**Successful subcutaneous desensitization to certolizumab**

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Certolizumab pegol (CZP) is a recombinant, humanized antibody Fab' fragment against tumour necrosis factor alpha (TNFα), conjugated to polyethylene glycol (PEG) with an approximate molecular weight of 20.000 g/mol. It has been approved to treat chronic autoimmune and inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis and plaque psoriasis. The recommended dose is 400 mg (2 subcutaneous injections of 200 mg each on one day) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every two weeks [1]. Adverse effects, including paradoxical psoriasiform eruptions or hypocomplementemic urticaria-vasculitis have been reported [2,3]. Besides, hypersensitivity reactions after CZP administration have been described, both to the anti-TNF portion of the antibody and to the PEG component [4, 5].

We present a 30-year-old woman with medical history of spondyloarthritis treated for two years with CZP, until its suspension due to severe pain at the injection site. A year later, CZP had to be reintroduced, because of ineffective treatment with golimumab. Within 60-90 minutes of the first subcutaneous injection, the patient developed the skin lesions the first subcutaneous injection of 400mg of CZP, she developed pruritic, erythematous papules on the neck, trunk and extremities. A 4-day treatment with oral methylprednisolone 40 mg and ebastine 10 mg was indicated with complete resolution of the lesions without residual hyperpigmentation or desquamation. Two weeks later, she received again 400 mg of subcutaneous CZP, presenting a similar reaction; so, the treatment was interrupted and the



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patient was referred to the Allergy Service.

After obtaining written informed consent, the patient underwent skin prick test (SPT) with certolizumab (200 mg/ml) and intradermal test (IDT) at 2, 20 and 200 mg/ml. A positive result (5-mm wheal) was obtained at 20 minutes reading of the 200 mg/ml IDT. Four 4 hours after the 200 mg/ml IDT immediate positive results, the patient develop several slightly pruritic erythematous papules on the right forearm (where the IDT was performed). These lesions resolved within 24 hours after application of topical corticosteroid. These concentrations were found to be non-irritating in four healthy control subjects. Further, SPTs with alginate antacid Gaviscon strawberry flavour chewable tablets (containing PEG 20.000) were performed at 0.25, 2.5, 25 and 250mg/ml with negative results, ruling out allergy to the excipient. Based on the results, the avoidance of TNFα inhibitors drugs was recommended.

After a 13 months period of treatment with secukinumab (IgG1/κ monoclonal antibody), which proved to be ineffective; the patient was referred again to the Allergy Service to consider the possibility of prescribing etanercept, another TNFα inhibitor. SPT (50 mg/ml) and IDTs (0.5 mg/ml and 5 mg/ml) to etanercept yielded negative results, thus a drug challenge was performed with negative result (cumulative dose of 50 mg). Unfortunately, this treatment, as well as the subsequent ixekizumab (anti IL-17A antibody) were unsuccessful, so they were discontinued and the patient was referred to the Allergy Department to perform a desensitization procedure wiht certolizumab.

Pretreatment with cetirizine 10mg and ranitidine 50 mg was administered 30 min. before the procedure. CZP was administered in a 3-solution, 8-step regimen with an initial subcutaneous dose of 2 mg that was gradually increased every 30 minutes until a cumulative dose of 400 mg was reached (Table 1). Cetirizine 10mg and famotidine 40 mg was prescribed daily for 3 days after the procedure. No incidents were reported. An identical procedure was carried out 2 weeks later with no adverse reactions. For the third dose, as the interval of 14 days did not go over 2 half-lives of the medication, full dose of 400 mg was administered divided between



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both arms with no adverse reactions. The next dose was 200 mg, which the patient received in a single dose in a pre-filled syringe with good tolerance (for 12 weeks) until its withdrawal due to loss of efficacy.

The positive skin test to CZP proves that an immune mechanism could be involved in the reaction presented by our patient. Among the TNFα inhibitors the highest number of hypersensitivity reactions have been described with infliximab [6], but there are hardly any data in the literature on cross-reactivity between drugs in this group. Reactions to infliximab and subsequent tolerance to adalimumab have been reported [7,8]. However, there are no cross-reactivity studies between certolizumab Pegol and Etarnercept. For this reason, in our case, after confirming hypersensitivity to certolizumab, an allergy study to etanercept was carried out, verifying its tolerance.

Desensitization procedures allow allergic patients to receive the best treatment option for their disease. Cases series of subcutaneous desensitization with biolologic drugs have been described. Regarding TNFα inhibitors desensitization protocols to adalimumab and etanercept are also available, however, to date, no desensitization protocols to golimumab or certolizumab have been published [9].

To the best of our knowledge, we describe the first desensitization protocol to certolizumab, in a case of confirmed allergy to certolizumab with tolerance to another TNFα inhibitor, etanercept.

**Clinical Implications box**

Hypersensitivity reactions after certolizumab pegol (CZP) administration have been described. We report the first successful case subcutaneous desensitization to certolizumab. Clinicians should be aware of hypersensitivity reactions to TNFα-inhibitor considering the increasingly widespread use of these drugs.





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**Conflict of interest**

R. Mielgo has received fees for her collaboration as a speaker and/or consultant in advisory boards, research projects, and congresses and for course attendance for Novartis, Sanofi, GSK, Astra, ALK Abello, Allergy Therapeutics, Organon, LETI, Shire, Behring, FAES, and Chiesi, all outside the current work.

Other authors declare that they have no relevant conflicts of interest.

The patient written consent to publication have been obtained.

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**Table 1**. Desensitization protocol to certolizumab.

| DESENSITIZATION | | | | | | |
|---|---|---|---|---|---|---|
| **Step** | **Time (minutes)** | **Concentration (mg/ml)** | **Volume (ml)** | **Dose administered with this step (mg)** | **Cumulative Dose (mg)** | **Comment** |
| **1** | 0 | 2 | 1 | 2 | 2 | |
| **2** | 30 | 20 | 0.2 | 4 | 6 | |
| **3** | 60 | 20 | 0.4 | 8 | 14 | |
| **4** | 90 | 20 | 0.8 | 16 | 30 | |
| **5** | 120 | 200 | 0.16 | 32 | 62 | |
| **6** | 150 | 200 | 0.32 | 64 | 126 | |
| **7** | 180 | 200 | 0.64 | 128 | 254 | |
| **8** | 210 | 200 | 0.73 | 146 | 400 | |
| **Observation :** 60 minutes | | | | | | |
| **Total time:** 270 minutes | | | | | | |





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