Deferasirox Desensitization

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Clinical Implications: Deferasirox is the only oral iron chelator approved for pediatric use in the United States, however it is known to cause a maculopapular rash in up to 10% of patients. Desensitization to deferasirox is possible using a conservative outpatient desensitization protocol.

Key words: Deferasirox, iron overload, iron chelator, maculopapular rash, desensitization

To the Editor:

Iron overload is a common complication of frequent blood transfusions often requiring years of treatment with iron chelators. Deferasirox is an oral iron chelator taken daily.¹ It is the only oral iron chelator currently approved for pediatric use by the United States Food and Drug Administration. It is available as a tablet that is dissolved in water or juice. It is often preferred to the alternative iron chelator, deferoxamine, which must be given subcutaneously and requires daily infusions over 10-12 hours.¹

Deferasirox has been reported to cause a maculopapular eruption in up to 10% of patients.¹ Some rashes have been associated with systemic symptoms, as was reported in a 75 year old female with history of acute myeloid leukemia.² That patient had initial onset of maculopapular rash 15 days after starting the medication that improved with IV and topical steroids as well as antihistamines. The rash recurred within 4 hours of restarting the medication 3 weeks later and was associated with fever and hypotension. A patch test to deferasirox was subsequently negative.

Our patient is a 17 year old male with relapsed acute lymphocytic leukemia and iron overload due to repeat blood transfusions. He experienced a pruritic maculopapular rash after increasing his dose of deferasirox. He had previously been on deferasirox at a dose of 500mg daily for one month, but had also been on dexamethasone during that time as part of his chemotherapy regimen that also included 6-mercaptopurine and methotrexate. The day his dexamethasone was stopped, his dose of deferasirox was increased to 1000mg. He also received a replacement dose of IVIG for hypogammaglobulinemia. He developed a pruritic, blotchy rash limited to his palms only several hours later at home. His parents held his deferasirox for 2 days, during which time the rash spontaneously cleared without treatment. At the follow-up appointment with his oncologist, the rash was believed to be due to IVIG and the patient was told to restart deferasirox at 1000mg. He then developed a pruritic maculopapular rash 8-12 hours later and fever to 102°F. His rash initially started on his face then spread to his trunk and genitalia, finally progressing outward to the extremities over 7-10 days (see figure 1). He was treated with oral steroids, H1 and H2-blockers initially as an inpatient until his fever defervesced, then as an outpatient with gradual resolution of rash over 2-3 weeks. A T-cell mediated, non-IgE mechanism was suspected given the delayed onset of rash and fever. No skin tests were performed given low suspicion for an IgE-mediated reaction.

The patient's initial ferritin level was 3771 ng/ml (normal range 24-336). He was expected to require daily iron chelation therapy for up to 2-3 years. The daily 10-12 hour subcutaneous infusions required for deferoxamine treatment combined with the patient's fear of needles made deferoxamine an unwieldy option for the patient and

family. They and their oncologist requested desensitization to deferasirox as an alternative.

Initially, we attempted desensitization as an inpatient, starting at 1/1000 of the goal dose, modeling our protocol after TMP-SMX outpatient desensitization protocols.³ The patient was premedicated with cetirizine 10mg. Unfortunately, he developed itchy palms followed by pruritic rash and flushing 3 hours after the second dose and the procedure had to be terminated. The rash and pruritus were similar to his first reaction but less severe. He was treated with oral steroids and hydroxyzine with gradual resolution of rash over 3 days.

We then decreased the starting dose to 1/100,000 of the goal dose and doubled the dose every 3-4 days. This was done as an outpatient and was successful until the 500mg dose, when the patient was unable to tolerate a full doubling of the dose due to itching. We then increased at a slower rate as described in Table 1 until reaching the goal 2000mg dose.

It took 3 months to achieve goal dose using this regimen. The patient's ferritin level decreased >1000 ng/ml during the desensitization period. He was then able to continue on his goal dose for at least 9 months without problems. He then developed nausea and vomiting from the medication which is a known side effect reported in 10% of patients. He discontinued deferasirox due to gastrointestinal intolerance. His ferritin had decreased to 1048 ng/ml when he stopped the medication

To our knowledge, this is the first report of a successful desensitization to deferasirox.

Given that deferasirox is the only pediatric approved oral iron chelator in the United

States and that maculopapular rash is a known adverse reaction of the medication, it leaves pediatric patients with deferoxamine as their only other option for iron chelation therapy. Compliance with deferoxamine is often sub-optimal given the need for time-intensive daily subcutaneous infusions.⁴ For this reason, it is important for allergists to know that a slow, conservative desensitization protocol can be successful in an outpatient setting. Deferasirox desensitization may allow patients an improved quality of life and increase medication compliance for the treatment of iron overload.

References:

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Figure Legends

Table 1: Deferasirox Desensitization Protocol

Each dose was given daily for the number of days specified in the interval column before increasing to the subsequent dose.

Figure 1: Initial maculopapular rash associated with fever

Figure I:

Table I:

Dose	Interval
0.05 mg	3 days
0.1 mg	4 days
0.2 mg	3 days
0.5 mg	4 days
1 mg	3 days
2 mg	4 days
4 mg	3 days
8 mg	4 days
16 mg	3 days
32 mg	4 days
64 mg	3 days
125 mg	4 days
250 mg	3 days
500 mg	7 days
750 mg	7 days
1000 mg	7 days
1500 mg	7 days
2000 mg	7 days