
Desensitization to imatinib in patients with leukemia

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Background: Imatinib mesylate is a tyrosine kinase inhibitor used for the treatment of chronic myeloid leukemia and hypereosinophilic syndrome. Imatinib is associated with a variety of adverse cutaneous reactions, including urticaria, maculopapular exanthem, generalized exanthematous pustulosis, exfoliative dermatitis, and Stevens-Johnson syndrome.

Objective: To evaluate the safety and efficacy of oral desensitization by administering incremental dosages of imatinib mesylate to patients with leukemia who have had rashes associated with prior exposure.

Methods: Ten patients with leukemia and imatinib-associated recurrent rash underwent a 4-hour outpatient oral desensitization procedure. Beginning with 10 ng, we administered oral imatinib elixir in increasing dosages every 15 minutes. Patient outcomes were monitored by a return clinic visit and by telephone follow-up for a median of approximately 3 years.

Results: No episodes of anaphylaxis or serious adverse effects occurred during or immediately after desensitization. Four patients (all with urticaria) had no recurrence of rash after desensitization, and 4 had recurrent rash that resolved after temporary glucocorticosteroid and antihistamine administration. Two patients developed a recurrent rash 5 hours and several days after the procedure and were unable to resume therapy.

Conclusion: This oral desensitization protocol appears to help some leukemic patients with recurrent rash tolerate imatinib mesylate, thus permitting continuation of this life-prolonging therapy. These findings suggest that some adverse cutaneous reactions to imatinib may be due to a hypersensitivity mechanism rather than a pharmacologic effect.

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INTRODUCTION

Imatinib mesylate (STI571, Gleevec; Novartis, Basel, Switzerland), a protein kinase inhibitor, competitively inhibits the adenosine triphosphate-binding site of specific kinases that inhibit the tyrosine phosphorylation of proteins involved in signal transduction.^{1,2} The specificity of its activity includes the *bcr-abl* (B-cell antigen receptor region-*abl* oncogene) kinase, platelet-derived growth factor, and the *c-kit* tyrosine kinases. Imatinib also arrests growth or provokes apoptosis in hematopoietic cells that express *bcr-abl* but has minimal effect on normal cells.^{3,4} Imatinib mesylate is useful for the treatment of chronic myeloid leukemia (CML), hypereosinophilic syndrome, gastrointestinal stromal tumor, and Philadelphia chromosome-positive acute lymphoblastic leukemia.^{5–10} Imatinib is associated with the development of adverse cutaneous drug reactions, including urticaria, macu-

lopapular rash, generalized exanthematous pustulosis, pityriasis rosea, exfoliative dermatitis, and Stevens-Johnson syndrome.¹¹ Some of these rashes have been attributed to dose-dependent pharmacologic effects rather than hypersensitivity.

A single case has been reported of a protracted, progressive challenge using weekly dosing increments, but no universally established algorithm exists for managing patients with adverse cutaneous reactions to imatinib, although a number of approaches have been suggested.^{12–15} Rapid oral desensitization has been an effective therapy for treatment of adverse drug reactions secondary to antibiotics and some other pharmaceuticals.^{16–21} We administered oral desensitization to 10 patients with leukemia with a prior history of refractory rash associated with imatinib in an attempt to resume imatinib therapy.

REPORT OF CASES

Patient 1

A 44-year-old woman who was diagnosed as having chronic-phase CML was treated initially with interferon, which was not tolerated secondary to arthralgias, fatigue, night sweats, and fevers. Six weeks after discontinuing use of interferon, she was given imatinib, 400 mg/d. Two weeks after beginning imatinib therapy, she experienced rash, facial and throat swelling, myalgias, and diffuse arthralgias. Imatinib therapy was discontinued, and she was given an 8-day burst of oral prednisone, with notable resolution of the rash and complete resolution of arthralgias. Physical examination was negative for rash, signs of synovitis, and muscle tenderness. Labora-

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tory evaluation revealed a white blood cell count of 13,600/mm³, with 93% polymorphonuclear leukocytes, 1% bands, 3% lymphocytes, 1% metamyelocytes, and 2% myelocytes. The comprehensive chemistry profile was normal. The erythrocyte sedimentation rate was 15 mm/h (reference range, 0–20 mm/h). Antinuclear antibody was present in a titer of 1:160 with a speckled pattern; antinative DNA antibody assay (Crithidia) results were negative. Urinalysis revealed no hematuria or proteinuria.

Differential diagnosis included the following: serum sickness, autoimmune phenomenon related to long-term interferon, de novo autoimmune disease, vasculitis, leukocytoclastic vasculitis, and urticaria with arthralgias. Use of prednisone and imatinib was discontinued, and the patient returned 2 weeks later for desensitization.

Patient 2

A 42-year-old woman was treated with imatinib, 400 mg/d, for chronic-phase CML. Within several days she developed a fine, pruritic, generalized urticarial eruption with minimal facial involvement that spared the palms and soles. There was no mucous membrane involvement. Diphenhydramine was prescribed. Physical examination revealed diffuse generalized erythema, most pronounced on the trunk. There was no evidence of synovitis, myositis, organomegaly, or adenopathy. Laboratory evaluation revealed the following: white blood cells, 5,200/mm³; hemoglobin, 11.1 g/dL; and platelets, 135,000/mm³. Antihistamine therapy with diphenhydramine was discontinued, and 4 days later she underwent oral desensitization. Before the desensitization, she had given informed consent and underwent skin testing.

Patient 3

A 30-year-old man was diagnosed as having chronic-phase CML and was initially treated with hydroxyurea followed by interferon alfa. He experienced signs of disease acceleration, interferon therapy was discontinued and hydroxyurea therapy restarted. Imatinib became available and was begun at a dose of 400 mg/d. He experienced acute urticaria 9 days later, for which he was treated in an emergency department with diphenhydramine, 25 mg orally every 6 hours, and discharged. The following day, he was febrile with a temperature of 101.9°F and was seen again in the urgent care department. Imatinib therapy was discontinued, and he received intramuscular doses of ceftriaxone (1 g) and hydroxyzine hydrochloride (75 mg). Cultures were negative, and the cause of the fever was not definitively proven. His pruritus temporarily improved, the rash gradually resolved, and he was referred for desensitization.

Patient 4

A 47-year-old woman was diagnosed as having CML and was given hydroxyurea for 1 year followed by interferon alfa, 5,000,000 U 3 times weekly, for several years. She was switched to imatinib (400 mg/d) and developed a generalized, diffuse, macular, pruritic rash 7 to 10 days after initiation of imatinib therapy. She experienced blistering and sloughing of

the epidermis of the hands. The imatinib therapy was stopped for 2 weeks and then restarted at 100 mg. The rash recurred in the next 24 to 48 hours, resulting in desquamation of the palms, joint pains, and myalgias. Complete blood cell count revealed the following: white blood cells, 10,800/mm³ with 76% polymorphonuclear leukocytes, 4% bands, 7% lymphocytes, 6% monocytes, 3% eosinophils, and 4% basophils; hemoglobin, 11.8 g/dL; platelets, 502,000/mm³; Westergren erythrocyte sedimentation rate, 33 mm/h; C-reactive protein, 1.3 mg/dL (reference range, 0–1 mg/dL); antinuclear antibody, 1:80 in a cytoplasmic pattern (reference range, <1:40); IgG, 1,450 mg/dL (reference range, 700–1,500 mg/dL); IgA, 366 mg/dL (reference range, 60–400 mg/dL); and IgM, 156 mg/dL (reference range, 60–300 mg/dL). She was referred for desensitization.

Patient 5

A 53-year-old woman was diagnosed as having CML and prescribed interferon and cytosine arabinoside for a 4-month period and then 5,000,000 U/d of interferon for several years. She switched to imatinib, 400 mg/d, and 18 days after initiation she developed a macular rash on her trunk, abdomen, and forearms that was mildly pruritic. She was given diphenhydramine, and the imatinib therapy was discontinued. She was then seen 3 weeks later, at which time there was a salmon-colored macular rash that involved the lateral forearm, upper abdomen, and anterior thighs. She took diphenhydramine for the pruritus for 3 more days, during which time the rash resolved and desensitization was performed.

Patient 6

A 65-year-old woman was diagnosed as having chronic-phase CML, and imatinib therapy was begun later that month at a dose of 400 mg/d. During the ensuing 18 months, she experienced adverse effects, including nausea, periorbital edema, and muscle cramps; the cramps improved with calcium administration, and the periorbital edema was intermittent. She noted an erythematous rash on her arms and legs, which became progressively more confluent and pruritic throughout several days until she stopped using the imatinib. The rash resolved during a 4-day period, and she restarted using the imatinib. The rash recurred within 24 to 48 hours and involved the forearms, upper arms, lower legs, and outer aspects of the calves down to the ankles. She was treated symptomatically with hydroxyzine hydrochloride for the following 9 days. She was seen in April 2004, at which time the rash had resolved, and underwent desensitization.

Patient 7

A 65-year-old woman with chronic-phase CML was given imatinib, 400 mg/d. The patient developed a diffuse, erythematous, scaly, pruritic rash after 7 days, imatinib therapy was discontinued, and she received a 6-day oral course of methylprednisolone, with resolution of the rash. She was taking imatinib, 100 mg/d, and experienced rash that was more severely erythematous and pruritic. The rash resolved

during the next 2 to 3 weeks, and she was referred for desensitization.

Patient 8

A 56-year-old woman was diagnosed as having chronic-phase CML. Her history was significant for rheumatoid arthritis, for which she had received prednisone, 5 mg/d, for 25 years. Imatinib, 400 mg/d, was initiated, and she developed diarrhea (4 to 5 stools per day) after 2 weeks, which persisted for 5 days, followed by the development of a blotchy, pruritic rash on the cheeks and anterior chest. Use of imatinib was discontinued, and loperamide was prescribed. The diarrhea resolved and the rash improved. She was referred for oral desensitization, at which time the physical examination results were remarkable for a faint, erythematous macular rash on the anterior aspect of the chest between the breasts.

Patient 9

A 68-year-old woman was diagnosed as having chronic-phase CML and was given imatinib, 400 mg/d. Approximately 10 days later, she developed a pruritic, bullous rash that involved the arms and legs, with alopecia and bilateral lower-extremity edema. Imatinib therapy was discontinued, and the rash improved. Imatinib therapy was restarted and again discontinued 8 days later because of recurrent rash. She then received interferon alfa therapy for the next 12 months, which was discontinued before referral for imatinib desensitization.

Patient 10

A 25-year-old woman underwent a matched-related donor peripheral blood stem cell transplantation for Philadelphia chromosome-positive acute B-lymphoblastic leukemia. She experienced acute graft-vs-host disease of the skin when immunosuppression was weaned; a biopsy specimen was then taken of the area with the rash, revealing lichenoid chronic graft-vs-host disease and again requiring intensification of immunosuppressive therapy. Eleven months after transplantation, imatinib therapy was begun (400 mg/d) because of detection of recipient DNA by peripheral blood analysis of short tandem repeats. She developed a generalized rash and anasarca approximately 10 days after the initiation of imatinib, so imatinib therapy was discontinued, although it was unclear that the rash was related to the imatinib. Psoralen-UV light therapy was initiated, with continued use of rapamycin, glucocorticosteroids, and mycophenolate mofetil, and she received aggressive diuretic therapy. The rash improved significantly. Imatinib therapy was restarted at 100 mg/d at 12 months after transplantation. Eight days later, she noted mild facial flushing with mild swelling of the face and arms bilaterally within 30 to 45 minutes of taking the imatinib. She then underwent oral desensitization.

METHODS

Oral Desensitization

Stock suspensions of imatinib were prepared by the Pharmacy Department at Indiana University School of Medicine,

University Hospital, Indianapolis, IN, by dissolving the contents of 100-mg capsules in glycerin to concentrations of 1 and 10 mg/mL. Serial dilutions were then formulated, using sterile water as diluent in the following concentrations: 0.0001 mg/mL (0.1 mL), 0.01 mg/mL (0.1 mL), 0.1 mg/mL (0.5 mL), 1 mg/mL (0.1 mL), 1 mg/mL (0.5 mL), 1 mg/mL (1 mL), 1 mg/mL (3 mL), 10 mg/mL (0.6 mL), 10 mg/mL (0.9 mL), 10 mg/mL (1.8 mL), 10 mg/mL (3.6 mL), 10 mg/mL (7.2 mL), 10 mg/mL (10 mL), and 10 mg/mL (20 mL). After June 2004, capsules were no longer manufactured, and we instead used 100-mg tablets dissolved in sterile water.

Each patient signed informed consent for oral desensitization in a closely supervised clinical setting beginning with 10 ng and incrementally increasing dosages (Table 1). No premedication was given. After close observation for signs of adverse reactions, the patient was discharged from the clinic with instructions to take 100 mg of imatinib in the evening and 400 mg of imatinib once daily thereafter.

Skin Testing

Stock suspensions were prepared as described herein. Serial dilutions were formulated at the following concentrations: 0.0001 mg/mL, 0.001 mg/mL, 0.01 mg/mL, and 0.1 mg/mL. Epicutaneous and intradermal skin tests using histamine controls were administered to patient 2.²² Immediate reactions were measured according to Turkeltaub.²³ The patients were treated in a busy hematology/oncology outpatient facility, where the logistics of routine skin testing were not tenable and the product underwent a revision of vehicle from capsule during the period of evaluation of this cohort of patients.

Table 1. Desensitization Protocol*

Step†	Concentrate	Volume, mL	Dose, mg
1	10 ng/mL	1,2,4	0.00007
2	100 ng/mL	1,2,4	0.00075
3	1 µg/mL	1,2,4	0.0075
4	10 µg/mL	1,2,4	0.075
5	100 µg/mL	1,2,4	0.75
6	1 mg/mL	1,2,4	7.5
7	10 mg/mL	1,2,4	75.00
8	100 mg tab	1	100
9	2- to 100-mg tablets	2	200

* The 10-mg/mL solution could not be made using tablets; because of the change from capsules to tablets (after patient 9), on step 7 the dosages used were 25 mg, 50 mg, and 75 mg. After close observation for signs of adverse reactions, the patient was discharged from the clinic with instructions to take 100 mg of imatinib in the evening and 400 mg of imatinib once daily thereafter.

† Steps were as follows: (1) make concentrations of imatinib 1 and 10 mg/mL; (2) start with step 6 and mix 1 mL of 1 mg/mL of imatinib with 9 mL of water; (3) take 1 mL of the above mixture with 9 mL of water for step 5; (4) take 1 mL of the above mixture and mix with 9 mL of water for step 4; (5) continue until all dilutions are mixed; (6) step 7 is straight solution of 10 mg/mL; and (7) steps 8 and 9 are tablets.

RESULTS

Patient 1 was given increasing oral dosages every 10 to 15 minutes to the peak dose of 200 mg. She experienced blotchy redness of the face and some itching after the fourth dose, which resolved spontaneously. There was no shortness of breath, feeling of impending doom, hives, nausea, vomiting, or fever. She was asked to take 100 mg that evening and to begin the regular dose of 400 mg/d the following morning. She was given hydroxyzine hydrochloride, 25 mg, to take 3 times daily as needed for itching or rash. Eight days after the desensitization procedure, she experienced transient urticaria on the anterior abdomen, which resolved spontaneously. She took imatinib, 400 mg/d, for more than 12 months with impunity and without concomitant antihistamines before dying of the disease.

Patient 2 was administered epicutaneous and intradermal skin tests with imatinib and histamine controls before oral desensitization. She experienced a small wheal-and-flare reaction to the epicutaneous test with concentrations of 0.01 and 0.1 mg/mL, which we thought were equivocal. Intradermal concentrations of 0.001, 0.01, and 0.1 mg/mL elicited erythema of orthogonal diameters of 75, 83, and 111 mm, respectively (Fig 1). She experienced no symptoms during the desensitization procedure and has taken imatinib, 400 mg, without antihistamine therapy.

Patient 3 tolerated the procedure well and took 400 mg/d of imatinib without symptoms or rash for more than 18 months before dying of progressive CML.

Ten patients tolerated the 4-hour oral desensitization procedure: 8 (80%) were able to continue daily imatinib without recurrent rash or other adverse effects. Patient 7 developed a

pruritic, erythematous, diffuse rash beginning 5 hours after the desensitization procedure and was unable to resume imatinib therapy. A second patient, with relapsed acute lymphoblastic leukemia and graft-vs-host disease after allogeneic hematopoietic cell transplantation, developed recurrent rash several days after desensitization and was not rechallenged. Table 2 summarizes the patient characteristics of the cohort.

DISCUSSION

The first report of adverse rash secondary to imatinib was the interim analysis of the initial cohort of patients with interferon-refractory chronic-phase CML in which 16 (19%) of 83 patients developed a rash, one of whom discontinued therapy because of a persistent and progressive rash.⁶ Seventeen (29%) of 58 patients enrolled in a companion phase 1 study experienced rash, and 1 experienced exfoliative dermatitis, which was considered by the authors to be a serious adverse event, possibly related to imatinib.⁹ Kantarjian et al treated 532 patients with late-phase CML that had not responded to previous therapy with interferon alfa, and after a mean follow-up of 18 months, 171 (32%) of the patients experienced a rash, 16 (3%) of which were grade 3 (generalized symptomatic macular, papular, or vesicular eruption) or 4 (exfoliative dermatitis or ulcerating dermatitis) as per the Eastern Cooperative Oncology Group common toxicity criteria.^{10,24} The rashes were typically of 3 varieties: maculopapular, urticarial, and desquamative.¹⁰ A number of subsequent reports have documented or reviewed the adverse cutaneous drug reactions associated with imatinib, including urticaria, generalized exanthematous pustulosis, pityriasis rosea, depigmentation, exfoliative dermatitis, and Stevens-Johnson syndrome.^{11,25-38}

Imatinib mesylate is designated chemically as 4-[(4-methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino]phenyl] benzamide methane. Rash is not mentioned in the precautions section of the prescribing information brochure, despite being listed as an adverse effect. Three percent to 5% or approximately 30 to 50 of 1,027 patients experienced grade 3 to 4 rash (Novartis, East Hanover, NJ). The mechanism(s) of rash development after imatinib administration is not known. Urticarial and macular rashes are most common. With regard to pustulosis, the element mercury also induces acute generalized exanthematous pustulosis and interferes with tyrosine kinase activity.¹¹ In addition, imatinib is also an inhibitor of platelet-derived growth factor receptors and c-kit receptor kinases, which play critical roles in normal pigmentation. Mutations that reduce or abrogate these enzyme activities may interrupt melanocyte development. Immune reactions to small molecular compounds, such as drugs, can cause a variety of diseases that involve the skin, liver, kidney, and lungs.

Drugs may also stimulate T cells, acting as haptens and binding covalently to peptides or via structural features that allow them to interact directly with T-cell receptors. Immunohistochemical and functional studies of drug-reactive T cells in patients with distinct forms of exanthema reveal that

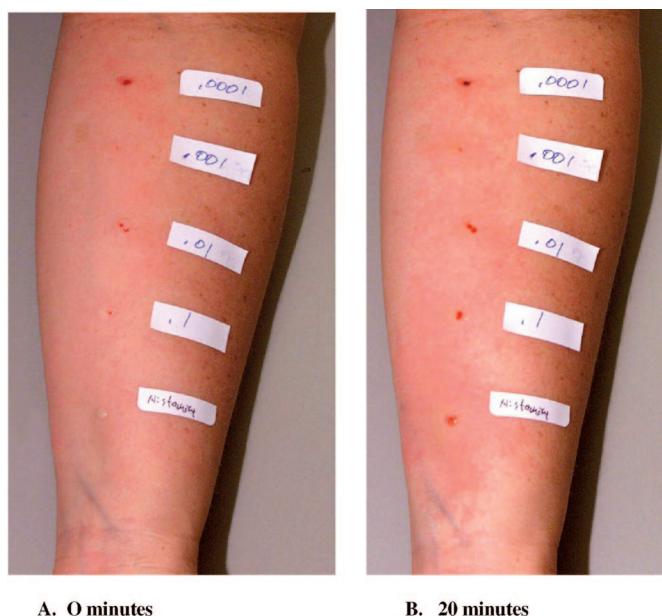


Figure 1. Intradermal skin testing in patient 2. Top to bottom: 0.0001 mg/mL, 0.001 mg/mL, 0.01 mg/mL, 0.1 mg/mL, and histamine control.

Table 2. Clinical Characteristics and Outcomes

Patient No./sex/age, y	Diagnosis	Adverse cutaneous reaction	Onset (time from imatinib initiation to cutaneous reaction)	Result of desensitization	Clinical course of patient
1/F/42	CML	Generalized urticaria	5 days	No recurrence of urticaria	In chronic phase, tolerating imatinib
2/F/44	CML	Rash and facial swelling	2 weeks	No recurrence of rash or facial swelling	Tolerated imatinib, but disease progressed, patient died 10 months later
3/M/30	CML	Urticaria	9 days	No recurrence of urticaria	Tolerated imatinib, but disease progressed, patient died 7 months later
4/F/47	CML	Diffuse, macular pruritic rash, blistering of hands	7 days	No recurrence of rash or blistering	Tolerating imatinib with stable blood cell counts
5/F/53	CML	Macular, mildly pruritic rash on trunk, abdomen and forearms	18 days	No recurrence of rash	Tolerating imatinib, in chronic phase of disease
6/F/65	CML	Erythematous, pruritic rash on arms and legs	19 months	No recurrence of rash	Tolerating imatinib
7/F/65	CML	Diffuse erythematous pruritic rash	7 days	Five hours after desensitization, rash recurred on legs and trunk	Started taking hydroxyurea 9 months later, in chronic phase of disease
8/F/56	CML	Blotchy, pruritic rash on cheeks and anterior chest	14 days	No recurrence of rash	Tolerating imatinib
9/F/68	CML	Pruritic, bullous rash on arms and legs	10 days	No recurrence of rash	Tolerating imatinib
10/F/25	Acute B-lymphoblastic leukemia	Generalized rash	10 days	Blistering rash recurred 8 days after desensitization	Imatinib not administered further; rash possibly caused by graft-vs-host disease

Abbreviation: CML, chronic myeloid leukemia.

distinct T-cell functions lead to different clinical phenotypes. Interpretation of these data has prompted Pichler to subclassify delayed hypersensitivity reactions (type IV) as to those T-cell-mediated reactions that occur in conjunction with the release of certain cytokines and chemokines that may preferentially activate and recruit monocytes (type IVa), eosinophils (type IVb), or neutrophils (type IVd).³⁹ Furthermore, cytotoxic functions by either CD4⁺ or CD8⁺ T cells (type IVc) seem to participate in all type IV reactions.

The wheal-and-flare reaction observed in the single patient who was skin tested suggests that a hypersensitivity mechanism rather than a pharmacologic effect may be

responsible for reactions in some patients. Oral administration of increasing dosages of a number of medications has been shown to be effective for desensitizing individuals, and the strategy that we used was borrowed from the work of Hughes and others, who established the procedure for patients with trimethoprim-sulfamethoxazole sensitivity.¹⁷ Given the occasional serious reaction observed with sulfa desensitization, we observed all of these patients in an outpatient infusion facility equipped with resuscitative supplies and equipment.⁴⁰ The package insert states that administration of imatinib is contraindicated in patients with known hypersensitivity to imatinib or to any other

component product. This may be a difficult choice to make for individuals whose alternative therapies are fraught with even greater potential complications; CML is a fatal disease when left untreated. Some patients experience recurrent rash that is sufficiently severe to warrant discontinuation of this life-extending drug, as is indicated for patients who experience a severe desquamative rash.

One method of managing maculopapular or urticarial rash in patients receiving imatinib is to temporarily stop use of the drug and restart at a lower dose after the rash has disappeared, then increase again to the desired dose (Dr Stephens, personal communication, Novartis, East Hanover, NJ). A significant number of patients in the present cohort tolerated long-term administration without recurrent rash after oral desensitization. Observations of greater numbers of patients who undergo this procedure will be required to confirm the efficacy of oral desensitization and to illuminate the mechanism of rash development in patients with recurrent or recalcitrant rash. Oral desensitization appears to be an option for patients with recurrent cutaneous drug reactions to imatinib, which may permit clinicians to safely administer imatinib to some patients with leukemia who experience adverse cutaneous reactions to this life-prolonging medication.

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