

Table 2. Clarithromycin Oral Desensitization Protocol^a

Dose no.	Concentration, mg/mL	Dose	
		mL	mg
1	0.025	1.25	0.03
2	0.025	2.5	0.06
3	0.025	5	0.125
4	0.25	1	0.25
5	0.25	2	0.5
6	0.25	4	1
7	2.5	0.8	2
8	2.5	1.6	4
9	2.5	3.2	8
10	2.5	6.4	16
11	25	1.3	32
12	25	2.5	64
13	25	5	125
14	25	10	250
Cumulative dose			503

^a Serial 10-fold dilutions of a clarithromycin suspension of 125 mg/5 mL (25 mg/mL) were performed to make clarithromycin solutions at 2.5, 0.25, and 0.025 mg/mL. Each dose was administered in 15-minute intervals.

negative after desensitization to clarithromycin further supports immunologic cross-reactivity.

Drug desensitization is a procedure used to induce temporary tolerance to a drug. Although the mechanism of drug desensitization is not clear, reversal of positive to negative SPT results has been demonstrated in many patients. We describe a patient with a confirmed allergy to azithromycin who underwent successful oral desensitization to clarithromycin using a protocol based on penicillin desensitization. Holmes et al⁵ reported their experience of clarithromycin desensitization; however, the patient's allergy was based on history alone and was not verified with SPT. The present patient had a history consistent with IgE-mediated hypersensitivity to macrolides confirmed with positive SPT results. In addition, after desensitization, the positive SPT reactions to clarithromycin and azithromycin reverted to negative after 6 weeks. Although drug desensitizations are often performed in the inpatient setting, data from Castells et al⁶ demonstrated the overall safety of desensitizations performed in an outpatient setting. Because allergists' offices are equipped to treat anaphylactic reactions due to immunotherapy, outpatient drug desensitizations can be performed if appropriate.

In macrolide-allergic individuals who require macrolide therapy, drug desensitization seems to be an effective option. The frequency of clinical and immunologic cross-reactivity among macrolides as seen in this patient deserves further study.

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SEVERE CUTANEOUS REACTION AND FEVER DUE TO ADALIMUMAB

Adalimumab is a 148-kDa, recombinant, human, high-affinity IgG1 monoclonal antibody against tumor necrosis factor α (TNF- α) that prevents cytokine binding to its receptor and lysing cells that express TNF- α on their surface.¹ The most common adverse reactions with adalimumab are injection site reactions (eg, erythema, pruritus, and pain or swelling around the site of injection), which are usually described as mild and generally do not require discontinuation of drug use.^{1–5}

A 58-year-old woman with severe psoriasis began treatment with subcutaneous adalimumab (40 mg) in April 2009. The first dose was well tolerated, and the second dose was administered 1 week later. Thirteen days after this dose the patient developed a morbilliform exanthema that affected all the skin, even the palms, soles, and scalp, with a burning sensation, malaise, headache, and fever (temperatures of 38°C–39°C). Infiltration was evident at injection sites. Physical examination revealed neither mucosal involvement nor adenopathies, and the Nikolsky sign was negative. Chest radiography results were normal, and laboratory values (eg, hemogram, erythrocyte sedimentation rate, biochemistry, urinalysis, and antinuclear, extractable nuclear antigen, and anti-DNA antibody titers) were within their respective reference ranges. Skin biopsy specimens were obtained from the involved skin of the thigh, showing exocytosis of lymphocytes, vacuolar degeneration of the basal layer, and slight necrotic keratinocytes in the epidermis spongiosis and a moderate-intense lymphocytic perivascular infiltrate in the dermis (suggesting a drug skin reaction). The patient was treated with systemic corticosteroids and antihistamines for 4 weeks. The fever disappeared within 4 days, and skin lesions evolved to superficial desquamation and faded within 1 month.

We performed cutaneous tests with adalimumab and other anti-TNF- α drugs (infliximab and etanercept) 4 months after the reaction following the same methods as in previous reports^{6,7} (Table 1). Seven days after having performed intradermal tests with adalimumab, the patient presented with a local reaction (11 × 6 cm) on the forearm around the injection areas, with erythema and pruritus lasting for 2 weeks. The skin biopsy specimen of the area with this reaction showed the same findings as a previous specimen taken

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Table 1. Cutaneous Tests With Adalimumab and Other Anti-Tumor Necrosis Factor α Drugs

Drug	Patch test (48–96 h)		Prick test (15 min)		Intradermal test (15 min, 24–48 h)	
	mg/mL	Result	mg/mL	Results	mg/mL	Results
Etanercept	25	Negative	25	Negative	2.5/25	Negative ^a /negative ^a
Infliximab	10	Negative	10	Negative	1/10	Negative ^a /negative ^a
Adalimumab	50	Negative	50	Negative	5/50	Negative ^b /negative ^b and positive on day 7 ^b

^a Negative results also on day 7.

^b Intradermal test results in 10 control patients were negative.

during the acute phase of the reaction. The preservatives used in adalimumab preparation have been tolerated by the patient. The results of skin prick tests with commercial extracts of latex and specific IgE against latex were negative. Later, the patient was treated with etanercept, with no reactions.

Hypersensitivity reactions have been reported rarely after adalimumab administration.^{1–5} We describe a case of severe generalized exanthema and fever related to the administration of adalimumab, an event not previously reported in the medical literature. The results of the biopsy and intradermal tests support the diagnosis, and it is interesting to note the usefulness of intradermal tests with positive results at day 7 and a biopsy specimen identical to the specimen taken during the acute phase of the reaction. Only 2 cases of generalized rash due to adalimumab have been reported to date. In both cases, the rash appeared 7 days after the first injection of adalimumab, involved the thorax and limbs, and improved in a few days after adalimumab therapy was discontinued. The biopsy specimen showed a periadnexal and medial superficial perivascular dermatitis.⁸ Also noteworthy in our case are the presence of fever and the affection of all the skin, which improved within 1 month with evident desquamation.

The mechanisms underlying this undesirable effect have yet to be elucidated. Campi et al³ suggest 2 hypotheses to explain hypersensitivity reactions to TNF- α antagonists: (1) these molecules are recognized as foreign antigens and symptoms are due to the appearance of antibodies or cells directed to these antigens and (2) these patients are prone to these diseases and TNF- α antagonists induce a cytokine imbalance that favors their appearance; in particular, there would be a switch to a T_H2 response.³ Previous studies in cases of injection site reactions due to adalimumab propose both an immediate reaction, possibly IgE mediated, and a cell-mediated reaction regarding the results of prick and intradermal tests.⁶ Paltiel et al⁷ describe 2 patients with a history of worsening injection site reactions to adalimumab. Findings from skin testing, biopsy, and a histamine release assay suggest a type I hypersensitivity reaction. In our case, taking into account the delayed beginning of the clinical reaction and the cutaneous test results, a cell-mediated reaction is probable, but more than 1 immune mechanism could be involved.

In summary, we describe a patient with a generalized exanthema and fever due to adalimumab, an event not previously reported in the literature, to our knowledge. Intradermal tests have been useful for diagnosis, showing a delayed positive result with a biopsy specimen identical to the specimen taken during the acute phase of the reaction. Etanercept was an alternative therapeutic option in our case.

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EXPERT PANEL REPORT ON ASTHMA: SOME CONCERNS

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3),¹ published by the National Heart, Lung, and Blood Institute, is the most authoritative source for information on the diagnosis and management of asthma in the United States. The report offers guidance on many aspects of care. Two elements of particular importance are a clear definition of asthma control and specific recommendations for stepwise treatment.

However, the document has several flaws. Most serious is that the report does not display a diary, although it mentions one on

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