Successful Desensitization to Oral Dasatinib in Immediate Hypersensitivity Reaction

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Chronic myeloid leukemia (CML) is caused by abnormal myeloid cell proliferation in bone marrow, resulting in the BCR-ABL fusion gene and a constitutively active tyrosine kinase [1]. Recent progress in CML treatment has led to the introduction of targeted tyrosine kinase inhibitors (TKIs) for long-term remission [1]. Imatinib, the first approved TKI for CML, is now joined by second-generation drugs, such as dasatinib, bosutinib, and nilotinib, as well as the third-generation ponatinib. While safety profiles vary, all TKIs are associated with common adverse reactions (ARs), such as nausea, myopathy, rash, diarrhea, and fatigue, as well as late-onset hematologic responses, such as myelosuppression.

Imatinib triggers muscle pain, headaches, and edema; dasatinib is linked to pleural effusion and pulmonary hypertension; bosutinib can impair liver function and cause rash; nilotinib is associated with cardiovascular abnormalities, QT interval prolongation, and hyperglycemia; and ponatinib poses risks for liver disorders and pancreatitis [2,3]. Consequently, close monitoring of patients' hematologic, metabolic, and cardiovascular profiles is imperative for effective disease management.

Desensitization is vital for IgE-mediated hypersensitivity reactions necessitating discontinuation of therapy when no equivalent treatments are available [4]. Here, we present the case of a patient with CML who experienced an immediate hypersensitivity reaction to dasatinib and successfully underwent desensitization to dasatinib.

The patient was a 53-year-old woman with no known drug allergy and a history of ischemic heart disease. She was diagnosed with CML in December 2019 and started first-line imatinib at 400 mg daily.

She tolerated imatinib well, with a good hematologic response, having reached a state of major molecular response [1]. During the first month, the only AR was eyelid edema, which improved with diuretics, until she reported that the skin on her hands had become increasingly fragile and prone to erosion. A dermatologist diagnosed the lesion by means of a skin biopsy, which was consistent with imatinib-induced pseudoporphyria, leading to discontinuation of treatment.

CML subsequently worsened, and the patient started treatment with dasatinib 100 mg every 24 hours. Less than 2 hours after the first dose, a nonpruritic maculopapular exanthema appeared on her arms. After the second dose of dasatinib, the exanthema became generalized and was accompanied by severe headache; therefore, the patient called the clinical team from home. Her vital signs remained unaltered. Neither tryptase nor IL-6 was measured. The symptoms improved gradually with oral antihistamines and corticosteroids over 3 days prescribed on an outpatient basis. Treatment was suspended, and the patient was referred to the allergy unit. A skin prick test (SPT) and basophil activation test (BAT) were performed with dasatinib and bosutinib, as a potential alternative.

In the SPT, a 50-mg dasatinib and a 500-mg bosutinib capsule were diluted with sterile water. For BAT, 10 mL of heparinized blood was obtained and taken immediately to the laboratory, where it was analyzed using the Flow2CAST kit. Basophils were identified by flow cytometry (FACS-Canto-II, BD-Biosciences). A minimum of 800 basophils was gated, and expression of $CD63^+$ and $CD203c^+CD63^+$ as markers of activation was assessed. A stimulation index (SI) above 2 was considered positive.

The result of the SPT with dasatinib was negative, and the BAT result was positive at all concentrations tested (SI<2) (see Figure and Figure S1); for bosutinib, all test results were negative. Considering these findings and the need to continue treatment of the patient's CML, it was decided to initiate bosutinib 500 mg/24 h and to monitor the patient closely for a response. Unfortunately, the patient reported nausea, abdominal pain, diarrhea, and headache. These symptoms gradually became incapacitating over the following days, with both regular and reduced doses of bosutinib 200 mg, which eventually led to discontinuation. The symptoms resolved completely after 24 hours.

Since the patient needed to continue TKI treatment, we proposed a rapid dasatinib desensitization protocol (Table S1), aiming for a 100-mg dose, which is the standard approach for effective treatment of CML.

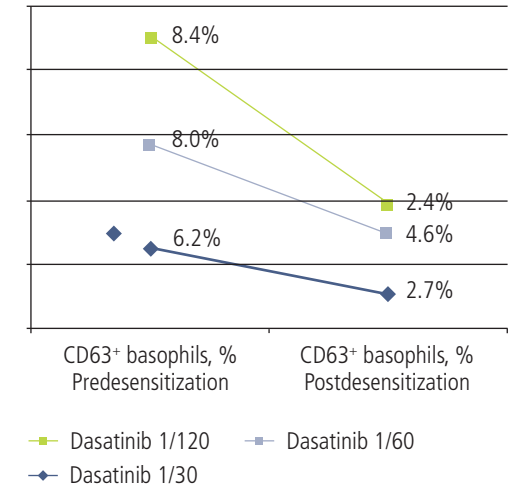
The dasatinib desensitization protocol was successful, and the patient continues to tolerate dasatinib 100 mg/24 h.

After more than a year of daily dasatinib, the BAT result became negative, indicating reduced basophil reactivity (Figure).

The patient provided her written informed consent for the SPT and desensitization procedure, as well as for the publication of this report.

Treatment of CML poses significant challenges, with inherent TKI-induced toxicity, and requires the contribution of a multidisciplinary team to assess drug safety and explore alternative treatments. Cutaneous effects have been reported, especially with imatinib, including facial edema, which affects most patients, pruritic rash that typically develops at 9 weeks of treatment and can in some cases be severe, and other inflammatory eruptions, which have also been observed with

A



B

Table.

	Before desensitization		After desensitization	
	Gated basophils	$CD63^+$ basophils, %	Gated basophils	$CD63^+$ basophils, %
C (–) (SB)	1817	1.0	1076	1.0
C (+) (anti-FcεRI)	952	15.3	1000	59.0
Dasatinib 1/30	1136	6.2	1026	2.7
Dasatinib 1/60	1129	8.0	1036	4.6
Dasatinib 1/120	1116	8.4	1038	2.4

Abbreviations: C (–), negative control; SB, buffer; C (+), positive control.

Figure. Basophil activation test with dasatinib. A, $CD63^+$ basophils (%) before and after desensitization; B, Positive and negative controls of the basophil activation test and number of gated basophils for each dasatinib dilution before and after desensitization.

dasatinib [2,5]. However, the underlying mechanisms have not been studied.

In this case, the patient had imatinib-associated pseudoporphyria, a rarely reported AR. Given the absence of cases of skin fragility in their report, Martínez-Mera et al [6] recommended switching to dasatinib or nilotinib for imatinib-associated pseudoporphyria. Dasatinib was chosen here owing to cardiovascular ARs linked to nilotinib (contraindicated in patients with a history of ischemic heart disease) [3].

Desensitization protocols for imatinib have been described. Nelson et al [7] conducted a 4-hour oral desensitization protocol for 10 patients with imatinib-induced rash, succeeding in 8 cases. Klaewsongkram et al [8] outlined a slow desensitization protocol for severe nonimmediate skin reactions, resulting in reduced $CD5^+$, $CD25^+$, and $CD135^+$ T cells.

Karaatmaca et al [9] reported 2 pediatric cases of delayed hypersensitivity to dasatinib that were successfully treated with a 1-day rapid desensitization protocol [9]. However, in many cases, allergology studies were not conducted or yielded negative results.

We present a case of successful desensitization to dasatinib in a patient with immediate hypersensitivity. The success of the protocol was confirmed by a positive BAT result. The patient could not tolerate other TKIs. While the literature hints at TKI cross-reactivity, the positive BAT result for dasatinib and the negative result for bosutinib suggest otherwise in the present case. Notably, more than 1 year after successful desensitization, the patient continued to tolerate daily dasatinib, and the BAT result turned negative.

In conclusion, desensitization with older-generation TKIs such as imatinib has shown promising results, although few cases have been published [7,10]. While a literature search revealed a dasatinib desensitization protocol for 2 pediatric patients with delayed reactions and negative allergy test results [9], this report highlights the first successful dasatinib desensitization protocol in an adult patient with immediate hypersensitivity reaction confirmed by a positive BAT and no viable alternative TKIs owing to severe adverse effects.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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