

Successful Oral Dasatinib Desensitization in Immediate Hypersensitivity

Ruano-Zaragoza M^{*1,2,3}, Torrent-Rodríguez A^{*4}, Araujo-Sanchez G^{1,2,3}, Ribó P¹, Loli-Ausejo D¹, Solis K¹, Sánchez-Fernández MC¹, Bolaños J⁵, Bolós U⁵, López C⁴, Ruiz S⁴, Pascal M^{3,5}, Bartra J^{1,2,3}, Muñoz-Cano R^{1,2,3}

¹Allergy Department, Hospital Clinic, Barcelona, Spain

²Clinical & Experimental Respiratory Immunoallergy, Institut Investigacions Biomediques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

³RETIC Asma, Reacciones Adversas y Alergia (ARADyAL) and RICORS Red de Enfermedades Inflamatorias (REI), Madrid, Spain

⁴Pharmacy Department, Hospital Clinic, Barcelona, Spain

⁵Immunology Department, Centre de Diagnòstic Biomèdic (CDB), Hospital Clínic de Barcelona, Barcelona, Spain

*These authors contributed equally to this work and should be considered co-first authors.

Corresponding Author:

Rosa Muñoz-Cano

Allergy Department, Hospital Clinic, Barcelona, Spain

Villarroel, 170. 08036 Barcelona

E-mail: rmunoz@clinic.cat

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0985

Key words: Oral desensitization. Dasatinib, drug allergy, tyrosine kinase inhibitors, basophil activation test.

Palabras clave: Desensibilización oral. Dasatinib. Alergia a fármacos. Inhibidores de tirosin-kinasa. Test de activación de basófilos.

Chronic myeloid leukemia (CML) results from abnormal myeloid cell proliferation in the bone marrow, resulting in the BCR-ABL fusion gene and a constitutively active tyrosine kinase[1]. Recent progress in CML treatment has introduced targeted tyrosine kinase inhibitors (TKI) for long-term remission[1]. Imatinib, the first approved TKI for CML, is now joined by second-generation drugs like dasatinib, bosutinib, and nilotinib, as well as third-generation ponatinib. While safety profiles vary, all TKIs are associated with common adverse reactions (AR), such as nausea, myopathy, rash, diarrhea, and fatigue, as well as late-onset hematologic responses like 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 issues, 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 therapy discontinuation when no equivalent treatments are available[4]. Here, we present a case of a CML patient with an immediate hypersensitivity reaction to dasatinib who successfully underwent dasatinib desensitization.

Case presentation

We present a 53-year-old woman with no known drug allergy, a history of ischemic heart disease, and diagnosed with CML in December 2019, starting on first-line imatinib 400mg daily.

She tolerated imatinib well, with a good hematologic response, being in a major molecular response state[1]. During the first month, the only AR was eyelid edema, improving with diuretics, until she reported that she'd been presenting increasingly fragile and prone to erosion skin on her hands. A dermatologist diagnosed the lesion performing a skin biopsy, which was consistent with imatinib-induced pseudoporphyria, leading to treatment discontinuation.

Afterward, the patient developed clinical worsening of CML and started treatment with dasatinib 100mg every 24h. Less than 2h after the first dose, a nonpruritic maculopapular exanthema appeared on her arms. After the 2nd dose of dasatinib, the exanthema became generalized accompanied by a severe headache, so the patient called the clinical team, while she was at home. Vital signs remained unaltered. No tryptase or 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. Skin prick test (SPT) and basophil activation test (BAT) were performed with dasatinib and bosutinib, as a potential alternative.

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

Dasatinib SPT was negative, and BAT was positive at all concentrations tested, $SI < 2$ (*see Figures 1 and SI*); for bosutinib, all tests were negative. Considering these and the need to continue treatment of the patient's CML, it was decided to initiate treatment with bosutinib 500mg/24h and to monitor the patient closely for response. Unfortunately, the patient referred nausea, abdominal pain, diarrhea, and

headache which gradually became incapacitating over the next days, either with regular or reduced doses of bosutinib 200mg, which eventually prompted to discontinuation, with complete resolution of symptoms after 24h.

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

The patient provided informed consent for the SPT and desensitization procedure. The dasatinib desensitization protocol was successful and the patient continues tolerating dasatinib 100mg/24h.

After more than a year of daily dasatinib, BAT became negative, indicating reduced basophil reactivity (*see Figure 1*).

Discussion/Conclusion

CML treatment poses significant challenges with inherent TKI toxicity, requiring a multidisciplinary team to assess drug safety and explore alternative treatments. Cutaneous effects have been reported especially with imatinib, including facial edema, which may occur in the majority of patients, pruritic rash that typically develops at 9 weeks of treatment and in some cases can be severe, and other inflammatory eruptions, that have also been observed with dasatinib[2,5]. However, underlined mechanisms have not been studied.

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

Desensitization protocols for imatinib have been described. *Nelson et al* conducted a 4-hour oral desensitization for 10 patients with imatinib-induced rash, succeeding in 8 cases[7]. *Kleawsongkram et*

al outlined a slow desensitization for severe non-immediate skin reactions, resulting in reduced CD5+, CD25+, and CD135+ T cells[8].

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

We present a case of successful dasatinib desensitization in a patient with immediate hypersensitivity, confirmed by a positive BAT. The patient couldn't tolerate other TKIs. While literature hints at TKI cross-reactivity, our patient's positive BAT for dasatinib and negative results for bosutinib may suggest otherwise. Notably, after over a year of daily dasatinib tolerance post-successful desensitization, dasatinib BAT turned negative.

In conclusion, desensitization with older generation TKIs such as imatinib has shown promising results, but few published cases[7,10]. While a literature search revealed a dasatinib desensitization protocol for two pediatric patients with delayed reactions and negative allergy tests[9], this case presents the first successful dasatinib desensitization in an adult patient with immediate hypersensitivity reaction confirmed by a positive BAT, and no viable TKI alternatives due to severe side effects.

Ethics

This study was conducted according to the Declaration of Helsinki, good clinical practice, and local regulations. Informed written consent signed by the patient was obtained for the publication of this clinical case, in accordance with ethical standards.

Funding sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Acknowledgements

The present study has been supported by the Institute of Health Carlos III of the Ministry of Economy and Competitiveness (grants cofounded by European Regional Development Fund (ERDF) (RETIC ARADyAL RD16/0006/0007, PI16/00696 and PI19/01861, PI22/01572) and the Spanish Society of Allergy (Fondo de Investigacion de la Fundacion de la SEAIC 2015).

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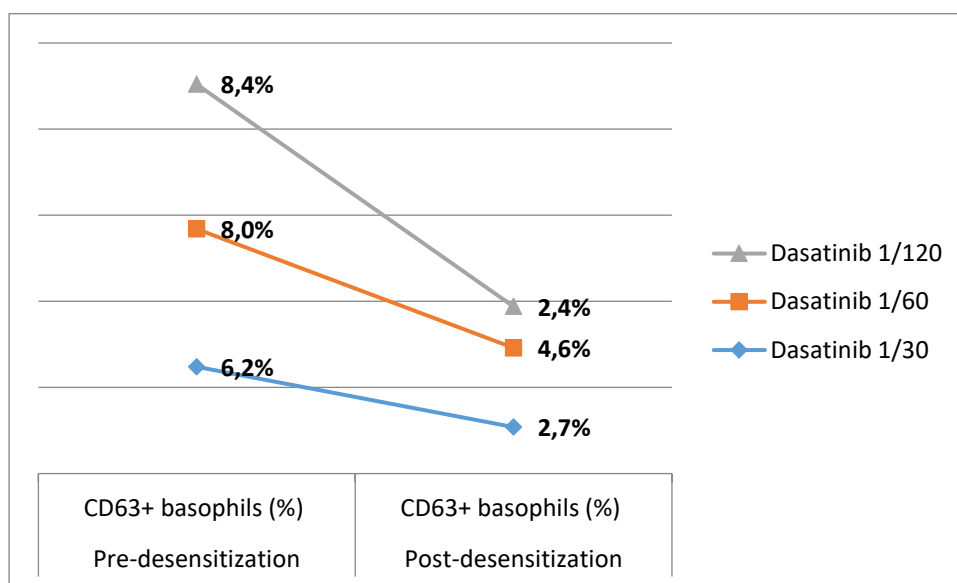
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FIGURES

Figure 1. Basophil activation test with dasatinib. **1a)** CD63+ basophils (%) between pre and post-desensitization; **1b)** Positive and negative controls of the basophil activation test and number of gated basophils for each dasatinib dilution, comparing pre and post-desensitization.

1a.



1b.

	<i>Pre-desensitization</i>		<i>Post-desensitization</i>	
	<i>Gated basophils</i>	<i>CD63+ basophils (%)</i>	<i>Gated basophils</i>	<i>CD63+ basophils (%)</i>
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

Notes: C(-): negative control; SB: buffer; C (+): positive control.