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### Hypersensitivity to Imatinib: Successful Desensitization in a Skin Test–Positive Patient

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Imatinib mesylate is a tyrosine kinase inhibitor used to treat chronic myelogenous leukemia, acute lymphocytic leukemia, gastrointestinal stromal tumors, systemic mastocytosis, and myelodysplastic syndromes. Cutaneous adverse reactions are one of the most common adverse effects. Their frequency is reported to range from 7% to 88.9% depending on the series [1]. Most reactions are mild and dose-dependent and are attributed to a direct pharmacologic effect of the drug (ie, inhibition of the physiologic function of cutaneous protein kinases). They generally occur at a dosage of 400-600 mg daily [2]. The most common cutaneous reaction is pruritic maculopapular erythematous rash, which often arises after several weeks of therapy. In the case of severe maculopapular rash, it is necessary to suspend imatinib and administer corticosteroids and antihistamines. When imatinib is readministered, it is mandatory to start at a lower dose and coadminister oral corticosteroids, which can gradually be tapered [3,4]. Critical cutaneous adverse events that are resistant to supportive measures warrant suspension of imatinib therapy. However, the frequency of such events is small (<1%) [5].

Hypersensitivity reactions to imatinib include swelling, urticaria, acute generalized exanthematous pustulosis, exfoliative dermatitis, and Stevens-Johnson syndrome [2]. In the case of severe adverse reactions, the drug must be definitively discontinued. In the absence of an equivalent therapeutic option for cutaneous rashes, oral desensitization to imatinib can be attempted. A limited number of cases have been reported [6-8].

We describe the case of an 85-year-old man who developed a hypersensitivity reaction to imatinib and was successfully treated with desensitization.

The patient was receiving imatinib 400 mg daily for chronic myelogenous leukemia. After 8 weeks of therapy, he progressively developed a diffuse pruritic erythematous rash that persisted even after treatment with prednisone 25 mg daily. Imatinib was discontinued, with complete remission of symptoms. Nine days later, imatinib was restarted at a lower

dosage (200 mg daily) in combination with cetirizine 10 mg daily. Two days later, the erythematous rash reappeared, and the patient was prescribed prednisone, although the cutaneous manifestation persisted. Imatinib was finally discontinued, and the patient's condition resolved.

We performed skin testing to investigate hypersensitivity to imatinib. A 100-mg capsule was diluted in sterile water, and a skin prick test with 0.1 mg/mL was performed, as was an intradermal test with 0.001 mg/dL: both tests were positive at the immediate reading, with a wheal measuring 8 mm in diameter, erythema, and pruritus.

Since the patient needed to continue treatment with imatinib in the absence of an equivalent therapeutic option, he underwent desensitization based on a slow protocol (Table) [7]. The solutions at different concentrations of imatinib were prepared by the Department of Pharmacy. Following this protocol, the patient was expected to reach the cumulative dose of 400 mg in 24 days.

At day 8, about 6 hours after administration, the patient developed intense pruritus on his arms and legs. He was treated with oral antihistamine, and the protocol was not modified. The full dose of 400 mg was reached on day 24, and the patient continued therapy. A month later, he presented with mild pruritus; therefore, imatinib was reduced to 300 mg/d, with total remission of pruritus, and therapy was continued.

Six months after the desensitization protocol, the skin test was repeated. The result of a skin prick test with imatinib 0.1 mg/mL was negative. Similarly, the results of an intradermal test with 0.001 and 0.01 mg/mL were negative, while that of an intradermal test with 0.1 mg/mL was positive, with a wheal measuring 8 mm in diameter and erythema.

The patient provided his signed informed consent for the skin tests and desensitization procedure.

We present the case of a patient with chronic myelogenous leukemia who developed a cutaneous rash after 8 weeks of treatment with imatinib. The reaction was resistant to a reduced dose of imatinib and treatment with oral corticosteroids. Despite the fact that onset was delayed, the positive skin test result suggested the involvement of an IgE-mediated hypersensitivity mechanism. The patient underwent desensitization and was able to tolerate a dose that was appropriate for his disease, with reduced skin test reactivity.

Hypersensitivity to imatinib has been poorly investigated, and very few cases of patients who underwent skin testing have been reported. Nelson et al [6] described a series of 10 patients with adverse cutaneous reactions to imatinib that were treated with rapid desensitization. Only 1 patient who developed an urticarial eruption had a positive result in skin testing. Di Paolo et al [7] reported the case of a patient with a negative skin test result who was successfully treated with a slow desensitization protocol after a rapid one was unsuccessful [7]. Skin testing for imatinib needs to be validated in a larger number of treated patients who do not experience a skin reaction.

In the case we present, the skin test was performed as previously reported [6,7]. As far as we know, this is the first description of reduced skin test reactivity after desensitization, since the prick test was negative, and the intradermal reaction was positive at 100 times the concentration after treatment.

Table. Imatinib Desensitization Protocol<sup>a</sup>

Day	Concentration	Volume	Cumulative Dose, mg
1	10 ng/mL	1, 2, 4 mL	0.77
	100 ng/mL	1, 2, 4 mL	
	1 µg/mL	1, 2, 4 mL	
	10 µg/mL	1, 2, 4 mL	
	100 µg/mL	1, 2, 4 mL	
2	1 mg/mL	1, 2, 4 mL	7
3, 4, 5	10 mg/mL	1, 2, 4 mL	70
6, 7, 8	100 mg cap	1 cap	100
9	100 mg cap	1 cap	107
	1 mg/mL	1, 2, 4 mL	
10, 11, 12	100 mg cap	1 cap	170
	10 mg/mL	1, 2, 4 mL	
13, 14, 15	100 mg cap	2 caps	200
16	100 mg cap	2 caps	270
	10 mg/mL	1, 2, 4 mL	
17-22	100 mg cap	3 caps	300
23	100 mg cap	3 caps	370
	10 mg/mL	1, 2, 4 mL	
24	100 mg cap	4 caps	400

<sup>a</sup>Increasing doses on the same day were administered every 20 minutes.

Desensitization is a therapeutic option for hypersensitivity reaction to first-line chemotherapy drugs, which are irreplaceable or more effective than alternatives. It is contraindicated in cases of severe, life-threatening immunocytotoxic reactions, vasculitis, or bullous skin diseases such as Stevens-Johnson syndrome/toxic epidermal necrolysis and drug hypersensitivity syndrome [9]. Very few cases of desensitization to imatinib have been reported, and both rapid protocols [6] and slow ones [7,8] have been applied. The literature suggests that slower protocols tend to be more effective for delayed reactions [10]. Considering the delayed presentation of the diffuse erythematous rash and the positive skin test results, we chose a slow protocol starting at a very low dosage.

Cutaneous rashes during imatinib therapy are very common. Most are due to pharmacological effects and are dose-dependent. The case we report suggests that some of them, particularly the most severe and those not responsive to dose tapering, may be due to hypersensitivity reactions. In this case, desensitization can be an effective therapeutic option to prevent treatment from having to be discontinued.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### Previous Presentation

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