EUROPEAN JOURNAL OF Haematology

European Journal of Haematology 92 (337–340)

ORIGINAL ARTICLE

Continuation of deferiprone therapy in patients with mild neutropenia may not lead to a more severe drop in neutrophil count

Amal M. El-Beshlawy[1], Mohsen S. El-Alfy[2], Teny T. Sari[3], Lee L. Chan[4], Fernando Tricta[5]

[1]Hematology Department, Pediatric Hospital, Cairo University, Cairo; [2]Children Hospital, Ain Shams University, Cairo, Egypt; [3]Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [4]University of Malaya, Kuala Lumpur, Malaysia; [5]ApoPharma Inc., Toronto, ON, Canada

Abstract

Approximately 6% of patients with thalassemia receiving deferiprone develop neutropenia. Present practice is to monitor absolute neutrophil count (ANC) weekly and to interrupt treatment at the first sign of neutropenia, lest continuation lead to progressive neutrophil reduction. In a 6-month study evaluating the safety and efficacy of a liquid form of deferiprone in 100 children, ANC was initially checked weekly for all patients. For individuals experiencing mild neutropenia, deferiprone was continued but monitoring was increased to daily until resolution. Therapy was to be suspended only if the episode was prolonged or if it worsened. Four patients experienced single episodes of mild neutropenia, and two others each experienced two episodes. All eight episodes resolved within 4–7 d despite continued therapy. (One patient later developed agranulocytosis and had treatment terminated.) This study showed that not all cases of mild neutropenia during deferiprone therapy develop into agranulocytosis, and suggests that many may not be caused by deferiprone. Transient declines in ANC to levels defined as neutropenic are common even in healthy individuals, particularly children; and it could be that the frequent monitoring of ANC mandated during deferiprone therapy may reveal cases of transient neutropenia that would otherwise have gone undetected and resolved on their own without clinical consequences. In patients with thalassemia, several factors increase the probability of a transient fall in ANC. These findings raise the question of whether deferiprone should be routinely stopped in cases of mild neutropenia, provided that such patients have their ANC monitored more frequently during the neutropenic episode.

Key words neutropenia; agranulocytosis; thalassemia; deferiprone

Correspondence Fernando Tricta, MD, ApoPharma Inc., 200 Barmac Drive, Toronto, ON M9L 2Z7, Canada. Tel: 416 401 7332; Fax: 416 401 3867; e-mail: ftricta@apopharma.com

Accepted for publication 11 November 2013 doi:10.1111/ejh.12241

Severe neutropenia or agranulocytosis, defined as an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/L (1), occurs in 1–2% of patients with thalassemia being treated with deferiprone (2). Less severe episodes of neutropenia (ANC $< 1.5 \times 10^9$/L but $>0.5 \times 10^9$/L) occur in approximately 6% of such patients (2). In clinical trials, it was determined that neutropenia of all severities resolved upon interruption of deferiprone. This observation led to the recommendation that all deferiprone recipients be monitored weekly to detect a drop in ANC as soon as reasonably possible and that treatment be interrupted at the first sign of neutropenia lest continuation lead to progressive reduction in neutrophil count. Published data, however, have demonstrated that patients with thalassemia frequently experience transient episodes of mild or moderate neutropenia irrespective of the chelation therapy they are on (3, 4). These transient episodes normally go undetected unless there is frequent monitoring of the neutrophil count. The realization that such episodes occur in thalassemia patients with or without deferiprone raises the question of whether interruption of deferiprone should be required for all patients who experience mild neutropenia during therapy. A further question is whether or not continued use of deferiprone during mild neutropenia does in fact increase the likelihood of progression to agranulocytosis.

These questions were addressed in a study evaluating the safety and efficacy of a liquid formulation of deferiprone (Ferriprox®; ApoPharma Inc., Toronto, ON, Canada) in 100 transfusion-dependent children aged 1–10 yr requiring iron chelation therapy. Participants received this formulation for 6 months, at doses ranging from 50 to 100 mg/kg/d. A report on the overall feasibility of the liquid solution compared with the tablet formulation in young children has been published elsewhere (5). A unique monitoring regimen was instituted in this trial whereby at the initiation of therapy, ANC was checked weekly for all patients, and if an individual experienced an episode of mild neutropenia (defined as two consecutive ANC values between 1.5 and 1.0×10^9/L), deferiprone was not interrupted but ANC monitoring was increased to daily. Daily monitoring continued until resolution of the event (defined as two consecutive ANC > 1.5×10^9/L). Therapy was suspended only if the episode was still ongoing after 2 wk or if two consecutive ANC values went below 1.0×10^9/L (moderate neutropenia). If the ANC went below 0.5×10^9/L (severe neutropenia or agranulocytosis), therapy was interrupted immediately, and ANC was monitored daily until resolution. The study was approved by the local ethics committees, and written informed consent was obtained from the patients' parents.

During the 6-month study, four patients (4%) experienced single episodes of neutropenia, all of them mild; one patient experienced two episodes, both mild; one patient experienced two mild episodes that resolved but then a third episode that progressed to agranulocytosis; and one patient experienced an event of agranulocytosis that was not preceded by neutropenia.

Of the four patients with single episodes, all had β-thalassemia major; three were male and one was female; all were non-splenectomized; and ages ranged from 2 to 6 yr. The lowest neutrophil counts for each patient during those events ranged from 0.62 to 1.35×10^9/L. Onset of neutropenia occurred within 60–152 d of starting deferiprone therapy, and all episodes resolved within 4–7 d despite continued therapy.

The patient who experienced two episodes of neutropenia was a 9-yr-old non-splenectomized boy with hemoglobin E β-thalassemia. The first episode began 49 d after starting deferiprone and resolved in 4 d, and the second began 3 months later and resolved in 10 d. Both episodes were mild; the lowest neutrophil counts were 1.35 and 1.11×10^9/L, respectively. Deferiprone therapy was continued in both cases.

The patient who experienced three episodes was a 4-yr-old non-splenectomized boy with β-thalassemia major. He had two separate episodes of neutropenia, both of which resolved, and then a subsequent episode of neutropenia that progressed to agranulocytosis. The first neutropenia event began 4 months after the start of therapy and resolved in 12 d, and the second began 2 d after resolution of the first and resolved in 5 d. Both events were mild, with lowest neutrophil counts of 1.01 and 0.94×10^9/L, respectively. Deferiprone therapy was continued in both cases. Seventeen days after resolution of the second event, the patient experienced another episode of mild neutropenia, with a neutrophil count of 1.31×10^9/L at onset. Deferiprone was continued for another 6 d, but moderate neutropenia was then confirmed with two consecutive values of $0.59\ 10^9$/L, at which point deferiprone was discontinued. The ANC continued to drop, reaching levels that were categorized as agranulocytosis: 0.24, 0.17, and 0.08×10^9/L. The patient was administered G-CSF for 10 d, and the event resolved 11 d after interruption of deferiprone. The patient was not rechallenged.

The patient who experienced agranulocytosis not preceded by neutropenia was an 8-yr-old non-splenectomized girl with β-thalassemia major and a history of hypothyroidism. The event began 9 wk after the start of therapy, with a precipitous drop in ANC to 0.48×10^9/L and a further decrease the next day to 0.17×10^9/L. Chelation therapy was immediately discontinued, and the patient was hospitalized and treated with G-CSF. The event resolved 10 d after discontinuation of deferiprone. The patient was not rechallenged.

The ANC values over the course of the trial of the seven patients with neutropenia or agranulocytosis, with an indication of the point at which the event(s) began, are shown in Fig. 1.

Discussion

This study examined whether maintenance of deferiprone therapy during episodes of mild neutropenia triggers the occurrence of agranulocytosis. No published data have been available up to now to address this question, in part because the recommended management is to interrupt deferiprone at the first sign of neutropenia of any severity. These data provide insight into the question.

Of 100 children who received deferiprone therapy for 6 months, six experienced one or more episodes of neutropenia, which matches the reported incidence of 6% in trials in which therapy was interrupted at the onset of neutropenia and patients were not rechallenged (2, 6). Eight of the nine episodes of neutropenia resolved, while one progressed to agranulocytosis. One further patient (1%) experienced agranulocytosis that was not preceded by neutropenia. As mandated, therapy was stopped immediately at the diagnosis of agranulocytosis.

In patients with thalassemia, neutropenia may be a result of factors other than chelation therapy. For instance, hypersplenism, a condition that is often associated with thalassemia, could induce neutropenia. Previous studies have demonstrated that neutropenia occurs significantly more often in patients with thalassemia who have not undergone splenectomy than in those who have (2, 6). In the present

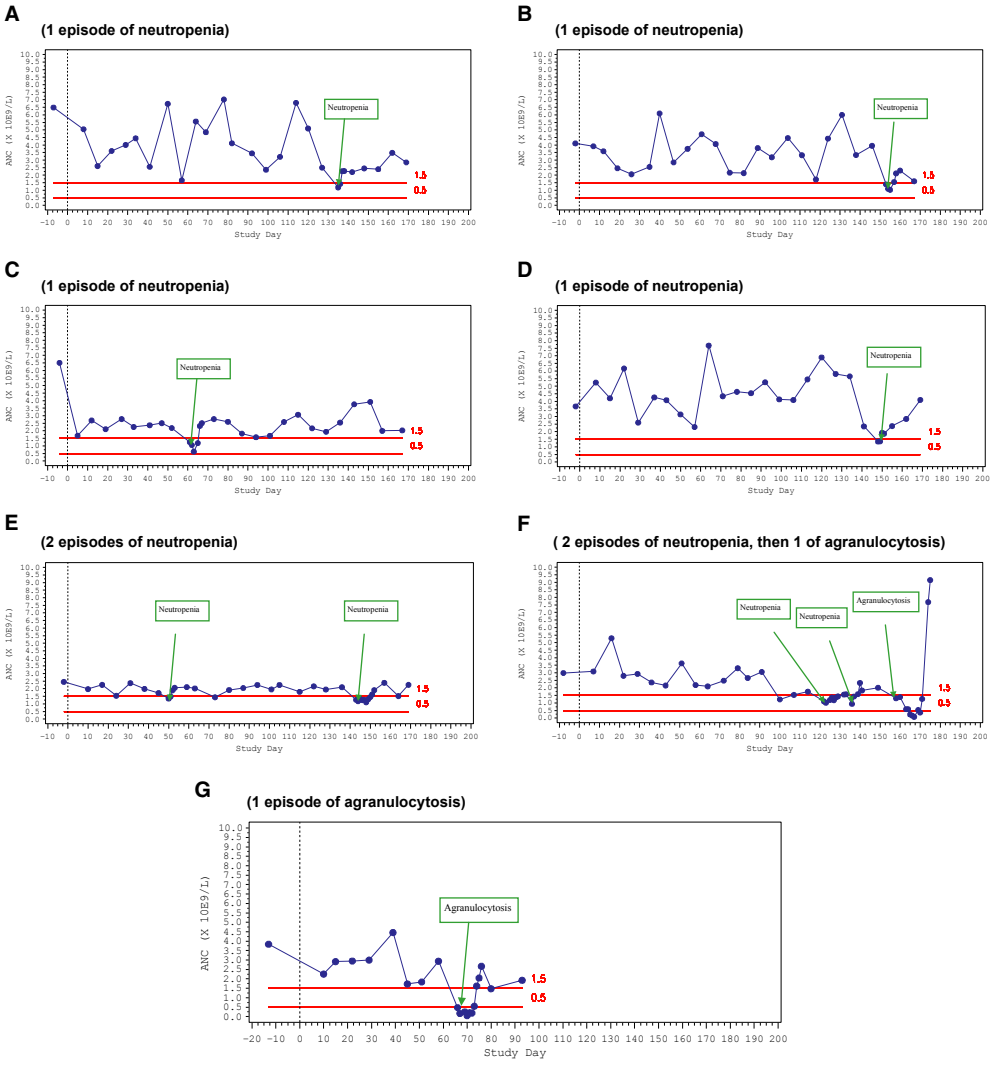

Figure 1 ANC values in patients who developed neutropenia or agranulocytosis.

study, all seven patients described above were non-splenectomized. The role of the spleen in depleting circulating neutrophil levels and in the development of neutropenia and agranulocytosis needs to be examined further. In addition, some viral infections, particularly parvovirus, may cause neutropenia independent of chelation therapy (7).

A possible explanation for the detection of neutropenia during deferiprone therapy is the frequency at which neutrophil counts are monitored. Transient declines in neutrophil counts to levels defined as neutropenic are common even in healthy individuals, particularly in children (8). It is likely that the frequent monitoring of neutrophil count mandated during deferiprone therapy has unveiled the occurrence of cases of transient neutropenia that would otherwise have gone undetected and resolved on their own without clinical consequences.

An intriguing possibility is that neutropenia and agranulocytosis seen in deferiprone-treated patients with systemic iron overload may not simply be quantitatively different but are in fact distinct phenomena arising from different causes: that is, that the milder event of neutropenia is at least partially attributable to the patient's underlying condition while the rarer and more severe event of agranulocytosis is attributable only to the treatment. Some support for this suggestion comes from the ApoPharma Inc. combined safety database of 11 clinical trials of deferiprone, looking at the data of patients with similar medical histories who received either deferiprone (N = 642; 1339 patient-yr) or deferoxamine (N = 118; 129 patient-yr). Despite the imbalance in total exposure, there was no significant difference in the rate of neutropenia between the two populations: 6.7% for deferiprone vs. 4.2% for DFO; P = 0.4111. (As DFO recipients did not undergo the weekly ANC monitoring required of deferiprone recipients, it is possible that cases of transient neutropenia that resolved on their own went undetected in this group and that the true difference between the groups was even less.) In contrast, agranulocytosis

was seen in 11 (1.7%) deferiprone recipients but not in a single DFO recipient.

In deferiprone-treated thalassemia patients who develop agranulocytosis, therapy must always be interrupted, as there have been serious complications in cases where this was not performed (9). However, it appears from published data that deferiprone-induced agranulocytosis in patients with thalassemia occurs against a backdrop of periodic episodes of less severe episodes of neutropenia, making it difficult to determine whether the patient is experiencing a drug-induced event or a transient event that is unrelated to deferiprone administration. The present practice is to always discontinue therapy in all patients who experience a decline in neutrophils below 1.5×10^9/L, irrespective of the potential cause of the neutropenia. On the one hand, this interruption may be warranted as a precautionary measure, but on the other hand, it may be unnecessarily precluding patients from continuing to receive a therapy that is beneficial to them. Justification for the discontinuation of therapy would be valid only if it would prevent the development of an ANC level low enough to put patients at risk of serious infections. This study shows that not all cases of mild neutropenia during deferiprone therapy develop into agranulocytosis, and suggests that many episodes of neutropenia may not be caused by deferiprone. In patients with thalassemia, natural fluctuations in ANC and factors such as viral illnesses or hypersplenism will increase the probability of a transient fall in the neutrophil count to a level defined as neutropenia (6). These findings therefore raise the question of whether there is justification in routinely stopping deferiprone therapy in patients who experience mild neutropenia. While treatment would always be stopped for any patient whose count falls below 0.5×10^9/L, the findings of this study raise the question of whether it should be routine practice to end it in patients whose drop is less severe. If such patients can have their ANC monitored more frequently during the neutropenic episode, and if there are no signs or symptoms of infection, it may be reasonable to either continue treatment (with stepped-up monitoring) or to suspend it and then resume once the count has returned to normal. It is possible that such a strategy would find the incidence of agranulocytosis to be higher in rechallenged patients than in those with no previous episodes of neutropenia; the present study sample is too small to draw conclusions regarding that risk. Given the concern over terminating treatment in patients with significant iron overload, particularly cardiac siderosis, it may be that the best strategy is to base the decision on the risk vs. benefit for each individual patient.

The mechanism of deferiprone-induced agranulocytosis has not yet been elucidated. Consistent with observations in other trials, there were no demographic traits, aspects of medical history, or baseline ANC values that differentiated the two individuals who developed agranulocytosis from the rest of the study patients. There may possibly be a genetic predisposition, similar to that in patients with congenital neutropenia or those with a human neutrophil antigen (HNA-1b) (7, 10), Patients who are enrolled in current Apo-Pharma clinical trials of deferiprone are asked to voluntarily provide a blood sample for genetic testing in the hope of finding some identifying factor for that predisposes some individuals to agranulocytosis during deferiprone therapy; however, there are no findings to date (Galanello R, personal communication). Regardless of the outcome, there is a need to establish whether or not deferiprone therapy should routinely be interrupted in cases of mild neutropenia. Further assessment of the regimen described here may help to establish whether an approach of stopping deferiprone only in patients whose neutrophil count drops below 1.0×10^9/L would be a more appropriate strategy.

References

1. Andres E, Zimmer J, Affenberger S, Federici L, Alt M, Maloisel F. Idiosyncratic drug-induced agranulocytosis: update of an old disorder. *Eur J Intern Med* 2006;**17**:529–35.
2. Ferriprox® (Deferiprone) Summary of Product Characteristics (SmPC). http://ec.europa.eu/health/documents/community-register/html/h108.htm.
3. Bertola U, Collell M, Piga A, Visconti RM, Cohen A. Neutropenia in homozygous b-thalassemic patients on desferrioxamine (DFO) treatment. In: *Proceedings of the 8th International Conference on Oral Chelation in the Treatment of Thalassemia and Other Diseases*, Corfu, Greece: 1997:90.
4. Pennell DJ, Berdoukas V, Karagiorga M, *et al.* Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. *Blood* 2006;**107**:3738–44.
5. El Alfy MS, Sari TT, Lee CL, Tricta F, El Beshlawy A. The safety, tolerability, and efficacy of a liquid formulation of deferiprone in young children with transfusional iron overload. *J Pediatr Hematol Oncol* 2010;**32**:601–5.
6. Cohen AR, Galanello R, Piga A, De Sanctis V, Tricta F. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone. *Blood* 2003;**102**:1583–7.
7. Palmblad JE, dem Borne AE. Idiopathic, immune, infectious, and idiosyncratic neutropenias. *Semin Hematol* 2002;**39**: 113–20.
8. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. *Ann Intern Med* 2007;**146**:486–92.
9. Henter JI, Karlén J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. *Blood* 2007;**109**:5157–9.
10. Wallis JP, Haynes S, Stark G, Green FA, Lucas GF, Chapman CE. Transfusion-related alloimmune neutropenia: an undescribed complication of blood transfusion. *Lancet* 2002;**360**:1073–4.