

Rates of severe neutropenia and infection risk in patients treated with deferiprone: 28 years of data

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Abstract:

Patients treated with deferiprone for transfusional iron overload may experience idiosyncratic drug-induced neutropenia (IDIN) that may put them at risk of infection. The purpose of this analysis was to examine the rates of severe IDIN and risk of serious infections at different ANC levels in patients treated with deferiprone. Events of severe IDIN (ANC $<0.5 \times 10^9/L$) and associated serious infections from clinical trials and postmarketing setting were analyzed by 3 discrete ANC levels: Group 1, $0.2-0.5 \times 10^9/L$; Group 2, $0.1-0.199 \times 10^9/L$; Group 3, $<0.1 \times 10^9/L$. In clinical trials, 22 events of severe IDIN were observed (Group 1, $n=9$; Group 2, $n=3$; Group 3, $n=10$); total deferiprone exposure was 1990.26 patient-years; and rates of severe IDIN per 100 patient-years were 0.45 in Group 1, 0.15 in Group 2, and 0.50 in Group 3. All serious infections were in Group 3 (3/10, 30.0%). In the postmarketing setting, 176 events of severe IDIN were reported (Group 1, $n=65$; Group 2, $n=20$; Group 3, $n=91$); total deferiprone exposure was 111,570.24 patient-years; and rates of severe IDIN per 100 patient-years were 0.06 in Group 1, 0.02 in Group 2, and 0.08 in Group 3. Rates of serious infection were 7.7% ($n=5/65$) in Group 1, 10% ($n=2/20$) in Group 2, and 13.2% ($n=12/91$) in Group 3. Our findings suggest that in patients receiving deferiprone, ANC below $0.2 \times 10^9/L$ carries a high risk of serious infections, consistent with the recent neutropenia guidelines that agranulocytosis with ANC $<0.2 \times 10^9/L$ is associated with a high risk of serious infections.

Conflict of interest: COI declared - see note

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Running title:

Deferiprone-related infection and severe neutropenia

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Key points:

- In patients treated with deferiprone, ANC levels below $0.2 \times 10^9/L$ conferred the highest risk of serious infections.
- An ANC of less than $0.2 \times 10^9/L$ may be a clinically relevant threshold to define agranulocytosis with a high risk of infection.

Abstract

Patients treated with deferiprone for transfusional iron overload may experience idiosyncratic drug-induced neutropenia (IDIN) that may put them at risk of infection. The purpose of this analysis was to examine the rates of severe IDIN and risk of serious infections at different ANC levels in patients treated with deferiprone. Events of severe IDIN ($ANC < 0.5 \times 10^9/L$) and associated serious infections from clinical trials and postmarketing setting were analyzed by 3 discrete ANC levels: Group 1, $0.2-0.5 \times 10^9/L$; Group 2, $0.1-0.199 \times 10^9/L$; Group 3, $< 0.1 \times 10^9/L$. In clinical trials, 22 events of severe IDIN were observed (Group 1, $n=9$; Group 2, $n=3$; Group 3, $n=10$); total deferiprone exposure was 1990.26 patient-years; and rates of severe IDIN per 100 patient-years were 0.45 in Group 1, 0.15 in Group 2, and 0.50 in Group 3. All serious infections were in Group 3 (3/10, 30.0%). In the postmarketing setting, 176 events of severe IDIN were reported (Group 1, $n=65$; Group 2, $n=20$; Group 3, $n=91$); total deferiprone exposure was 111,570.24 patient-years; and rates of severe IDIN per 100 patient-years were 0.06 in Group 1, 0.02 in Group 2, and 0.08 in Group 3. Rates of serious infection were 7.7% ($n=5/65$) in Group 1, 10% ($n=2/20$) in Group 2, and 13.2% ($n=12/91$) in Group 3. Our findings suggest that in patients receiving deferiprone, ANC below $0.2 \times 10^9/L$ carries a high risk of serious infections, consistent with the recent neutropenia guidelines that agranulocytosis with $ANC < 0.2 \times 10^9/L$ is associated with a high risk of serious infections.

Introduction

Acute, unforeseeable and transient declines in absolute neutrophil counts (ANC) can occur with the use of some medications, a condition here referred to as idiosyncratic drug-induced neutropenias (IDIN).¹⁻⁵ Although rare, IDIN may put patients at a high risk of serious and sometimes fatal infections, in particular if IDIN is profound and long-lasting.^{1,2,5-8} For example, it is estimated that as many as 60% of patients with severe IDIN develop septicemia if their infections are not treated aggressively.⁹ Because patients experiencing IDIN can progress rapidly from having no symptoms or fever to developing sepsis,⁴ early detection of IDIN and timely measures to increase ANC are critical to prevent serious infections.^{2,5,8}

While the clinical characterization of neutropenias into strata of mild (ANC $1-1.5 \times 10^9/L$), moderate (ANC $0.5-1 \times 10^9/L$), and severe (ANC $<0.5 \times 10^9/L$) helps in predicting the risk of infections in patients with any type of neutropenia, there is a need to further characterize the risk of infections in severely neutropenic patients with very low ANCs (ie, below $0.5 \times 10^9/L$) in order to establish algorithms for rapid interventions adjusted to ANC levels and specific drugs.

In a study involving 203 patients with severe IDIN, with a median (range) ANC of $0.08 \times 10^9/L$ ($0-0.48$) at the nadir, clinical features of sepsis with serious infections (eg, extensive pneumonia or septicemia) were observed in >38% of patients and intensive care required in 18% of patients.² The main clinical presentations during hospitalization were isolated fever (26%), septicemia/septic shock (21%), pneumonia (13%), and sore throat/tonsillitis (9%).² Additionally, a systematic review that included data from 980 case reports of nonchemotherapy drug-induced neutropenia found that patients with ANC $<0.1 \times 10^9/L$ had a significantly higher rate of localized infections, sepsis, and fatal complications compared with those with ANC $0.1 \times 10^9/L$ or above.¹ The newly published consensus-based guidelines by the EHA/EuNet-INNOCHRON COST state that the term agranulocytosis may be used for severe chronic neutropenias with ANC $<0.2 \times 10^9/L$.¹⁰ Thus, clinical observations and evidence suggest that

ANC of $<0.2 \times 10^9/L$ or $<0.1 \times 10^9/L$ may better identify patients at the highest risk of serious infections when compared with the broader range of ANC values of $0.2\text{--}0.5 \times 10^9/L$. The risks for serious infections vary not only with degree or depth of neutropenia, but also with drugs involved and duration of neutropenia. Thus, certain drugs are associated with IDINs that are more severe and longer lasting (eg, metamizole and clozapine)^{1,3,11} than others (eg, trimethoprim sulphamethoxazole),¹² probably relating to a drug-specific mechanism of interference with various stages of neutropoiesis.

Deferiprone (Ferriprox[®]) is an oral iron chelator that can be associated with transient episodes of neutropenia or severe neutropenia.^{5,13-16} Deferiprone is indicated for the treatment of transfusional iron overload in adult and pediatric patients with thalassemia, sickle cell disease (SCD), or other anemias.^{17,18} Treatment with deferiprone is associated with favorable safety and efficacy outcomes, both as monotherapy^{19,20} or in combination with other chelators.^{19,21} As described previously by Tricta et al, based on the ANC cutoff of $<0.5 \times 10^9/L$ (termed as agranulocytosis in the deferiprone US Prescribing Information [USPI]), the incidence of severe IDIN was 1.7% in pooled clinical trials of 642 patients with thalassemia syndromes and 1.5% in pooled clinical trials of 196 patients with SCD or other anemias.^{17,18,22} However, the risk of infection and rates of severe IDIN at ANC of $<0.2 \times 10^9/L$ or $<0.1 \times 10^9/L$ in patients treated with deferiprone have not been described.

In this analysis, we extracted events of severe IDIN from company-sponsored clinical trials of deferiprone and the postmarketing setting. We then examined the rates of severe IDIN as well as the risk of serious infections at three discrete ANC levels.

Methods

Data source

Company-sponsored clinical trials

Events of severe IDIN from clinical trials were extracted from data associated with all patients with systemic iron overload (thalassemia syndromes, SCD, or other conditions) who received at least 1 dose of deferiprone across 15 company-sponsored clinical trials from 1993 to 31 August 2021. Patients treated in more than 1 clinical trial were counted once. For this analysis, severe IDIN was defined as any reported event of agranulocytosis, which was defined as ANC $<0.5 \times 10^9/L$ in the study protocols, Investigator's Brochures, and deferiprone USPI.

Postmarketing setting

Events of severe IDIN were identified from individual case safety reports (ICSR) from the deferiprone postmarketing surveillance program since its approval on August 25, 1999, to August 31, 2021. Similar to the definition used in clinical trials, ICSRs with adverse drug reactions (ADRs) coded to the term agranulocytosis were extracted and defined as events of severe IDIN for this analysis. Some ICSRs coded to the term agranulocytosis did not have ANC values reported and confirmatory ANC values were not always available in the postmarketing setting. Events of severe IDIN that did not have ANC values were excluded, and those with at least 1 ANC value were included for analysis.

Patient narratives in the ICSRs were compiled from reports that were solicited and/or spontaneously reported by patients, caregivers, pharmacists, and/or healthcare providers. Patient narratives could include demographics, medical history, suspected and concomitant medications, description of the case (eg, ANC measurements, relevant laboratory tests, time to onset, duration, severity, outcome, and rechallenge), and causality assessment. Additional information relevant to each event was also collected. All patient data were de-identified prior to being reported to the pharmacovigilance department at Chiesi.

Analysis of rates of severe IDIN

Rates of severe IDIN were normalized to estimated deferiprone exposure, which was expressed as the number of severe IDIN events per 100 patient-years. In the postmarketing setting, exposure to deferiprone was estimated from the cumulative worldwide sales and a defined daily dose of 75 mg/kg. For tablet formulations (500 and 1000 mg both three times a day and twice a day formulation), one patient-year of exposure is considered equivalent to 1,643,625 mg of sales, as follows: at an average patient weight of 60 kg and the defined daily dose of 75 mg/kg, the daily dose requirement is 4500 mg, taken 365.25 days per year. For oral solution (100 mg/mL), one patient-year of exposure is considered equivalent to 1,095,750 mg of sales; since it is expected that most use of this formulation is by pediatric patients, a lower average patient weight is used than for the tablet formulations, as follows: at an average patient weight of 40 kg and the defined daily dose of 75 mg/kg, the daily dose requirement is 3000 mg, taken 365.25 days per year.

Analysis of serious infections

Infections that led to hospitalizations and life-threatening complications, including death, were reported as serious and/or severe based on CTCAE criteria. Serious and/or severe infections that occurred within 2 weeks of onset of severe IDIN were of particular interest for the purpose of this analysis. Reported data associated with infections were coded using the Medical Dictionary for Regulatory Activities (MedDRA). When available, additional data on patient medical history, concomitant medications, and associated adverse events (AEs) were used in the analysis of infection episodes.

Serious infectious events were defined as any event that resulted in death, was life-threatening, required or prolonged hospitalization, caused disability or permanent damage, resulted in a congenital anomaly or birth defect, required intervention to prevent permanent impairment or damage, or was classified as an important medical event. Life-threatening

infectious events were defined as any event that placed the patient at immediate risk of death. Severe infections were defined as any event that was incapacitating and required medical intervention.

Regulatory obligations require the reporting of 'serious' and 'severe'; however, 'serious' is not the same as 'severe'. The term 'serious' is based on patient/event outcome usually associated with events that pose a threat to a patient's life or functioning. The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, severe). For the purpose of this analysis, we are using the term 'serious' to indicate infections that were reported as serious, severe, or life-threatening in clinical trials and postmarketing ICSRs.

Data analysis

Events of severe IDIN as well as the associated serious infections were analyzed by 3 discrete ANC groups based on the nadir ANC: Group 1, ANC $0.2\text{--}0.5\times 10^9/\text{L}$; Group 2, ANC $0.1\text{--}0.199\times 10^9/\text{L}$; or Group 3, ANC $<0.1\times 10^9/\text{L}$. To examine any clinically significant trends, events of severe IDIN were additionally analyzed by 3 all-encompassing ANC thresholds: $<0.5\times 10^9/\text{L}$, $<0.2\times 10^9/\text{L}$, and $<0.1\times 10^9/\text{L}$.

The incidence of severe IDIN was analyzed in clinical trials, but not in the postmarketing setting owing to the uncertainty in the actual number of patients who received deferiprone and missing patient information. This analysis focused primarily on the rates of severe IDIN normalized to exposure per 100 patient-year to achieve consistency in data reporting between clinical trials and the postmarketing setting.

Results

Company-sponsored clinical trials

Overall, 22 events of severe IDIN were reported in deferiprone-treated patients enrolled across 15 clinical trials. Severe IDIN occurred predominantly in females (61.9%) and in patients diagnosed with thalassemia major (57.1%) (**Table 1**). The mean (SD) time from initiation of deferiprone to onset of severe IDIN was 736.2 days (1461.3 days). Severe IDIN resolved or patients recovered with permanent (n=15/22, 68.2%) or temporary (n=4/22, 18.2%) discontinuation of deferiprone; in the remaining events, 1 recovered with no action taken, 1 recovered and the action was not applicable as the patient had already ended exposure with deferiprone, and 1 resulted in a fatal outcome. In 14 of 22 (63.3%) events, granulocyte-colony stimulating factor (GCSF) treatment was initiated at a mean (SD) of 3.1 (3.8) days after onset of severe IDIN. The total deferiprone exposure was 1990.26 patient years. The total deferiprone exposure in clinical trials is based on a total of 977 patients with systemic iron overload who received at least 1 dose of deferiprone.

Stratification of severe IDIN events by discrete ANC groups demonstrated that 9 events were within Group 1, 3 events were within Group 2, and 10 events were within Group 3. Rates of severe IDIN per 100 patient-years were 0.45 for Group 1, 0.15 for Group 2, and 0.50 for Group 3 (**Table 2** and **Figure 1**). The median (range) durations of severe IDIN stratified by ANC groups were 16 days (3–93 days) within Group 1, 3 days (2–5 days) within Group 2, and 4 days (3–13 days) within Group 3. One event of severe IDIN in Group 1 lasted 93 days; excluding this event resulted in a median (range) duration of severe IDIN of 14 days (3–21 days).

The incidence of severe IDIN stratified by ANC levels ranged from 1.02%–0.31% among the clinical trial cohort. Based on the ANC groups, 9 events of severe IDIN occurred in 9 patients in Group 1 for an incidence of 0.92%, 3 events occurred in 3 patients in Group 2 for an incidence of 0.31%, and 10 events occurred in 10 patients in Group 3 for an incidence of 1.02%.

A summary of serious infections observed in the clinical trials is shown in **Table 3**. Of the 12 events of severe IDIN in Groups 1 and 2, none were associated with any serious infections. Of the 10 events in Group 3, three (30%) were associated with serious infections. Brief descriptions of these 3 patient cases are presented below. Note that patient case descriptions below may include the term ‘agranulocytosis’ per the terminology used for regulatory reporting in the deferiprone clinical development program.

One patient with hereditary spherocytosis had a parvovirus infection with diarrhea, a maculopapular rash, and pyrexia resulting in hospitalization. During hospitalization, the patient had ANC values that decreased from $3.25 \times 10^9/\text{L}$ to $0.56 \times 10^9/\text{L}$ and reached a nadir of $0 \times 10^9/\text{L}$. Deferiprone was discontinued and GCSF treatment initiated. After 3 days, the ANC increased to $1.56 \times 10^9/\text{L}$. This episode of agranulocytosis was reassessed as unlikely related to the use of deferiprone, but rather associated with parvovirus infection, considering manifestation of signs of infection prior to the onset of agranulocytosis. The parvovirus infection was deemed serious and not related to deferiprone.

A second patient with hereditary hemochromatosis was receiving deferiprone for severe cardiac iron overload and had a history of neutropenia before initiating deferiprone. The patient was hospitalized for 13 days with their ANC ranging from 0.01 – $0.06 \times 10^9/\text{L}$. While there were no signs or symptoms of infections prior to noting agranulocytosis, the patient developed esophageal candidiasis and respiratory tract infection after developing agranulocytosis. Deferiprone was discontinued, GCSF was initiated, and the patient recovered with mild sequelae. The infections were considered non-serious but severe and likely to be related to deferiprone-induced agranulocytosis.

A third patient also had hereditary hemochromatosis and a history of multiple comorbidities, including hypertension, chronic obstructive pulmonary disease, liver cirrhosis, and congestive heart failure. This patient developed agranulocytosis (ANC of $0.1 \times 10^9/\text{L}$) approximately 3 months after initiation of deferiprone therapy and was hospitalized with

Pseudomonas sepsis. Deferiprone was discontinued. The patient had ANC values ranging from $0 \times 10^9/L$ to $3.2 \times 10^9/L$ during the 5-day hospitalization, developed complications of atrial fibrillation, experienced acute kidney failure, and died. The cause of death was multisystem organ failure secondary to *Pseudomonas* sepsis, hospital-acquired pneumonia, and deferiprone-induced agranulocytosis. The comorbidity of ischemic heart disease and a recent episode of congestive heart failure might have also contributed to the onset of atrial fibrillation, kidney failure, and subsequent death.

Postmarketing setting

To determine if what we observed in sponsored clinical trials is consistent with real-world settings, we analyzed data from the deferiprone postmarketing surveillance program. We extracted a total of 238 events that were reported as agranulocytosis (i.e., ICSRs that coded to the term ‘agranulocytosis’, with or without ANC values reported) and defined as events of severe IDIN for the purpose of this analysis. Severe IDIN occurred predominantly in females (56.8%) and those diagnosed with thalassemia syndromes (69.9%) in the postmarketing setting (**Table 4**). The mean (SD) time from initiation of deferiprone to severe IDIN was 398.2 days (716.3 days) among 185 events with evaluable data. Most events of severe IDIN either resolved ($n=171/238$, 71.8%), were resolving ($n=14/238$, 5.9%), or resolved with sequelae ($n=2/238$, 0.8%); other cases were associated with ongoing ($n=4/238$, 1.7%), unknown ($n=28/238$, 11.8%), or fatal ($n=19/238$, 8.0%) outcomes. Cumulative deferiprone exposure was estimated to amount to 111,570.24 patient-years.

Of these 238 events, 176 had at least 1 ANC value reported and were analyzed. There were 65 events of severe IDIN in Group 1, 20 events in Group 2, and 91 events in Group 3. Rates of severe IDIN stratified by ANC groups and all-encompassing ANC thresholds are summarized in **Table 2** and **Figure 1**.

As with the clinical trial setting, in the postmarketing setting the occurrence of serious infections was higher with lower ANC levels. A total of 19 serious infectious events were identified; all infectious events required hospitalization and resulted in either recovery ($n = 6$), death ($n = 12$), or unknown outcome ($n = 1$). A summary of these infectious events is shown in **Table 5**.

In Group 1, 5 serious infectious events were reported in 5 patients among the 65 total severe IDIN events (7.7%). Of these 5 infectious events, 3 (4.6%) resulted in deaths, all due to sepsis.

In Group 2, 2 serious infectious events were reported in 2 patients among the 20 total severe IDIN events (10.0%). One patient with β -thalassemia major had a life-threatening infection with high-grade pyrexia and ANC of $0.1 \times 10^9/L$ approximately 3 months after initiating deferiprone. Deferiprone was discontinued and ANC levels recovered in a week, but the patient developed pneumonia complicated by massive hemoptysis secondary to rupture of pulmonary artery aneurism. Pneumonia was considered serious and related to deferiprone-induced severe IDIN. A second patient with β -thalassemia died 7 months after the start of deferiprone when they developed sore throat with progressive worsening. The lowest reported ANC was $0.1 \times 10^9/L$. The preliminary cause of death was septic shock, and autopsy report was not available for this patient.

In Group 3, 12 serious infectious events were reported by 12 patients among the 91 total severe IDIN events (13.2%). Of these, 8 (8.8%) were fatal, all due to sepsis. Among the non-fatal serious infectious events, one patient with transfusion-dependent red cell aplasia with a history of cardiac transplant and end-stage renal failure developed neutropenia and neutropenic sepsis within 3 months of starting deferiprone. The patient had a nadir ANC of $0 \times 10^9/L$, which resolved in about 3 weeks. A second patient with β -thalassemia and diabetes developed pancytopenia after 1.5 months on deferiprone therapy. Deferiprone was discontinued when the patient became neutropenic (ANC of $1.1 \times 10^9/L$). However, the patient developed oropharyngeal

pain, fever, and diarrhea with a nadir ANC of $0 \times 10^9/L$, requiring hospitalization and GCSF and eventually recovered within a week. A third patient with β -thalassemia and a history of severe cardiac iron overload developed severe neutropenia (ANC of $0 \times 10^9/L$) 3 weeks after starting deferiprone and was diagnosed with invasive mucormycosis. The infection was considered to be related to deferiprone-induced neutropenia but resolved with sequelae. A fourth patient with β -thalassemia developed lymphopenia and severe neutropenia on deferiprone with a nadir ANC of $0 \times 10^9/L$, approximately 4 years after deferiprone initiation. The patient was hospitalized for sepsis and disseminated herpes simplex along with extensive mucositis. ANC levels recovered after 7 days with GCSF treatment, and the event was considered to be associated with deferiprone.

Discussion

The most significant adverse drug reaction associated with deferiprone use is a decline in absolute neutrophil count below $0.5 \times 10^9/L$, defined as severe IDIN. Several studies have reported rates of severe IDIN ranging from 0.5% to 3.6% with deferiprone use.²³⁻²⁵ Although the incidence of severe IDIN decreases after the first year of therapy,²² its occurrence is associated with a high risk of infection.

Despite the risk of serious infections related to the degree and duration of neutropenia, most patients experiencing severe IDIN usually recover over time with supportive care and timely treatment.²⁶ Without immediate medical intervention, patients with ANC $<0.5 \times 10^9/L$ can develop septicemia with clinical signs of pneumonia, anorectal, skin, or oropharyngeal infections and septic shock.^{2,26} With deferiprone-associated severe IDIN, most patients recover neutrophil counts with continued treatment and monitoring,²⁷ and rarely is permanent discontinuation required.

In this analysis of severe IDIN events in patients treated with deferiprone in clinical trials and the postmarketing setting, we found that ANC levels $<0.1 \times 10^9/\text{L}$ or $<0.2 \times 10^9/\text{L}$ are consistently associated with a higher risk of serious infection and/or mortality compared with ANC levels of $0.2\text{--}0.5 \times 10^9/\text{L}$. In clinical trials, all (100%) serious infections, including 1 fatality, occurred in patients with ANC $<0.1 \times 10^9/\text{L}$, and no serious infections occurred in patients with ANC ranging from $0.1\text{--}0.5 \times 10^9/\text{L}$. No serious infections or fatalities occurred in Group 1 despite the generally longer duration of severe IDIN compared with Groups 2 and 3 in clinical trials. In the postmarketing setting, serious infections were generally more common with ANC of $<0.2 \times 10^9/\text{L}$ (10.0% in Group 2 and 13.2% in Group 3) compared with ANC of $0.2\text{--}0.5 \times 10^9/\text{L}$ (7.7%), with fatal outcomes being more likely when ANC dropped $<0.2 \times 10^9/\text{L}$ (9 deaths in Groups 2 and 3 vs 3 deaths in Group 1). Despite discontinuation of deferiprone at the first sign of infection or fever and treatment with GCSF, in most of the fatal cases reported in the deferiprone clinical development program, the patient progressed to developing septic shock or septicemia. Additionally, we found that severe IDIN was generally more common in female patients than males, which is consistent with evidence that female sex is an independent risk factor for developing neutropenia.²⁸ The findings that mean time to severe IDIN was approximately 2 years in clinical trials and 1 year in the postmarketing setting highlight the importance of monitoring ANC, and signs and symptoms of infection during the first years of deferiprone treatment.

Our findings suggest that patients taking deferiprone are at the highest risk of serious infections at the lowest ANC levels. Several case studies on deferiprone-induced severe neutropenia have described life-threatening conditions, including two fatal cases, where ANC dropped below $0.1 \times 10^9/\text{L}$ with a complete lack of neutrophils reported in some patients.^{13,15,16,29-}

³² Two of these cases occurred in patients with Diamond Blackfan anemia, where deferiprone was associated with an abrupt drop in ANC to $0.1 \times 10^9/\text{L}$ or less within 6–9 weeks of therapy initiation.^{13,31} Both patients presented with persistent high grade fever and were treated with

broad spectrum antibiotics; one of them also received GCSF but eventually died. To date, four incidents of deferiprone-induced severe neutropenia have been recorded in patients with thalassemia, and in all of those cases, ANC levels precipitously dropped to $<0.1 \times 10^9/L$, with one patient dying due to multi-organ failure.^{15,16,29,32} Additionally, Newburger and Dale³³ observed that while ANC of $0.2\text{--}0.5 \times 10^9/L$ is associated with an increased risk of infection in most patients, ANC of $0.2 \times 10^9/L$ or less carries a risk of severe, life-threatening infections with susceptibility to opportunistic organisms. In summary, our findings in this systematic and comprehensive analysis in a very large cohort of patients treated with deferiprone confirm anecdotal reports in the literature that the degree of ANC decline is a critical predictor of risk of infections.

The newly published consensus-based guidelines by the EHA/EuNet-INNOCHRON COST suggest that severe chronic neutropenias with ANC $<0.2 \times 10^9/L$ might be termed ‘agranulocytosis’ and are associated with a high risk of severe, life-threatening infections.¹⁰ Additionally, some clinicians use an ANC threshold of $<0.1 \times 10^9/L$ to denote agranulocytosis with the highest risk for infection.⁵ Here, we have provided clinical evidence for supporting lower ANC threshold than the previously used $<0.5 \times 10^9/L$ to define agranulocytosis. However, due to the diurnal variations in ANC and other causes of ANC variability together with lack of precision in measuring very low ANC levels, it is less relevant to differentiate between sharp ANC cutoffs of 0.1 or $0.2 \times 10^9/L$. Therefore, we suggest that the term agranulocytosis may be used for severe IDIN with ANC $<0.2 \times 10^9/L$,³⁴ as suggested by the EHA/EuNet-INNOCHRON COST.¹⁰

According to the deferiprone product label, incidence of severe IDIN (termed as agranulocytosis in deferiprone label) is 1.7% among patients with thalassemia syndromes.¹⁷ Additional studies have reported incidence of severe IDIN ranging from 0.5% to 3.6% with deferiprone use based on ANC cutoff of $<0.5 \times 10^9/L$.^{23-25,35,36} In our clinical trial cohort of a total 977 patients, 22 events of severe IDIN (ANC $<0.5 \times 10^9/L$) occurred in 21 patients for an incidence of 2.15%, 13 events occurred in 12 patients with ANC $<0.2 \times 10^9/L$ for an incidence of

1.23%, and 10 events occurred in 10 patients with ANC $<0.1 \times 10^9/L$ for an incidence of 1.02%. Based on the EHA/EuNet-INNOCHRON COST guidelines¹⁰ as well as our analysis, using the clinically relevant ANC cutoff of $<0.2 \times 10^9/L$ reduces the incidence of agranulocytosis from 2.15% to 1.23%. Using the threshold of ANC $<0.1 \times 10^9/L$, the incidence of agranulocytosis declined from 2.15% to 1.02%. Based on these trends, it appears that ANC cutoffs of $<0.2 \times 10^9/L$ or $<0.1 \times 10^9/L$ may be better thresholds to define deferiprone-induced agranulocytosis.

A limitation of this study is that individual case reports of severe IDIN in the postmarketing setting vary in quality, completeness, and accuracy despite attempts to collect all available relevant information. Due to missing or under-reporting of unique patient identifiers, we were unable to perform an accurate analysis of the incidence of severe IDIN from the postmarketing setting. In addition, the low number of severe IDIN cases in the clinical setting also precluded the ability to provide accurate and meaningful statistical correlation analyses between serious infections and various factors (eg, duration of neutropenia, presence of organ failure). Further, external factors (eg, environmental or social factors) are difficult to account for but may also influence the rates of severe IDIN in the clinical trial and postmarketing settings. Nevertheless, this study represents the largest analysis of all severe IDIN cases in patients treated with deferiprone in clinical trials or postmarketing setting.

In conclusion, our analysis has demonstrated that lower ANC thresholds of $<0.2 \times 10^9/L$ or $<0.1 \times 10^9/L$ are clinically relevant to define deferiprone-induced agranulocytosis associated with a higher risk of serious infections. By using these lower thresholds, clinicians may be able to better assess the risk associated with deferiprone use. While the idiosyncratic nature of deferiprone-induced agranulocytosis is not a reliable predictor of the ANC trend or the duration of the event, a proactive approach to detecting early signs of infection is recommended for all patients regardless of the severity of neutropenia. Furthermore, this potential change in risk

stratification and definition of agranulocytosis may help to improve patients' access to adequate chelation regimens, leading to lower iron overload and better clinical outcomes.

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Authorship Contributions:

FT, NTT, CF, LL, and AR analyzed the results and made the figures. SMB, JP, FT, NTT, CF, LL, AR, and SS designed the research and wrote the paper.

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SMB received consultancy fees from Chiesi, bluebird bio, Vertex Pharmaceuticals, Forma Therapeutics, Novo Nordisk, Global Blood Therapeutics, Pfizer, Bristol Myers Squibb, and Editas Medicine.

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References:

1. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med.* 2007;146(9):657-665.
2. Andres E, Mourot-Cottet R, Maloisel F, et al. Idiosyncratic drug-induced neutropenia & agranulocytosis. *QJM.* 2017;110(5):299-305.
3. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med.* 1966;64(2):328-340.
4. Tesfa D, Keisu M, Palmblad J. Idiosyncratic drug-induced agranulocytosis: possible mechanisms and management. *Am J Hematol.* 2009;84(7):428-434.
5. Rattay B, Benndorf RA. Drug-induced idiosyncratic agranulocytosis - infrequent but dangerous. *Front Pharmacol.* 2021;12:727717.
6. Andres E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. *Curr Opin Hematol.* 2008;15(1):15-21.
7. Boxer LA. How to approach neutropenia. *Hematology Am Soc Hematol Educ Program.* 2012;2012:174-182.
8. Curtis BR. Non-chemotherapy drug-induced neutropenia: key points to manage the challenges. *Hematology Am Soc Hematol Educ Program.* 2017;2017(1):187-193.
9. Pick AM, Nystrom KK. Nonchemotherapy drug-induced neutropenia and agranulocytosis: could medications be the culprit? *J Pharm Pract.* 2014;27(5):447-452.
10. Fioredda F, Skokowa J, Tamary H, et al. The European guidelines on diagnosis and management of neutropenia in adults and children: A consensus between the European Hematology Association and the EuNet-INNOCHRON COST action. *Hemasphere.* 2023;7(4):e872.
11. Andrade S, Bartels DB, Lange R, Sandford L, Gurwitz J. Safety of metamizole: a systematic review of the literature. *J Clin Pharm Ther.* 2016;41(5):459-477.
12. Keisu M, Wiholm BE, Palmblad J. Trimethoprim-sulphamethoxazole-associated blood dyscrasias. Ten years' experience of the Swedish spontaneous reporting system. *J Intern Med.* 1990;228(4):353-360.
13. Henter JI, Karlen J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. *Blood.* 2007;109(12):5157-5159.
14. Lecornec N, Castex MP, Reguerre Y, et al. Agranulocytosis in patients with Diamond-Blackfan anaemia (DBA) treated with deferiprone for post-transfusion iron overload: A retrospective study of the French DBA cohort. *Br J Haematol.* 2022;199(2):285-288.
15. Mainou M, Kotsiafti A, Klonizakis P, et al. A case of fatal agranulocytosis that developed in a patient with beta-thalassemia major treated with deferiprone. *Hemoglobin.* 2016;40(6):435-437.
16. Masera N, Tavecchia L, Longoni DV, Maglia O, Biondi A, Masera G. Agranulocytosis due to deferiprone: a case report with cytomorphological and functional bone marrow examination. *Blood Transfus.* 2011;9(4):462-465.
17. FERRIPROX® (deferiprone) Tablets, for oral use. Cary, NC, USA: Chiesi USA, Inc.; 2021.

18. FERRIPROX[®] (deferiprone) Oral Solution, for oral use. Cary, NC, USA: Chiesi USA, Inc.; 2021.
19. Botzenhardt S, Felisi M, Bonifazi D, et al. Long-term safety of deferiprone treatment in children from the Mediterranean region with beta-thalassemia major: the DEEP-3 multi-center observational safety study. *Haematologica*. 2018;103(1):e1-e4.
20. Elalfy MS, Hamdy M, El-Beshlawy A, et al. Deferiprone for transfusional iron overload in sickle cell disease and other anemias: open-label study of up to 3 years. *Blood Adv*. 2023;7(4):611-619.
21. Tanner MA, Galanello R, Dessi C, et al. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation*. 2007;115(14):1876-1884.
22. Tricta F, Uetrecht J, Galanello R, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. *Am J Hematol*. 2016;91(10):1026-1031.
23. al-Refaie FN, Hershko C, Hoffbrand AV, et al. Results of long-term deferiprone (L1) therapy: a report by the International Study Group on Oral Iron Chelators. *Br J Haematol*. 1995;91(1):224-229.
24. Ceci A, Baiardi P, Felisi M, et al. The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. *Br J Haematol*. 2002;118(1):330-336.
25. 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(5):1583-1587.
26. Andres E, Villalba NL, Zulfiqar AA, Serraj K, Mourot-Cottet R, Gottenberg AJ. State of Art of Idiosyncratic Drug-Induced Neutropenia or Agranulocytosis, with a Focus on Biotherapies. *J Clin Med*. 2019;8(9):1351.
27. El-Beshlawy AM, El-Alfy MS, Sari TT, Chan LL, Tricta F. Continuation of deferiprone therapy in patients with mild neutropenia may not lead to a more severe drop in neutrophil count. *Eur J Haematol*. 2014;92(4):337-340.
28. Lorenzo-Villalba N, Alonso-Ortiz MB, Maouche Y, Zulfiqar AA, Andres E. Idiosyncratic Drug-Induced Neutropenia and Agranulocytosis in Elderly Patients. *J Clin Med*. 2020;9(6):1808.
29. al-Refaie FN, Veys PA, Wilkes S, Wonke B, Hoffbrand AV. Agranulocytosis in a patient with thalassaemia major during treatment with the oral iron chelator, 1,2-dimethyl-3-hydroxypyrid-4-one. *Acta Haematol*. 1993;89(2):86-90.
30. al-Refaie FN, Wonke B, Hoffbrand AV. Deferiprone-associated myelotoxicity. *Eur J Haematol*. 1994;53(5):298-301.
31. Hoffbrand AV, Bartlett AN, Veys PA, O'Connor NT, Kontoghiorghes GJ. Agranulocytosis and thrombocytopenia in patient with Blackfan-Diamond anaemia during oral chelator trial. *Lancet*. 1989;2(8660):457.
32. Sheikh-Taha M, Koussa S, Inati A, Taher A. Febrile neutropenia and hemorrhagic stroke in a thalassemia major patient. *Hemoglobin*. 2007;31(4):499-501.
33. Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. *Semin Hematol*. 2013;50(3):198-206.

34. Shultz W. Über Eigenartige Halserkrankungen. *Dtsch Med Wochenschr.* 1922;48:1495-1497.
35. Maggio A, Kattamis A, Felisi M, et al. Evaluation of the efficacy and safety of deferiprone compared with deferasirox in paediatric patients with transfusion-dependent haemoglobinopathies (DEEP-2): a multicentre, randomised, open-label, non-inferiority, phase 3 trial. *Lancet Haematol.* 2020;7(6):e469-e478.
36. Kwiatkowski JL, Hamdy M, El-Beshlawy A, et al. Deferiprone vs deferoxamine for transfusional iron overload in SCD and other anemias: a randomized, open-label noninferiority study. *Blood Adv.* 2022;6(4):1243-1254.

Figure 1. Rates of severe IDIN in patients treated with deferiprone across the clinical development program. Stratification of rates of severe IDIN from clinical trials or postmarketing setting by discrete absolute neutrophil count (ANC) groups based on the nadir ANC: Group 1, ANC $0.2\text{--}0.5 \times 10^9/\text{L}$; Group 2, ANC $0.1\text{--}0.199 \times 10^9/\text{L}$; or Group 3, ANC $<0.1 \times 10^9/\text{L}$. Rates of severe IDIN were normalized to estimated deferiprone exposure and expressed as the number of severe IDIN events per 100 patient-years. IDIN, idiosyncratic drug-induced neutropenia.

Table 1. Demographics in sponsored clinical trials

Demographics	Cases of severe IDIN n, (%) (N=21 ^a)
Sex	
Female	13 (61.9)
Male	8 (38.1)
Age category, years	
0–5	3 (14.3)
6–11	6 (28.6)
12–16	1 (4.8)
17–35	5 (23.8)
36–64	6 (28.6)
Diagnosis	
Thalassemia major	12 (57.1)
Thalassemia intermedia	1 (4.8)
Hereditary hemochromatosis	2 (9.5)
Hereditary spherocytosis	2 (9.5)
Myelodysplasia	2 (9.5)
Sickle cell anemia	1 (4.8)
Sickle cell disease	1 (4.8)

IDIN, idiosyncratic drug-induced neutropenia.
^aIn 1 case, 1 patient had 2 events of severe IDIN.

Table 2. Summary of occurrence of events of severe IDIN in patients treated with deferiprone

	Severe IDIN					
	ANC Thresholds, $\times 10^9/L$			ANC Groups, $\times 10^9/L$		
	<0.5	<0.2	<0.1	Group 1 0.2–0.5	Group 2 0.1–0.199	Group 3 <0.1
Cumulative Deferiprone Exposure in Clinical Trials ^a = 1990.26 patient-years						
Events, n (rate/100 patient years)	22 (1.11)	13 (0.65)	10 (0.50)	9 (0.45)	3 ^b (0.15)	10 ^b (0.50)
Cumulative Deferiprone Exposure in the Postmarketing Setting = 111,570.24 patient-years						
Events ^c , n (rate/100 patient years)	176 (0.16)	111 (0.10)	91 (0.08)	65 (0.06)	20 (0.02)	91 (0.08)

^aTotal of 977 patients with systemic iron overload were treated with deferiprone in clinical trials.

^bOne patient had 2 events of severe IDIN, the event with ANC $0.18 \times 10^9/L$ was counted in Group 2 and the event with ANC $0 \times 10^9/L$ was counted in Group 3.

^cEvents of severe IDIN in postmarketing setting are defined as adverse drug reactions coded to agranulocytosis that had at least 1 ANC value.

ADR, adverse drug reaction; ANC, absolute neutrophil count; IDIN, idiosyncratic drug-induced neutropenia.

Table 3. Summary of serious infections in patients treated with deferiprone in sponsored clinical trials

Total patients, N = 977							
					Characteristics of infection		
ANC range, ×10 ⁹ /L	Primary diagnosis	Serious/severe Infections, n	Preferred term	Nadir ANC, (×10 ⁹ /L)	Severity Seriousness	Causality to DFP	Outcome
Group 1 (0.2–0.5)	—	0	—	—	—	—	—
Group 2 (0.1–0.199)	—	0	—	—	—	—	—
Group 3 (<0.1)	Hereditary spherocytosis	3	Parvovirus	0	Severe Serious	Not related	Hospitalized, recovered
	Hereditary hemochromatosis		Pseudomonal sepsis	0.01	NA Serious	Related	Hospitalized, fatal
	Hereditary hemochromatosis		RTI and esophageal candidiasis	0.01	Severe Not serious	Related	Hospitalized, recovered with sequelae

ANC, absolute neutrophil count; NA, not applicable; RTI, respiratory tract infection.

Table 4. Demographics in the postmarketing setting

Demographics	Cases of severe IDIN n (%) (N=236)
Sex	
Female	134 (56.8)
Male	99 (41.9)
Missing data	3 (1.3)
Age category, years	
0–5	11 (4.7)
6–11	18 (7.6)
12–16	31 (13.1)
17–35	91 (38.6)
36–64	42 (17.8)
≥65	22 (9.3)
Missing data	21 (8.9)
Diagnosis	
Thalassemia major	165 (69.9)
Other	71 (30.1)

IDIN, idiosyncratic drug-induced neutropenia.

Table 5. Summary of serious infections in patients treated with deferiprone in the postmarketing setting

Total DFP exposure, patient years: 111570.24							
ANC range, $\times 10^9/L$	Primary diagnosis	Infections, n	Preferred term, Infection term	Medical history	Nadir ANC, $\times 10^9/L$	Outcome	Reported cause of death
Group 1 (0.2–0.5)	β -Thalassemia major	5	Septic shock	Episode of mild leukopenia	0.4	Hospitalized, recovered	N/A
	β -Thalassemia major		Breast abscess	Severe cardiopathy	0.4	Hospitalized, recovered	N/A
	Hereditary Hemochromatosis		Fungal sepsis	Inborn hemochromatosis, micronodular cirrhosis, diabetes	0.2	Hospitalized, fatal	Septic shock
	β -Thalassemia major		Septic shock	No significant history	0.48	Hospitalized, fatal	Septic shock
	Diamond Blackfan Anemia		Sepsis	Hypothyroidism	0.27	Hospitalized, fatal	Sepsis
Group 2 (0.1–0.199)	β -Thalassemia major	2	Infectious pleural effusion	No significant history	0.1	Hospitalized, recovered	N/A
	β -Thalassemia major		Sepsis	Positive serology for Hep C	0.1	Hospitalized, fatal	Agranulocytosis and sepsis
Group 3 (<0.1)	β -Thalassemia major	12	Oropharyngeal pain	Cardiomyopathy, T1D	0	Hospitalized, recovered	N/A
	Aplasia pure red cell		Neutropenic sepsis	Cardiac transplant, end stage renal failure	0	Hospitalized, recovered	N/A
	β -Thalassemia major		Mucormycosis	Severe cardiac iron overload, amenorrhea, osteoporosis, extramedullary hematopoiesis	0	Hospitalized, recovered with sequelae	N/A
	β -Thalassemia major		Herpes simplex	Severe neutropenia on deferiprone therapy	<0.1	Hospitalized, unknown	N/A
	β -Thalassemia major		Septic shock	Hypoparathyroidism	0	Hospitalized, fatal	Sepsis
	β -Thalassemia major		Rash pustular and septic shock	Regular transfusions	0	Hospitalized, fatal	Sepsis
	β -Thalassemia major		Sepsis	Hemosiderosis	0.05	Hospitalized, fatal	Not reported
	α -Thalassemia		Sepsis	Not reported	0.01	Hospitalized, fatal	Sepsis
	Secondary Hemochromatosis ^a		Furuncle	Lower UTI with right renal lithiasis, paroxysmal cardiac rhythm troubles, dyslipemia	0.01	Hospitalized, fatal	Infection
	β -Thalassemia major		Sepsis	Failed BMT	<0.1	Hospitalized, fatal	Sepsis and cardiac arrest
	β -Thalassemia major		Sepsis and lymphadenitis	Cardiac hemosiderosis, splenectomy	0.02	Hospitalized, fatal	Febrile neutropenia, multiple organ dysfunction syndrome, pneumonia, sepsis
	Congenital Sideroblastic Anemia		Septic shock and Streptococcal bacteremia	Severe RA, CHF, c.560G>A mutation in <i>SLC25A38</i>	0.05	Hospitalized, fatal	Cardiogenic shock, congestive cardiomyopathy, iron overload, septic shock, agranulocytosis, <i>Streptococcal</i> bacteremia

^aThe patient was diagnosed with secondary hemochromatosis about a year prior to the event of agranulocytosis at age 71 years, however, the patient narrative does not include the underlying cause of hemochromatosis.

ANC, absolute neutrophil count; BMT, bone marrow transplant; CHF, congestive heart failure; Hep C, hepatitis C virus; T1D, type 1 diabetes; RA, rheumatoid arthritis; UTI, urinary tract infection.

Figure 1

