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Letter to the Editor

Report of oral clarithromycin desensitization

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Antibiotic hypersensitivity can lead to significant morbidity, mortality and suboptimal treatment options. Rapid desensitization induces temporary immunological tolerance in a host with type 1 hypersensitivity reaction. We report a case of oral desensitization to clarithromycin. To our knowledge, this is the first protocol published for desensitization to macrolides.

A 68-year-old female with a history of giant cell arteritis treated with oral corticosteroids and steroid-induced diabetes presented with small nodules and ulcers on the pre-tibial surface of her legs. Despite multiple courses of oral and parenteral antibiotics for cellulitis, the lesions continued to develop. Skin biopsy of the lesion demonstrated suppurative granuloma formation with acid-fast bacilli on microscopy. The patient reported anaphylaxis to erythromycin 20 years previously and bronchospasm to roxithromycin 5 years previously. She was commenced on rifampicin and moxifloxacin for mycobacterial skin infection, and *Mycobacterium chelonae* was subsequently cultured. There was further clinical deterioration and her treatment was changed to doxycycline, intravenous amikacin and intravenous imipenem. Antibiotic susceptibility testing subsequently revealed the isolate was resistant to imipenem, so this was substituted with linezolid. Unfortunately, this was discontinued due to diarrhoea. Intravenous amikacin was not desired as a long-term treatment option due to risk of renal and ototoxicity.

Clarithromycin is the treatment of choice for *M. chelonae* infection [1], but the patient had a strong history of type 1 hypersensitivity with macrolide antibiotics. No published protocol for rapid drug desensitization was available for clarithromycin, so a clarithromycin desensitization protocol was developed (Table 1). The protocol was administered in an intensive care unit with careful observation on a medical ward for 36 h afterwards. No adverse reaction was noted.

The patient continued doxycycline and clarithromycin for a total of 18 months. There was an excellent clinical response and no adverse drug reactions were recorded.

Serious adverse drug reactions occur in 6.7% of hospitalized patients and rank from the fourth to sixth leading cause of death in these patients [2]. Since 1998 there has been a 2.6-fold increase in serious adverse drug reactions reported to the US Food and Drug Administration [3]. Type 1 (immediate) hypersensitivity reactions occur within minutes to hours of drug administration due to release of vasoactive substances from mast cells and basophils (often IgE-mediated). Clinical manifestations range from urticaria to life-threatening angio-oedema and anaphylaxis.

Desensitization procedures were first developed in the 1960s [4]. Rapid desensitization involves incremental exposure to drug antigens at increasing concentrations leading to a therapeutic dose. Antigen-specific mast cell desensitization is thought to be the underlying mechanism for drug desensitization [5]. By inducing temporary clinical and immunological tolerance, patients are able to receive optimal treatment while avoiding or minimizing anaphylaxis and anaphylactoid reactions. Tolerance is maintained only if drug antigens are administered at regular intervals, and repeated desensitizations can also be given [6]. Desensitization protocols have been developed for a variety of drugs including penicillins, cephalosporins, vancomycin, sulfonamides, rifampicin, nonsteroidal anti-inflammatory drugs and chemotherapeutic agents (taxanes, platins).

As specific skin prick testing to clarithromycin was not performed in our patient, we cannot be certain that an immediate hypersensitivity reaction would have occurred. However, given her previous immediate hypersensitivity reactions to other 14-membered macrolides erythromycin and roxithromycin, we felt that desensitization to clarithromycin was warranted. Skin prick testing has been well described for penicillins and cephalosporins, and is considered accurate for diagnosing penicillin allergy, as antigenic determinants have been well characterized [7]. Cross-sensitivity within the same antibiotic class is variable, however. There is little information available for diagnostic tests for macrolide allergy, as immediate hypersensitivity reactions are uncommon [8]. A patient in the literature with roxithromycin immediate hypersensitivity demonstrated positive skin prick testing to erythromycin and clarithromycin [9]. These macrolides have a similar chemical structure comprising a 14-membered carbon ring, compared with 15-membered macrolides (azithromycin) and 16-membered macrolides (spiramycin).

Use of first-line antibiotics in certain conditions have been shown to have greater efficacy, for example trimethoprim + sulfamethoxazole for *Pneumocystis jiroveci* pneumonia [10, 11] or penicillin for syphilis, especially in

Table 1

Oral clarithromycin desensitization protocol

Step (15-min intervals)	Clarithromycin suspension (mg ml^{-1})	Volume (ml)	Dose (mg)	Cumulative dose (mg)
1	0.05	0.1	0.005	0.0
2	0.05	0.2	0.01	0.0
3	0.05	0.4	0.02	0.0
4	0.05	1	0.05	0.1
5	0.05	2	0.1	0.2
6	0.05	4	0.2	0.4
7	0.5	0.8	0.4	0.8
8	0.5	1.6	0.8	1.6
9	0.5	3.2	1.6	3.2
10	0.5	6.4	3.2	6.4
11	5	1.2	6	12.4
12	5	2.4	12	24.4
13	5	4.8	24	48.4
14	50	1	50	98.4
15	50	2	100	198.4
16	50	4	200	398.4
17	50	8	400	798.4
18	50	10	500	1298.4

HIV-infected individuals [12]. Macrolide antibiotics have an important role in the treatment of nontuberculous mycobacterial infections [13]. In our case report clarithromycin was a desirable treatment option, and rapid oral desensitization to clarithromycin was successful with no adverse events reported. We believe this is the first published protocol for desensitization to macrolide antibiotics and anticipate that its use can be extended to other centres worldwide.

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