

Slow desensitization of imatinib-induced nonimmediate reactions and dynamic changes of drug-specific CD4⁺CD25⁺CD134⁺ lymphocytes



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ABSTRACT

Background: Imatinib is a tyrosine kinase inhibitor indicated for the treatment of gastrointestinal stromal tumors (GISTs) and certain neoplastic diseases; however, nonimmediate adverse reactions are common.

Objective: To describe the process of imatinib slow desensitization in patients who experienced non-immediate reactions to imatinib and the dynamic change in drug-specific CD4⁺CD25⁺CD134⁺ T-lymphocyte percentages.

Methods: Five patients diagnosed as having GISTs and with a recent history of imatinib-induced non-immediate reactions (maculopapular exanthema with eosinophilia, exfoliative dermatitis, palmar-plantar erythrodysesthesia, and drug rash with eosinophilia and systemic symptoms) were desensitized using a slow desensitization protocol. The reintroduced imatinib dosage was stepped up every week starting from 10 mg/d and increasing to 25, 50, 75, 100, 150, 200, and 300 mg/d until the target dose of 400 mg/d was achieved. Prednisolone of up to 30 mg/d was allowed if allergic reactions recurred. The percentages of CD4⁺CD25⁺CD134⁺ T cells present after incubating peripheral blood mononuclear cells with imatinib, at baseline and after successful desensitization, were analyzed using flow cytometric analysis.

Results: By using a slow desensitization technique, all patients were able to receive 400 mg/d of imatinib, and prednisolone was gradually tapered off. The percentages of imatinib-induced CD4⁺CD25⁺CD134⁺ T cells decreased from a mean (SD) of 11.3% (6.5%) and 13.4% (7.3%) at baseline to 3.2% (0.7%) and 3.0% (1.1%) after successful desensitization, when stimulating peripheral blood mononuclear cells with 1 and 2 μM of imatinib, respectively.

Conclusion: Slow desensitization is a helpful procedure in treating patients with imatinib-induced non-immediate reactions other than simple maculopapular exanthema. The reduced percentages of imatinib-induced CD4⁺CD25⁺CD134⁺ T cells in these patients may be associated with immune tolerance.

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Introduction

Imatinib mesylate is one of the first-generation tyrosine kinase inhibitors indicated for the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors (GISTs), and some other neoplastic diseases.^{1,2} In terms of molecular and clinical responses, the

introduction of imatinib results in significant improvement in therapeutic outcomes.^{3,4} Nonetheless, being a biological agent, several types of adverse reactions to imatinib can occur.⁵ Minor adverse effects, such as superficial periorbital edema, nausea, musculoskeletal pain, rash, and diarrhea, are common and need only supportive treatment.⁶ It was found that discontinuation of imatinib use was required in at least 5% of patients because of safety or intolerance problems.⁷ Newer generations of tyrosine kinase inhibitors, such as nilotinib, sunitinib, or dasatinib, may be an option as an alternative agent in imatinib-intolerant patients.⁸ However, access to alternative tyrosine kinase inhibitors may be limited in some patients, and these drugs are generally more expensive. Although some patients who experience a mild hypersensitivity reaction to imatinib without danger signs could be “treated through,” along with symptomatic therapy, those who

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have failed supportive modalities are often referred to allergists for proper management.

In the case of IgE-mediated reaction to tyrosine kinase inhibitors, rapid desensitization protocols have been described.⁹ Generalized maculopapular exanthema (MPE) resulting from imatinib is common, is usually self-limited, and requires only symptomatic treatment.¹⁰ Rapid desensitization has also been reported to be helpful in patients with imatinib-associated recurrent macular rash.¹¹ In contrast to an immediate reaction, data on the role of desensitization in the management of imatinib-induced nonimmediate reactions, other than MPE, are scarce.¹² Imatinib-induced exfoliative dermatitis is not common but can also occur.^{13,14} A previous case report indicated that imatinib-induced exfoliative dermatitis and peripheral blood eosinophilia may be treated with systemic steroids plus topical emollient.¹³ This approach needs careful monitoring and is not yet recommended. A simple step-up graded challenge in a patient with a history of imatinib-induced exfoliative dermatitis with peripheral blood neutropenia and eosinophilia was attempted but failed to reach the target dose.¹⁴ A sporadic case report was published of successful gradual dose escalation in patients with imatinib-induced Stevens-Johnson syndrome, but such a report is very rare.¹⁵

Rapid drug desensitization for IgE-mediated reactions is an antigen-specific process inhibiting mast cell mediator release and is proven to be helpful in drug-induced immediate hypersensitivity.¹⁶ In contrast, there is no consensus on desensitization protocols for delayed drug hypersensitivity reactions. However, rapid protocols seem to have higher failure rates than slow protocols.¹⁷ Although drug desensitization in patients with a history of nonimmediate reactions to certain drugs (such as antimycobacterial agents and allopurinol) was successfully reported, its underlying mechanism has yet to be elucidated.^{17,18}

CD134, or OX40, a member of the tumor necrosis factor receptor family, is characterized as a costimulatory molecule regulating both T_H1 - and T_H2 -mediated reactions and has a critical role in the maintenance of an immune response. It is expressed on activated T cells on T-cell receptor triggering, peaking at 48 hours and disappearing after 72 to 96 hours.¹⁹ The interaction of OX40 with its ligand enhances T-cell proliferation.²⁰ Triggering of OX40 *in vivo* can break peripheral T-cell tolerance and play a role in tumor cell rejection and graft-vs-host disease.^{21,22} The coexpression of CD134 and CD25 after 48 hours of antigen stimulation can be used as a marker for antigen-specific $CD4^+$ T cells.²³ The presence of antigen-specific $CD4^+CD25^+CD134^+$ T cells could be demonstrated in various infectious diseases, such as human immunodeficiency virus, mycobacteria, and hepatitis C infections.²⁴ The percentages of $CD4^+CD25^+CD134^+$ T cells were also found to increase in autoimmune diseases, such as Wegener granulomatosis, and to correlate with disease activity.²⁵ It is of interest to see whether the proportion of drug-induced $CD4^+CD25^+CD134^+$ T cells changes in drug allergic patients undergoing drug desensitization.

Drug desensitization is a risky procedure. In general, patients who have experienced drug-induced severe nonimmediate reactions are contraindicated for drug desensitization because of the potentially life-threatening consequences. However, this technique may be the last resort in certain circumstances, such as in patients who have limited accessibility to the alternative drug or when the alternative drug is not available, but the risk-benefit ratio needs to be assessed carefully.

A beneficial role of slow desensitization in patients with imatinib-induced nonimmediate cutaneous reactions has rarely been described. We report the use of imatinib slow desensitization for the treatment of patients with a history of nonimmediate reactions. We also observed the dynamic changes in the drug-induced $CD4^+CD25^+CD134^+$ T-cell subset in peripheral blood after successful desensitization compared with baseline data.

Methods

Five patients from King Chulalongkorn Memorial Hospital with a recent history of imatinib-induced nonimmediate reaction and whose symptoms could not be controlled by symptomatic management (oral antihistamines, topical corticosteroids, and emollient) were referred to our allergy clinic for drug desensitization. All of them were diagnosed as having GISTs and had been taking imatinib for between 10 days and 3 months before the development of adverse reactions. Clinical presentations were confirmed by a dermatologist as exfoliative dermatitis in 2 cases, and MPE with eosinophilia, palmar-plantar erythrodysesthesia (PPE), and drug-induced rash with eosinophilia and systemic symptoms (DRESS) in one case each. Peripheral blood eosinophilia was found in all patients. Because of difficulties with accessibility to alternative tyrosine kinase inhibitors in these patients, imatinib desensitization was considered by oncologists to be the best option for GIST management.

In the first patient, MPE with eosinophilia had been exacerbated after rechallenging with 200 mg/d of imatinib. As a result, a short course of prednisolone had already been prescribed before she was referred to us. We therefore gradually increased the imatinib dosage before tapering off the prednisolone. Because the previous adverse reactions in the remaining 4 patients had been rather severe and the onset had been delayed, we decided to perform slow desensitization to minimize patient risk. Slow desensitization was conducted as described in the following protocol, after patients had provided written informed consent.

Imatinib (Glivec; Novartis International AG, Basel, Switzerland) was reintroduced using the graded challenge method, beginning at a dose of 10 mg/d on the first day and increasing by 2, 3, and 5 mg at 2-hourly intervals to make sure that there was no immediate reaction. If the patient could tolerate the drug, the imatinib dosage was increased once a week until achieving the target daily dose of 400 mg. Any suspected symptoms were discussed over the telephone, and clinical manifestations, complete blood cell counts, and liver function tests were monitored once a week during dose escalation. Prednisolone of up to 30 mg/d was allowed, along with oral antihistamines and topical corticosteroids, to control breakthrough adverse reactions if they occurred.

Imatinib exhibits antiproliferative effects on T cells.²⁶ To determine optimal concentrations of imatinib for *in vitro* experiments, peripheral blood mononuclear cells (PBMCs) from healthy individuals were incubated in 1 to 10 μ M of imatinib. On the basis of the trypan blue exclusion assay, the viability of PBMCs after incubation with 1 and 2 μ M of imatinib for 48 hours was comparable to that in control RPMI medium, whereas cell viability decreased to 90% or less with 5 and 10 μ M of imatinib (data not shown). The concentrations of 1 and 2 μ M of imatinib were then selected for further experiments.

Cryopreserved PBMCs from all patients except 1 were collected before desensitization, when patients could tolerate the therapeutic dose (400 mg/d) of imatinib, and after prednisolone use had been discontinued for 4 weeks. The percentages of $CD4^+CD25^+CD134^+$ cells after incubating PBMCs with 1 and 2 μ M of imatinib for 48 hours at 37°C in 5% carbon dioxide were analyzed as follows: in brief, 1×10^6 PBMCs were stained for the surface markers anti-CD4-PE-Cy5, anti-CD25-APC, and anti-CD134-PE (BD Biosciences, San Jose, California), incubated for 30 minutes at 4°C in the dark, and then washed in a cold staining buffer. The cells were then resuspended before flow cytometric analysis using a FACS Calibur platform (Becton-Dickinson, San Jose, California). The percentages of $CD4^+CD25^+CD134^+$ cells were later analyzed using FlowJo software version 9.7.6 (Tree Star, Ashland, Oregon) (Fig 1). Staphylococcal enterotoxin B at 1 μ g/mL was used as a positive control.

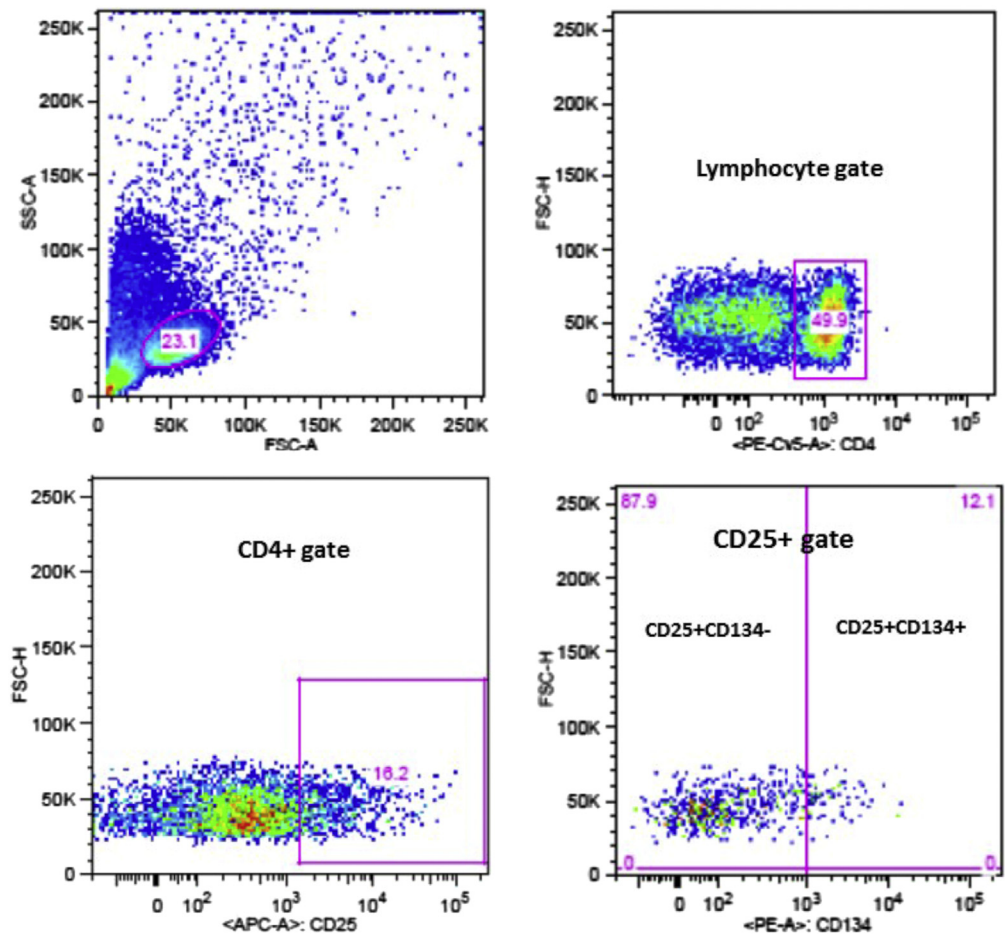


Figure 1. The identification by flow cytometric analysis of CD4⁺CD25⁺ cell populations expressing CD134 in patients with a history of imatinib-induced nonimmediate reaction. The percentages of imatinib-induced CD4⁺CD25⁺CD134⁺ cells were sequentially analyzed at baseline before imatinib desensitization, during desensitization, and after successful desensitization when patients could tolerate 400 mg/d of imatinib without the need for systemic corticosteroids.

Results

Baseline Characteristics and Clinical Course of Patients Who Underwent Imatinib Slow Desensitization

Five patients underwent imatinib desensitization in this study (Table 1). The first patient was a female diagnosed as having a GIST who developed imatinib-induced MPE with eosinophilia. Her

symptoms were exacerbated after rechallenging with 200 mg/d of imatinib. As a result, the oncologist had already prescribed 20 mg/d of prednisolone to control the rash before consulting us. Imatinib dosage was then gradually increased, whereas prednisolone could be tapered off within 12 weeks.

After imatinib was successfully reintroduced in the first case, we tried to desensitize the remaining 4 patients with imatinib, starting

Table 1
Clinical Characteristics of Patients With GISTs Undergoing Imatinib Slow Desensitization in this Study

Patient No./sex/age, y	Clinical manifestations	Symptom onset	Desensitization outcomes	Follow-up period, wk
1/F/44	Maculopapular exanthema; peripheral blood eosinophilia, 7.8% (523 cells/mm ³) ^a	10 d	Success in 3 weeks (started from 250 mg/d), tapered off prednisolone within 12 weeks	154
2/F/48	Exfoliative dermatitis; peripheral blood eosinophilia, 41.1% (4,440 cells/mm ³)	2 mo	Success in 9 weeks (started from 10 mg/d), tapered off prednisolone within 64 weeks	70
3/F/77	Palmoplantar erythrodysesthesia, peripheral blood eosinophilia, 7.5% (400 cells/mm ³) ^a	3 mo	Success in 8 weeks (started from 10 mg/d), tapered off prednisolone within 22 weeks	72
4/F/51 ^b	DRESS (high fever, generalized maculopapular exanthema, facial edema), peripheral blood eosinophilia, 37% (3,071 cells/mm ³); elevated liver enzymes (ALT, 78 U/L; AST, 104 U/L)	2 wk	Success in 11 weeks (started from 10 mg/d), tapered off prednisolone within 26 weeks	76
5/M/74	Exfoliative dermatitis, peripheral blood eosinophilia, 9.2% (640 cells/mm ³) ^a	1 mo	Success in 11 weeks (started from 10 mg/d), tapered off prednisolone within 18 weeks	10

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DRESS, drug rash with eosinophilia and systemic symptoms.
^aBaseline eosinophilia in patients 1, 3, and 5 were 1.1%, 3.9%, and 3.8%, respectively.
^bThe desensitization was performed as requested because of the limited accessibility to the alternative drugs for this patient after the risk of serious consequences was thoroughly explained.

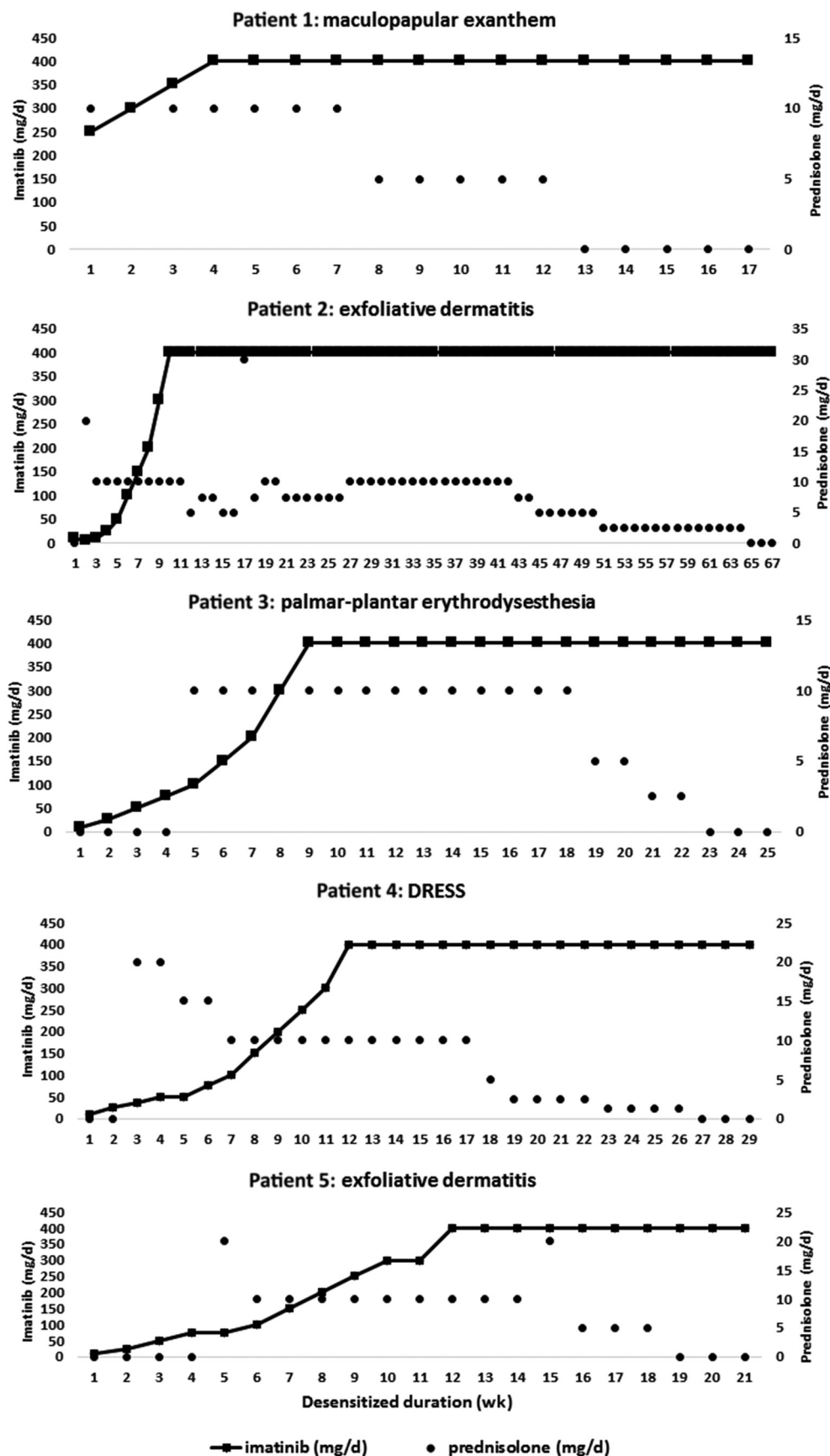


Figure 2. Timeline of slow desensitization in patients with a history of imatinib-induced nonimmediate reaction in this study. Schematic diagrams showing the association between desensitized duration, imatinib dosage, and oral prednisolone use in patients who underwent slow desensitization with imatinib. DRESS indicates drug-induced rash with eosinophilia and systemic symptoms.

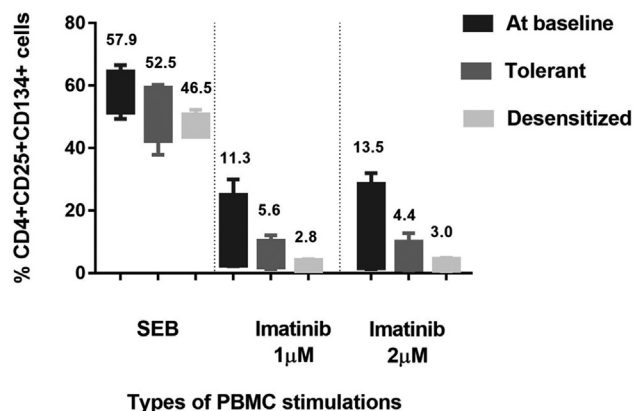


Figure 3. Proportions of imatinib-induced $CD4^+CD25^+CD134^+$ cells in peripheral blood at different stages of the slow desensitization period. Percentages of $CD4^+CD25^+CD134^+$ cells in response to imatinib stimulation in 4 patients with a history of imatinib-induced nonimmediate reaction were highest at baseline before desensitization (baseline), decreased when patients could tolerate 400 mg/d of imatinib (tolerant), and remained low after steroid withdrawal (desensitized). Error bars indicate SEM. PBMCs indicate peripheral blood mononuclear cells.

from 10 mg/d onward, because the reactions were more severe than MPE. Peripheral blood eosinophilia was demonstrated in all cases, whereas elevated liver enzyme levels were also evidenced in the patient with DRESS. According to our initial plan, imatinib dosage would be increased stepwise at 1-week intervals starting from 10 mg/d, through 25, 50, 75, 100, 150, 200, and 300 mg/d, up to the target of 400 mg/d. However, breakthrough cutaneous reactions occasionally delayed dose escalation, and short courses of 20 to 30 mg/d of prednisolone were required to control emerging symptoms before moving to a higher imatinib dosage. All patients were able to achieve the target daily dose of 400 mg at the end of desensitization period, and oral prednisolone was subsequently withdrawn (Fig 2).

Dynamic Changes of Imatinib-Induced $CD4^+CD25^+CD134^+$ Cells in Peripheral Blood During the Desensitization Period

The PBMCs from patients who started imatinib desensitization at 10 mg/d were used to study the dynamic changes in imatinib-induced T-cell responses. As shown in Figure 3, the percentages of $CD4^+CD25^+$ cells expressing CD134 (mean [SEM]) after stimulation with staphylococcal enterotoxin B were 57.9 (3.5), 52.5 (5.0), and 46.5 (2.0) at baseline before desensitization (baseline), when patients were able to tolerate 400 mg/d of imatinib (tolerant), and after prednisolone use had been discontinued for 4 weeks (desensitized), respectively. The percentages of imatinib-induced $CD4^+CD25^+CD134^+$ cells were highest at baseline before desensitization, decreased when patients were able to tolerate imatinib, and remained low even after prednisolone withdrawal (11.3 [6.5], 5.6 [2.3], and 2.8 [1.0], respectively, when stimulating PBMCs with 1 µM of imatinib and 13.5 [7.3], 4.4 [2.8], and 3.0 [1.1], respectively, when stimulating PBMCs with 2 µM of imatinib).

Discussion

Available data on imatinib desensitization were mostly limited to patients who had experienced an immediate reaction or a mild recurrent rash. We describe 5 patients with a recent history of imatinib-induced nonimmediate cutaneous reaction who could eventually use imatinib to treat GISTs after undergoing a slow desensitization protocol. Our study reveals the extended beneficial effect of slow desensitization in more severe forms of non-immediate reactions than simple MPE (eg, PPE, exfoliative dermatitis, and DRESS). This procedure may be a useful tool in treating

patients who experience an imatinib-induced nonimmediate reaction before switching to alternative drugs.

Considering that the onset of nonimmediate drug reactions is slow and difficult to predict, we reintroduced imatinib using the slow protocol so that breakthrough adverse reactions could be detected promptly. Although the underlying pathogenesis of PPE is not fully elucidated, the presence of peripheral blood eosinophilia in our patients suggests that an immune-mediated mechanism is a possibility. Data on drug desensitization in the literature were usually reported in unconfirmed cases of drug allergy; for that reason, the reported successful readministration of the suspected drug might have occurred in nonallergic individuals. Clinical exacerbation after imatinib rechallenge in our patients and dynamic changes in the imatinib-specific $CD4^+CD25^+CD134^+$ cell response in this study confirm the causal relationship between allergic reaction and the culprit drug.

To carefully monitor patients with rather severe nonimmediate reactions, our desensitization protocol was stretched throughout 2 months, using 9 dose increments. Mild breakthrough cutaneous reactions were managed with antihistamines plus emollients or topical corticosteroids. If the reaction persisted, we repeated the same dosage or went back 1 step to the previous tolerated dose, until the reaction disappeared. On the basis of our observations, the reemergence of eosinophilia is the warning sign of clinical relapse, and the step-up dosage could not be given. In the case of recalcitrant clinical symptoms or eosinophilia, a short course of prednisolone may be added to control allergic reactions before stepping up to the next dosage. Prednisolone could be tapered off after the therapeutic dose of imatinib had been achieved.

Our data indicate that markedly elevated peripheral blood eosinophilia is not absolutely contraindicated for drug desensitization, and low-dose prednisolone may be helpful in maintaining a patient's clinical tolerant status until the therapeutic goal is reached. However, whether concomitant steroid administration could shorten the desensitization period or increase the success rate of the desensitization procedure is still inconclusive. Although the time taken to achieve drug tolerant status varied, we observed a reduction in imatinib-induced $CD4^+CD25^+CD134^+$ T-cell percentages in peripheral blood after desensitization, and this remained low even after discontinued use of steroids. Our study suggests that the process of drug desensitization in nonimmediate hypersensitivity may lead to a diminished drug-specific T-cell response.

Some points should be considered when interpreting our preliminary study results. Although we successfully desensitized a case of imatinib-induced DRESS, drug desensitization is generally not recommended in patients with a history of life-threatening nonimmediate reactions if an alternative drug is still available because of the risk of potential fatal outcomes. More reported cases are needed to determine the success rate of this protocol. Mechanisms of drug desensitization in drug-induced nonimmediate reactions should be further explored. Clinical and immunologic parameters should be analyzed throughout the desensitization period to identify factors that determine desensitization outcomes in drug-induced nonimmediate hypersensitivity.

In conclusion, selected patients who experience nonimmediate reactions to imatinib other than simple maculopapular rash may safely receive the drug by using a slow drug desensitization technique. We report a successful desensitization protocol and demonstrate the reduction of imatinib-specific T-cell responses after tolerance induction in these patients.

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References

- [1] Guilhot F. Indications for imatinib mesylate therapy and clinical management. *Oncologist*. 2004;9:271–281.
- [2] Croom KF, Perry CM. Imatinib mesylate: in the treatment of gastrointestinal stromal tumours. *Drugs*. 2003;63:513–524.
- [3] Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med*. 2001;344:1031–1037.
- [4] O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348:994–1004.
- [5] Hausmann OV, Seitz M, Villiger PM, Pichler WJ. The complex clinical picture of side effects to biologicals. *Med Clin North Am*. 2010;94:791–804. xi–ii.
- [6] Marin D. Current status of imatinib as frontline therapy for chronic myeloid leukemia. *Semin Hematol*. 2010;47:312–318.
- [7] Fava C, Saglio G. Can we and should we improve on frontline imatinib therapy for chronic myeloid leukemia? *Semin Hematol*. 2010;47:319–326.
- [8] Hartmann JT, Haap M, Kopp H-G, Lipp H-P. Tyrosine kinase inhibitors: a review on pharmacology, metabolism and side effects. *Curr Drug Metab*. 2009;10:470–481.
- [9] Bar-Sela G, Kedem E, Hadad S, et al. Successful desensitization protocol for hypersensitivity reaction caused by sunitinib in a patient with a gastrointestinal stromal tumor. *Jpn J Clin Oncol*. 2010;40:163–165.
- [10] Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. *Dermatol Ther*. 2011;24:386–395.
- [11] Nelson RP Jr, Cornetta K, Ward KE, Ramanuja S, Fausel C, Cripe LD. Desensitization to imatinib in patients with leukemia. *Ann Allergy Asthma Immunol*. 2006;97:216–222.
- [12] Park MA, Volcheck GW, Guarderas JC. Successful progressive challenge after a cutaneous reaction to imatinib mesylate (Gleevec): a case report and review of the literature. *Allergy Asthma Proc*. 2004;25:345–347.
- [13] Banka N, Aljurf M, Hamadah I. Imatinib (STI-571)-induced exfoliative dermatitis in a Saudi patient with deck chair sign. *Dermatol Basel Switz*. 2003;207:329–330.
- [14] Hwang J-E, Yoon J-Y, Bae W-K, Shim H-J, Cho S-H, Chung I-J. Imatinib induced severe skin reactions and neutropenia in a patient with gastrointestinal stromal tumor. *BMC Cancer*. 2010;10:438.
- [15] Pavithran K, Thomas M. Imatinib induced Stevens-Johnson syndrome: lack of recurrence following re-challenge with a lower dose. *Indian J Dermatol Venereol Leprol*. 2005;71:288–289.
- [16] del Carmen Sancho M, Breslow R, Sloane D, Castells M. Desensitization for hypersensitivity reactions to medications. *Chem Immunol Allergy*. 2012;97:217–233.
- [17] Scherer K, Brockow K, Aberer W, et al. Desensitization in delayed drug hypersensitivity reactions: an EAACI position paper of the Drug Allergy Interest Group. *Allergy*. 2013;68:844–852.
- [18] Calogiuri G, Nettis E, Di Leo E, Foti C, Ferrannini A, Butani L. Allopurinol hypersensitivity reactions: desensitization strategies and new therapeutic alternative molecules. *Inflamm Allergy Drug Targets*. 2013;12:19–28.
- [19] Gramaglia I, Weinberg AD, Lemon M, Croft M. Ox-40 ligand: a potent costimulatory molecule for sustaining primary CD4 T cell responses. *J Immunol Baltim Md 1950*. 1998;161:6510–6517.
- [20] Kunitomi A, Hori T, Imura A, Uchiyama T. Vascular endothelial cells provide T cells with costimulatory signals via the OX40/gp34 system. *J Leukoc Biol*. 2000;68:111–118.
- [21] Tsukada N, Akiba H, Kobata T, Aizawa Y, Yagita H, Okumura K. Blockade of CD134 (OX40)-CD134L interaction ameliorates lethal acute graft-versus-host disease in a murine model of allogeneic bone marrow transplantation. *Blood*. 2000;95:2434–2439.
- [22] Bansal-Pakala P, Jember AG, Croft M. Signaling through OX40 (CD134) breaks peripheral T-cell tolerance. *Nat Med*. 2001;7:907–912.
- [23] Zaunder JJ, Munier ML, Seddiki N, et al. High levels of human antigen-specific CD4+ T cells in peripheral blood revealed by stimulated coexpression of CD25 and CD134 (OX40). *J Immunol Baltim Md 1950*. 2009;183:2827–2836.
- [24] Keoshkerian E, Helbig K, Beard M, et al. A novel assay for detection of hepatitis C virus-specific effector CD4(+) T cells via co-expression of CD25 and CD134. *J Immunol Methods*. 2012;375:148–158.
- [25] Wilde B, Dolff S, Cai X, et al. CD4+CD25+ T-cell populations expressing CD134 and GITR are associated with disease activity in patients with Wegener's granulomatosis. *Nephrol Dial Transplant*. 2009;24:161–171.
- [26] Dietz AB, Souan L, Knutson GJ, Bulur PA, Litzow MR, Vuk-Pavlovic S. Imatinib mesylate inhibits T-cell proliferation in vitro and delayed-type hypersensitivity in vivo. *Blood*. 2004;104:1094–1099.