time-lag between the administration of the drug and the appearance of the skin eruption was, however, not stated. Finally, beside a dermatitis within the frame of a DTH, also the occurrence of a so-called "psoriasiform" eczema has been observed in patients treated with secukinumab[6-10]. The latter, however, concerns a peculiar skin condition with clinical features of both psoriasis and dermatitis, often referred to as a 'paradoxical skin reaction', typically occurring with a delay of weeks to months after the initiation of treatment. The mechanism of these 'paradoxical reactions', mostly but not exclusively observed in patients treated with TNFα-inhibitors, is not completely understood; an increase of IFNγ[6] might play a role. Importantly, patch-test investigations are consistently negative in such cases, and a so-called "class effect" is usually present, meaning that a similar 'paradoxical skin eruption' is very likely to occur if a patient is treated with a member of the same drug class (e.g. TNFα-inhibitors). In our patient the 24 hours time delay, the localization of the abdominal dermatitis in relation to the s.c. injections, the eczematous morphology ("vesicular dermatitis"), and the evolution with desquamation of the skin after withdrawal of the drug, all favor a DTH. Furthermore, the positive patch test to

Cosentyx® (secukinumab) confirmed its culpability, whereas a patch test with Taltz® (ixekizumab), a molecule from the same class of biologic agents, remained entirely negative. Although both drugs belong to the same class of biologic agents, IgG1 antibodies (secukinumab) might result in a higher degree of immunogenicity as compared to IgG4 antibodies (ixekizumab)[11]. The present case illustrates that a DTH to the former molecule does not automatically imply that a patient will not tolerate the latter drug.

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Figure legends

Figure 1 (A-B-C-D): Cutaneous delayed-type hypersensitivity following a second, subcutaneous administration of Cosentyx® (secukinumab).

Figure 2. Positive patch test reaction on the back to Cosentyx®(secukinumab)[C], on day 2 following the application of the tests. Negative patch test reactions to polysorbate 80 [P] and Taltz®(ixekizumab)[T].

Figure 3. Positive patch test reaction on the abdomen to Cosentyx®(secukinumab)[C], and negative patch test reaction to Taltz®(ixekizumab)[T].

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