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Luspatercept for Transfusion-Dependent Beta-Thalassemia: Real-World Experience in a Large Cohort of Patients From Italy

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To the Editor,

The randomized, placebo-controlled phase III BELIEVE study led to the approval of luspatercept to promote erythroid maturation in the United States and Europe [1]. Given the need for scientific evidence on its efficacy, tolerability, and safety in clinical practice, we evaluated the effects of luspatercept in 231 patients with transfusion-dependent thalassemia (TDT) (Figure S1) who received their first dose of the drug post-marketing at 27 Italian specialized centers under the patronage of the Società Italiana Talassemia ed Emoglobinopatie (Tables S1 and S2).

The median treatment duration was 272 days (Q1–Q3: 150–531, range: 21–1007). At the time of data collection, 106 patients (45.9%) had discontinued the drug after a median time of 172 days of treatment (Q1–Q3: 99–307, range: 21–671) (Figures S2 and S3, Table S3). In part, the high number of patients who prematurely discontinued may be associated with the fact that the lives of these patients revolve around transfusions and the transfusion cycle governs every aspect of their existence. Consequently, the loss of a normal transfusion schedule and/or transfusion independence can create anxiety and insecurity. A solid doctor-patient therapeutic alliance is essential to begin therapy under optimal conditions for success.

In our study, both the primary and secondary endpoints of the BELIEVE trial were achieved at comparable or significantly higher rates. During the treatment period, 44 patients (19%) had a transfusion-free interval of at least 8 weeks (median: 14.9 weeks, range: 8–115 weeks). Their characteristics are reported in Table S4. Notably, the analysis revealed a likelihood gradient: the probability of a greater response increased from β0 genotype to the association between heterozygosity for β-thalassemia and triplication or quadruplication of the α-globin genes.

In the 13–24-week follow-up, 69 (29.9%) and 38 (16.4%) experienced ≥33% and ≥50% reduction in transfusion requirements, respectively ($p=0.05$ and $p=0.006$ compared with the BELIEVE study) [1]. Across the 12-week follow-up periods, 178 (77%) and 91 (39.3%) patients had ≥33% and ≥50% decrease in blood transfusion rate. A pairwise *t*-test focusing on the initial six 12-week

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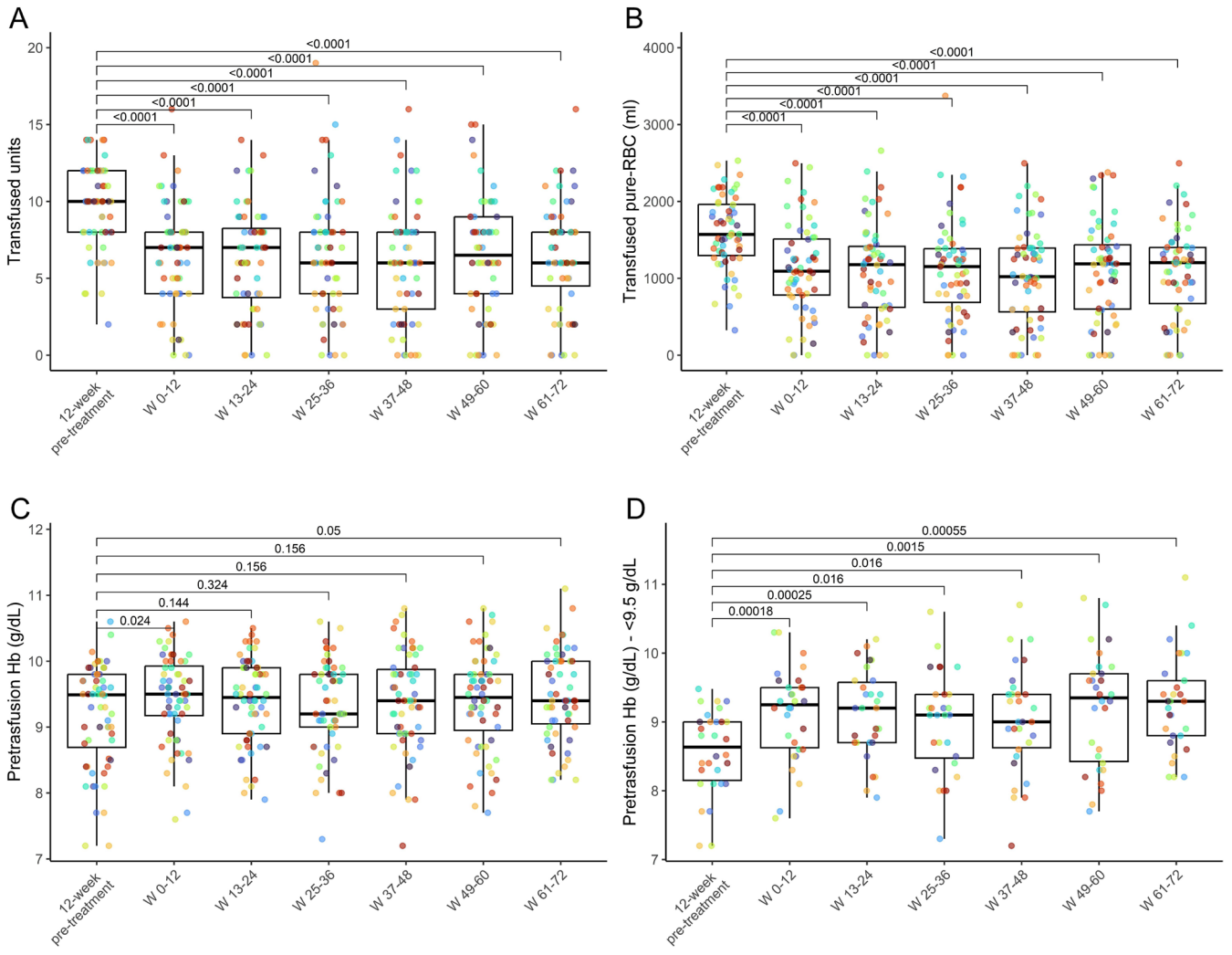
follow-up periods demonstrated a significant and sustained reduction in the number of units of packed red blood cells (pRBC) and pRBC volume at the first follow-up ($p < 0.001$) (Figure 1A,B). Adopting a modified version of the response grading proposed by Musallam et al. [2], 15.5% of patients had an excellent response, 43.9% of patients had a good response, 22.3% of patients had a satisfactory response, and 18.2% of the patients experienced no efficacy, falling within the remaining cases (Table S5).

The pre-transfusion hemoglobin (Hb) level following a non-clinically significant increase in the first 12 weeks ($p = 0.024$) did not differ from that of the pre-treatment period (Figure 1C). However, this observation varied when considering only patients who started luspatercept with suboptimal pre-transfusion Hb values according to the international guidelines (< 9.5 g/dL). At the first follow-up, Hb levels significantly improved ($p < 0.001$) and stabilized afterward (Figure 1D). Of the 109 patients with baseline Hb < 9.5 g/dL, 32 achieved optimal pre-transfusion Hb levels, while either maintaining the same transfusion requirements or reducing the need for blood transfusions. The estimated average increase in Hb level was 1.1 g/dL (95% CI: 0.9–1.3).

Using the same response criteria as in the BELIEVE trial, some of them would have been classified as non-responders. However, we believe that this outcome is just as significant as the reduction in blood transfusion since it may have substantial practical benefits. Recent evidence shows an association between higher pre-transfusion Hb levels and lower thalassemia-related mortality in adults with TDT [3]. This association seems to begin with Hb levels at or exceeding 9.5 g/dL, the cutoff that we considered in our analysis in reference to international guidelines, and protective effects are incremental with higher levels.

When examining patients classified as good or excellent responders, univariate logistic regression revealed a significant association between a positive response and splenectomy, therapy initiation at > 32 years of age, as well as older age at diagnosis of thalassemia and at start of regular transfusion (Table S6). Even correcting for age at first transfusion, older ages at baseline were associated with a better response to luspatercept but the strength of association significance decreased ($p = 0.057$). In other words, the best responders to the treatment seemed to be those with 'residual erythropoiesis', which is the retained or potential ability



Trends in transfused units (A) and transfused RBC volumes (B), pretransfusion Hb (all patients) and pretransfusion Hb in patients with values ≤9.5 g/dL at baseline (D) during the first 6 follow-up periods of 12 weeks each. Only the first 6 follow-up periods were considered due to the low number of patients in the subsequent periods.

FIGURE 1 | Erythroid response parameters.

to produce RBCs, in presence of determinants that facilitate the drug's therapeutic activity.

Consistent with this hypothesis and with the findings of Panzieri et al. [4], we observed a correlation between response probability and HbF levels: if HbF was < 0.6 g/dL at baseline, the probability of non-response was high (Figure S4).

Serum ferritin levels significantly decreased during treatment, and the reduction was rapid and stable (basal: median 549 ng/mL (Q1–Q3: 291–869 ng/mL); weeks 1–12: 343 ng/mL (202–810 ng/mL); weeks 13–24: 378 ng/mL (204–606 ng/mL)). These data confirm that the reduction in serum ferritin levels occurs early and is not always proportional to response in terms of blood consumption. However, categorizing patients into those with good and excellent response and those with no response, a statistically significant reduction in serum ferritin level was observed solely in the responder cohort (Figure 2A). Therefore, as already highlighted in the long-term analysis of the BELIEVE trial, a clear correlation existed between ferritin levels and drug response [5].

For the 63 patients who underwent magnetic resonance imaging (MRI) before and during treatment (30 weeks after treatment initiation, Q1–Q3: 6–42), liver iron concentration (LIC) did not significantly change in the entire cohort ($p = 0.16$) and in good or excellent responders ($p = 0.17$), while significantly increased in the non-responder cohort ($p = 0.008$) (Figure 2B). Heart T_2* did not vary across the entire cohort, regardless of treatment response. Iron chelation therapy was adjusted in 76 (33.9%) patients (Figure 2C).

Furthermore, a paired nonparametric test revealed significant differences between baseline and follow-up values for several laboratory parameters including erythropoiesis and iron metabolism markers as shown in Table S7, consistent with the findings reported by Garbowski et al. [6] in the BELIEVE study. It follows that a reduction in serum ferritin alone cannot be the sole criterion for reducing chelation therapy in patients treated with luspatercept, especially if it is not proportional to or synchronous with a reduction in transfusion requirements; moreover, luspatercept therapy must be accompanied by valid chelation therapy and regular scans.

A total of 157 patients (68%) reported at least one adverse event during luspatercept treatment, with a gradual reduction in incidence over time (Figure S5). No deaths or malignancies were reported. Bone pain, asthenia-fatigue, articular pain, and arterial hypertension requiring therapy or modifications of the previous treatment were the adverse events that occurred in ≥ 5% of the patients. Moreover, a few events that have rarely or never been associated with the drug occurred with some frequency. These include edema, both subjective and objective, increased heart rate, dysesthesia and paresthesia, and menstrual irregularities (mainly oligomenorrhea but also reversible cessation of menstruation) (Table S8). This finding is interesting because the decision to continue the clinical trial with luspatercept instead of sotatercept was based, among other factors, on the higher ligand selectivity, resulting in lower off-target effects and a lower risk of adverse effects on the hypothalamic–pituitary–gonadal axis.

Notably, the median number of platelets increased (Figure S6). Four patients developed superficial venous thrombosis, with one of them also experiencing facial neurological symptoms. Two patients experienced ischemic stroke, whereas the other two developed deep venous thrombosis and pulmonary thromboembolism (Table S9). Seven patients experienced worsening of pre-existing masses of extramedullary erythropoiesis (EMH) or the appearance of newly developed EMH (Table S10).

Although the incidence of thrombotic events in our study was comparable to that of the BELIEVE trial, unlike that, two patients who experienced thrombosis were not splenectomised. All patients with thrombotic events, except one, experienced the event within the first year of therapy. Furthermore, of eight patients (including the two with stroke), three experienced the event within the first two treatment cycles.

This early onset is also typical of other milder and often transient side effects, including pain, which is also experienced by TDT patients in the pre-transfusion phase, precisely due

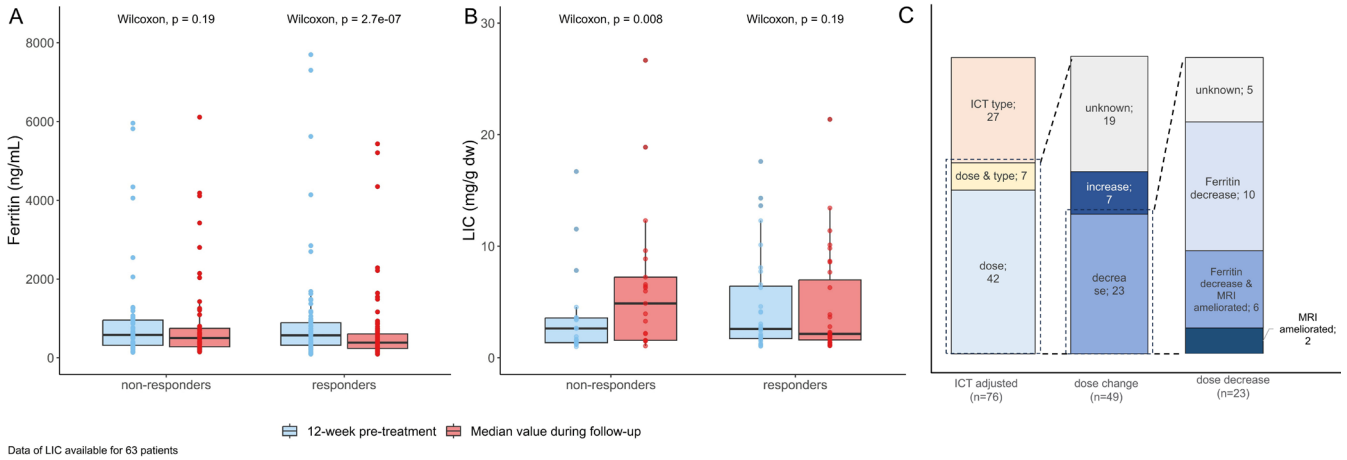


FIGURE 2 | Iron overload changes in patients treated with Luspatercept. Serum ferritin (A) and Liver Iron Concentration (B) trend during treatment with Luspatercept. (C) Variation of iron chelation therapy during treatment with Luspatercept. Responders: From good to excellent; non-responders: Satisfactory and non-responders. ICT, Iron chelation therapy; LIC, Liver iron concentration; MRI, Magnetic resonance imaging.

to medullary activation. This suggests that luspatercept, at least at an early stage, does not only increase effective erythropoiesis, it also increases ineffective erythropoiesis, with the possibility of severe adverse events in a subgroup of patients with underlying co-morbidities. This is consistent with the early increase in erythropoietin in these patients. One factor potentially supporting this hypothesis could be the early development of EMH. However, demonstrating that in this retrospective study is challenging because EMH may not be recognized unless actively sought, and only a small number of patients underwent MRI (at least of the spine) before luspatercept initiation and at regular intervals thereafter. Nevertheless, a review of existing literature, which includes examples of both volume reduction in preexisting masses during therapy and new mass development, reveals case reports of symptomatic compression masses consistently manifesting soon after starting treatment with luspatercept.

Given that all patients with EMH in our study, excluding one, had suboptimal Hb values, monitoring and correcting this aspect is crucial even in patients under treatment. As previously mentioned, the drug can, in this context, provide an opportunity.

Author Contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: R.O., B.G., F.L. Performed data acquisition: A.Z., A.R.D., M.A.D.G., R.S., I.M., D.L.P., R.R., A.B., M.C., A.M.P., L.D.F., R.D.M., V.M.P., P.M.G.S., P.R., G.B.R., F.S., D.R., G.B.F., E.D.M., F.A., I.F., S.M., A.P., G.S., E.R.T., G.C., C.F., F.P., D.R., A.S., F.L. Contributed to the data analysis and interpretation: G.L.F., M.D.C. Provided administrative support: A.G., A.Z. All authors discussed the results and contributed to the final manuscript.

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Ethics Statement

This study was approved by the Ethics Committee Sardegna on 02.26.2024, verbal number 28, attachment 2.14.

Consent

All participants provided informed consent in accordance with the Declaration of Helsinki.

Conflicts of Interest

R.O. has received speaker honoraria from BMS, Vertex, and Chiesi and received consultancy fees from BMS, Vertex, and Agios. V.M.P. was a member of the advisory board, part of the speaker's bureau for BMS, and a consultant for Vertex. F.L. was a consultant, a member of the advisory board, part of the speaker's bureau, and participated in educational events for BMS and Vertex. I.M. was a member of the advisory board of BMS, Vertex, and Sanofi, received honoraria for lectures from Bristol Myers Squibb and Sanofi, and research support from Sanofi. M.D.C. was a member of the advisory board for Sanofi Genzyme, BMS/Celgene, Vertex/CRISPR, Novo Nordisk, Pharmacosmos, and Agios. P.R. received honoraria from Agios Pharmaceuticals and BMS (Celgene) and was a member of the safety monitoring board/advisory board for Agios Pharmaceuticals and BMS (Celgene). R.R. received speaker honoraria and research support from Vertex and BMS. The other authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analyzed during the current study can be obtained from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.