

The Effect of Oral Iron Chelator Deferiprone on Iron Overload and Oxidative Stress in Patients with Myelodysplastic Syndromes: A Study by the Israeli MDS Working Group

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Keywords

Deferiprone · Iron-chelation therapy · Myelodysplastic syndromes · Iron overload · Oxidative stress

Abstract

Background: Most patients with lower risk myelodysplastic neoplasms or syndromes (MDSs) become RBC transfusion-dependent, resulting in iron overload, which is associated with an increased oxidative stress state. Iron-chelation therapy is applied to attenuate the toxic effects of this state. Deferiprone (DFP) is an oral iron chelator, which is not commonly used in this patient population, due to safety concerns, mainly agranulocytosis. The purpose of this study was to assess the effect of DFP, on oxidative stress parameters in iron-overloaded RBC transfusion-dependent patients with lower risk MDSs. **Methods:** Adult lower risk MDS patients with a cumulative transfusion burden of >20 red blood cell units and evidence of iron overload (serum ferritin >1,000 ng/mL) were included in this study. DFP was administered (100 mg/kg/day) for 4 months. Blood samples

for oxidative stress parameters and iron overload parameters were done at baseline and monthly: reactive oxygen species (ROS), phosphatidylserine, reduced glutathione, membrane lipid peroxidation, serum ferritin, and cellular labile iron pool. The primary efficacy variable was ROS. Tolerability and side effects were recorded as well. A paired *t* test was applied for statistical analyses. **Results:** Eighteen patients were treated with DFP. ROS significantly decreased in all cell lineages: median decrease of 58.6% in RBC, 33.3% in PMN, and 39.8% in platelets ($p < 0.01$ for all). Other oxidative stress markers improved: phosphatidylserine decreased by 57.95%, lipid peroxidase decreased by 141.3%, and reduced glutathione increased by 72.8% ($p < 0.01$ for all). The iron-overload marker and cellular labile iron pool decreased by 35% in RBCs, 44.3% in PMN, and 46.3% in platelets ($p < 0.01$ for all). No significant changes were observed in SF levels. There were no events of agranulocytosis. All AEs were grades 1–2.

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Conclusions: Herein, we showed preliminary evidence that DFP decreases iron-induced oxidative stress in MDS patients with a good tolerability profile (albeit a short follow-up period). No cases of severe neutropenia or agranulocytosis were reported. The future challenge is to prove that reduction in iron toxicity will eventually be translated into a clinically meaningful improvement.

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Introduction

Myelodysplastic syndromes (MDSs) are a heterogeneous group of clonal bone marrow (BM) stem cell malignancies characterized by cytopenia and/or dysfunction of at least one hematopoietic cell lineage, with possible leukemic transformation [1–3]. Approximately 90% of MDS patients presented with anemia at diagnosis or developed it during the course of the disease [4], many of whom required regular red blood cell (RBC) transfusions, resulting in systemic and tissue iron overload. Interestingly, iron overload may precede RBC transfusion dependence because of disease-associated ineffective erythropoiesis, which suppresses the production of hepcidin, the master iron regulator in the liver, leading to an increased iron uptake and accumulation [5, 6].

Iron is an essential element for living organisms but becomes toxic when its systemic and tissue concentrations exceed the physiological storage capacity [7]. Iron is transported in the circulation bound to transferrin [7]. Whenever plasma iron exceeds the iron-binding capacity of transferrin, it forms non-transferrin-bound iron (NTBI). Most NTBI is loosely bound to plasma proteins (e.g., hemoglobin and ferritin) and other molecules (protoporphyrins), but a small fraction is present as the labile iron pool, including labile plasma iron and intracellular labile iron pools. Both the plasma and cellular-free iron are redox-active forms, ensuing oxidative stress through the generation of reactive oxygen species (ROS) such as superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), the hydroxyl radical ($\bullet OH$), and singlet oxygen (1O_2) [8, 9] and decrease in antioxidants, such as reduced glutathione [8]. These free radicals interact with biological molecules, such as proteins, nucleic acids, and lipids, causing cellular and organ damage, including hepatic dysfunction, cardiomyopathy, atherosclerosis, bone marrow alterations, dyserythropoiesis, leukemic progression, and predisposition to infections [6, 9]. Certainly, iron overload can contribute to shortened survival and poorer clinical outcomes in lower risk MDS patients [6, 10].

The abovementioned pathophysiology is the basis for the clinical application of iron chelation in heavily transfused MDS patients [11]. Several treatment guidelines recommend iron chelation for lower risk patients with MDS based on transfusion burden, ferritin level, or iron overload imaging studies [12]. The two commonly used iron-chelation agents are (injected) desferoxamine and oral deferasirox [11]. A study by Angelucci et al. [13] recently demonstrated that treatment with deferasirox in transfusion-dependent MDS patients was associated with longer event-free survival, fewer cardiac- and liver-related events, and fewer transformations to acute myeloid leukemia compared with the placebo. Several retrospective and prospective single-arm trials confirmed that deferasirox can effectively reduce iron overload markers such as serum ferritin and labile iron pool, which is associated with improved hepatic function and peripheral blood cytopenias [14–16]. We have previously shown, in a short-term clinical study, that iron-chelation with deferasirox decreased oxidative stress parameters in MDS patients with iron overload [17]. Deferiprone (DFP) is an orally active hydroxypyridineone first used in humans in 1987. DFP is a bidentate iron chelator (3 molecules surround one iron ion). An advantage of this compound is that the iron chelate of DFP can penetrate membranes easily since it carries no net charge, allowing effective removal of potentially toxic iron from tissues [18]. A meta-analysis of 15 randomized controlled trials, involving 1,003 beta-thalassemia patients, concluded that DFP improved cardiac and endocrine function more than deferoxamine [19]. In sickle-cell disease and other transfusion-dependent anemias, it was found non-inferior to deferoxamine in the FIRST study and its 2-year extension period [20, 21] and to deferasirox in the DEEP-2 study [22]. DFP is currently approved for thalassemia, sickle cell disease, and other transfusion dependent anemias, regardless of prior iron-chelation therapy, given as a single-agent or in combinations with other chelators [23]. In MDS patients, chelation options are limited, since adherence to deferoxamine (a parenteral agent with a burdensome infusion regimen) might be challenging, and deferasirox requires close monitoring of renal and hepatic function. In fact, deferasirox is contraindicated in patients with renal impairment. This, among others, is a potential strength of DFP, as an iron-chelation option since it is well tolerated in patients with decreased renal function and no dose adjustment is required [24]. There are limited data on DFP use among MDS patients. Mostly due to concerns regarding severe neutropenia ($ANC < 0.5 \cdot 10^9/L$) and agranulocytosis ($ANC < 0.2 \cdot 10^9/L$), albeit rare and

reversible, this agent has been less frequently used in this disease [25]. This study's objective was to evaluate DFP use in heavily transfused MDS patients, i.e., its effect on oxidative stress and iron overload parameters, as well as its tolerability.

Methods

Study Design and Patients

This was an investigator-initiated, 4-month, single-arm, open-label study in heavily transfused (a cumulative transfusion burden of 20 or more RBC units) adult patients with lower risk MDS in 7 medical centers in Israel. The main objectives were to assess the effects of the oral chelator, DFP, on parameters of oxidative stress and iron overload, as well as its tolerability and safety in this patient population. Eligible patients were ≥ 18 years of age, with a documented MDS diagnosis according to WHO 2008 classification [26] with a revised IPSS (R-IPSS) score of very low, low, and intermediate risk, a cumulative transfusion burden of ≥ 20 RBC units and serum ferritin level over 1,000 ng/mL. All females of childbearing potential had a negative pregnancy test before enrollment. A 7-day washout period was required for patients who had been treated with deferoxamine or deferasirox, but in practice, all patients were chelation-naïve (at the time, deferasirox was not reimbursed in Israel for iron-overloaded MDS patients). Key exclusion criteria included severe neutropenia, abnormal liver, and kidney functions, unstable medical condition within 3 months prior to screening, QT interval prolongation, or recent history of ischemic heart disease or decompensated heart failure. The study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki; all patients provided written informed consent.

Study Treatment

DFP treatment was initiated at a dose of 50 mg/kg/day and increased in a stepwise manner by 25 mg/kg/day every 2 weeks to the final dose of 100 mg/kg/day, divided into 3 daily doses. DFP dose was modified in cases of suspected treatment-related adverse effects (AEs), as follows: from 100 mg/kg/day to 75 mg/kg/day, from 75 mg/kg/day to 50 mg/kg/day, from 50 mg/kg/day to 25 mg/kg/day. In cases that 25 mg/kg/day was not tolerated by the patient, DFP was stopped, and the patient was removed from the study.

Assessments

Patients had weekly blood counts and monthly follow-up, in which clinical and other blood work parameters were assessed (prior to receiving transfusions).

Clinical and Exploratory Variables

We aimed to assess the effects of DFP on parameters of oxidative stress, chelatable labile iron pool, labile plasma iron, and serum ferritin. The primary oxidative stress marker was ROS. Other parameters included reduced glutathione, membrane lipid peroxidation, and external phosphatidylserine. These were all measured at baseline (visit 1), and at each monthly visit (visits 2, 3, 4, and 5) in red blood cells (RBCs), polymorphonuclear white blood cells (PMNs), and platelets. Cellular labile iron pool and the oxidative stress parameters were measured by flow cytometry

and the results are expressed as the arithmetic mean of the fluoresce channel as previously described [27, 28]. The fluorescence readings of cells were directly proportional to the measured parameter except cases of membrane lipid peroxidation, which were reversely proportional to the amount of lipid oxidants in the sample.

Safety Parameters

Adverse events (AEs) were assessed in terms of severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf). Frequency, time to onset, duration, and relatedness to the treatment of each AE were recorded as well.

Statistical Analysis

All patients who received at least one dose of DFP were included in the full analytical set and safety population. Descriptive statistics were presented as means \pm standard deviations for continuous variables and percentages for categorical variables. A two-tailed p value <0.05 was considered statistically significant. The paired t test was used to examine the change from baseline of all cellular markers of oxidative stress, i.e., ROS, phosphatidylserine, reduced glutathione, membrane lipid peroxidation, serum ferritin, and cellular labile iron pool. Analysis was performed using R software (version 4.0.3; Vienna, Austria).

Results

Patient Demographics

Nineteen patients were enrolled in the study, but 1 patient withdrew their consent; therefore, only 18 patients were analyzed. Patients' demographics and baseline characteristics are shown in Table 1. Most patients (84%) were in the very low- or low-risk IPSS-R group; the remaining patients were intermediate risk. The median age was 72 years (range, 61–90 years), and 65% were males. The median number of transfusions received prior to enrollment was 69 (range, 21–116). All patients were chelation-naïve. At baseline, the mean levels of the exploratory oxidative stress and iron overload markers (labile iron pool and serum ferritin) were above normal, as expected in heavily transfused patients. Nineteen patients started treatment with a daily dose of 25–100 mg/kg DFP. Twelve patients received treatment for 120 days. The remaining 7 patients received treatment for <30 days ($n = 1$), 30 days ($n = 1$), 60 days ($n = 3$), or 90 days ($n = 2$). Reasons for early discontinuation were due to AEs ($n = 5$), ineligibility ($n = 1$), and death from an unrelated cause (motor vehicle accident, $n = 1$). Due to a technical issue, most blood samples collected at day 120 could not be analyzed, and thus samples collected at day 90 of the study were used as the longest comparison with baseline values.

Table 1. Patients' demographics and baseline oxidative stress and iron values

| | |
|---|---------------------|
| Enrolled patients, n | 19 |
| Male:female, n | 11/8 |
| Median age (range), years | 75.8 (61–90) |
| WHO 2016 classification (Arber et al. [29], 2016) | |
| MDS-SLD | 6 |
| MDS-MLD | 4 |
| MDS-RS | 6 |
| MDS-5q- | 1 |
| MDS-unclassifiable | 2 |
| R-IPSS | |
| Very low | 3 |
| Low | 13 |
| Intermediate | 3 |
| Median number of RBC transfusions before study period | 69 (21–116) |
| Oxidative stress parameters (Mean Fluorescence Channel) | |
| ROS in RBC | 61 (23–146) |
| ROS in platelets | 141 (80–293) |
| ROS in PMN | 3,427 (2,092–5,263) |
| GSH in RBC | 92 (38–157) |
| LP in RBC | 71 (12–230) |
| PS in RBC | 2 (0.09–6.7) |
| Iron-overload parameters (Mean Fluorescence Channel) | |
| LIP in RBC | 45 (23–66) |
| LIP in platelets | 66 (28–140) |
| LIP in PMN | 151 (27–420) |
| Geometric mean serum ferritin | 3,515 (941–7,475) |

GSH, reduced glutathione; LIP, labile iron pool; LP, lipid peroxidation; MDS-MLD, myelodysplastic syndrome with multilineage dysplasia; MDS-SLD, myelodysplastic syndrome with single-lineage dysplasia; PMN, polymorphonuclear leukocytes; PS, phosphatidylserine; RBC, red blood cells; ROS, reactive oxygen species; RS, ring sideroblasts; SLD, single-lineage dysplasia; WHO 2016 classification – see reference [29]. Note that 1 patient withdrew their consent before starting treatment with DFP.

Efficacy

Oxygen Stress and Clinical Parameters

Oxidative stress markers were measured monthly and declined significantly over time. As mentioned above, we compared the 4th visit parameters to their levels before DFP initiation. Compared to baseline, the primary efficacy variable, ROS, significantly decreased after treatment with DFP, in all 3 cell lineages: a median decrease of 58.6% in RBC ($p < 0.01$), 33.3% in PMN ($p < 0.01$), and 39.8% in platelets ($p < 0.01$) (shown in Fig. 1). DFP administration improved other cellular markers of oxidative stress in RBCs as well: phosphatidylserine decreased by 57.95% ($p < 0.01$), lipid peroxidase decreased by 141.3% ($p < 0.01$), and reduced glutathione increased by 72.8% ($p < 0.01$). The iron-overload marker, labile iron pool, decreased by 35% in RBCs ($p < 0.01$), 44.3% in PMN ($p < 0.01$), and 46.3% in platelets ($p < 0.01$). No significant changes were

observed in serum ferritin levels or in transfusion requirements (online suppl. Tables 1–3; for all online suppl. material, see <https://doi.org/10.1159/000535749>). The median number of RBC transfusions per patient during the study period was 11 (range, 2–20) units.

Safety

Toxicity Profile

Adverse events occurred in 13 patients. Seven patients reported more than one AE. Gastrointestinal (GI) symptoms (diarrhea, nausea, vomiting) were the most frequent AEs and were all grades 1–2 (i.e., mild–moderate). None of the patients experienced any severe AEs. Mild neutropenia was evident in 3 patients but returned to normal range within 10–14 days (treatment was not interrupted). Six patients discontinued treatment, because of AEs, throughout the study period.

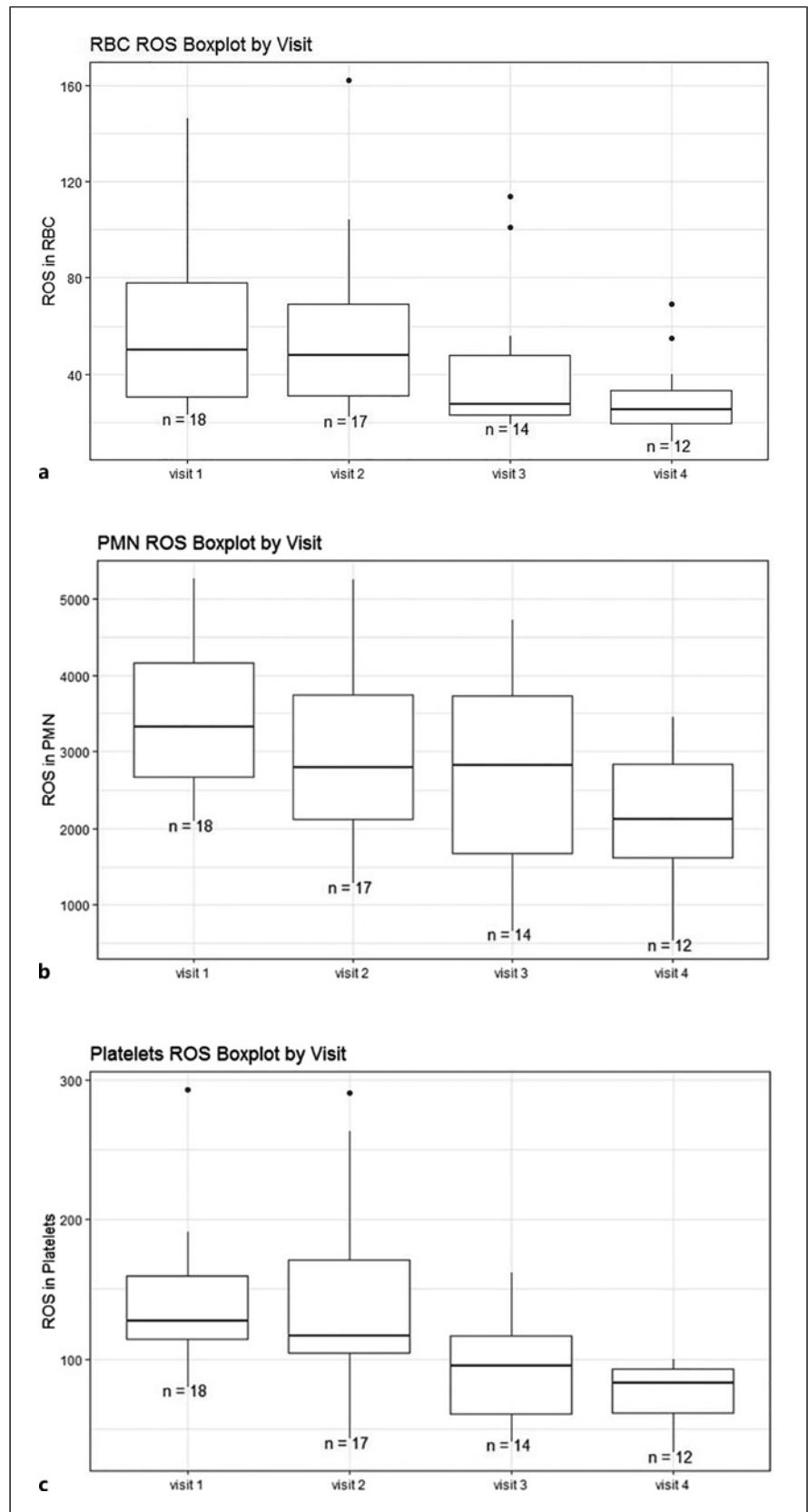


Fig. 1. Effect of deferiprone on ROS in MDS patients. Data represent average \pm SD. * $p < 0.001$; RBC (**a**), PMN (**b**), platelets (**c**).

Discussion

In this short open-label study of iron-chelation with DFP in 18 patients with lower risk MDSs, oxidative stress and iron overload parameters as well as tolerability were assessed. The baseline characteristics demonstrate high levels of oxidative stress and iron overload; levels of ROS were higher than the normal range, while levels of the antioxidant reduced glutathione were lower than normal. The treatment resulted in significant reductions in cellular markers of oxidative stress (shown in Fig. 1), demonstrating the benefits of short-term iron chelation in patients with MDSs. By day 120, treatment with DFP resulted in a significant decrease in ROS levels in RBC, PMN, and platelets. In RBC, we found a coordinated improvement in cellular oxidative stress signals. Namely, phosphatidylserine and membrane lipid peroxidation decreased, while a major cellular antioxidant agent, reduced glutathione, increased. Furthermore, we noticed a significant decrease in the iron-overload parameter, labile iron pool. No significant changes were observed in serum ferritin levels. Overall, the treatment was well-tolerated. The safety profile of DFP was acceptable and consistent with that previously described in other patient populations (thalassemia and sickle-cell disease) [21, 30]. Thirteen (65%) of the treated patients reported AEs, mainly GI toxicity, and 6 patients discontinued treatment owing to AEs. There were no signals of clinical concern. Altogether, we found DFP to be well-tolerated. Indeed, almost a third of the participants discontinued treatment with DFP due to AEs. This seems to be in keeping with another registry, which included 115 patients [31]. It is important to note the characteristics of our study population: relatively elderly patients (median age 75.8 years), with a high transfusion burden at baseline and significant iron overload, possibly directly contributing to a reduced functional status and low tolerance to drug toxicities.

The baseline parameters confirm our previous studies [17, 32], which also showed increased oxidative stress parameters in unchelated MDS patients. These findings highlight the relatively rapid effect of iron-chelation with DFP as an antioxidant, by decreasing intra- and extracellular toxic iron species and, consequently, oxidative stress. This is in keeping with previous studies on other chelators used in MDS patients [14–16]. The observed decrease in labile iron pool may have reduced the generation of tissue-damaging ROS, which potentially could contribute to an improved outcome with longer exposure [9]. No significant changes were observed in SF levels, which is not surprising given the short follow-up period [15]. DFP works in cells and organs to chelate intracel-

lular free/labile iron for excretion, and therefore, serum ferritin may not decline immediately. Indeed, in a recent study with a much longer follow-up, in which DFP was given to patients with sickle-cell disease and other chronic anemias, there was no significant change in serum ferritin from baseline after 1 year of DFP treatment, but decreases in serum ferritin were seen at 2 years and 3 years of treatment [21]. Agranulocytosis is the most serious recognized AE [33]. Cumulative data from clinical trials on DFP in thalassemia patients found agranulocytosis rate of 1.5%, and 78% of them occurred during the first year. These events appeared to be independent of the dose and were more common in females. Median time to count recovery was 11 days [33]. Interestingly, agranulocytosis seems to be separate and distinct from episodes of milder neutropenia during DFP use. The development of mild-to-moderate neutropenia is likely unrelated to DFP, as shown by the similar incidence of decreased neutrophil count during treatment with other chelators [34]. Notably, within the short follow-up period in our study, none of the patients developed agranulocytosis. In a recent real-world analysis of DFP use among 130 MDS patients, mean DFP exposure was 1.1 years, with 29.6% of patients receiving DFP for >12 months. It was well tolerated, most AEs were GI related, with 6 cases of severe neutropenia/agranulocytosis, of which 5 were resolved and 1 was not further reported [31]. Our study has several limitations. Being an investigator-initiated trial, it has a small sample size and a short follow-up period with some missing clinical and laboratory follow-up data. Therefore, the toxicity profile in this cohort, especially the agranulocytosis rate, should be interpreted with caution. Overall, we show that treatment with DFP is feasible in transfusion-dependent iron-overloaded MDS patients, with preliminary evidence that it decreases iron-induced oxidative stress. Notably, this was a very heavily transfused study population. It would be interesting to assess the efficacy of DFP in an earlier stage of iron overload and whether it is associated with better tolerability and perhaps even a better response rate. The toxicity profile of DFP was manageable. However, as laboratory observations do not necessarily indicate therapeutic benefit, whether this promise eventually translates into a clinically meaningful improvement remains to be determined in future studies.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Sheba Medical Center Committee, approval number 1908-15-SMC. Written informed consent was obtained from all participants to participate in the study. All participants were aged over 18; therefore, consent from parents/legal guardians was not required.

Conflict of Interest Statement

All other authors report there are no competing interests to declare.

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Author Contributions

All authors contributed equally to data curation, investigation, resources, validation, and writing of the manuscript in terms of review and editing. Drorit Merkel and Moshe Mittelman contributed to conceptualization, formal analysis, and methodology. Shelly Soffer and Irina Amitai wrote the original draft. Eitan Fibach and Mutaz Dana contributed to formal analysis of blood samples. Kalman Filanovsky, Andrei Braester, Yishai Ofran, Uri Greenbaum, and Arnon Nagler contributed equally to the acquisition, analysis, or interpretation of data for this work. All authors critically reviewed the work and approved the final version to be published. All authors had access to and verified the underlying data. Drorit Merkel and Shelly Soffer contributed equally as first authors. Irina Amitai and Moshe Mittelman contributed equally as last authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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