Editorial

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Beyond blood transfusions: exploring iron chelation therapies in transfusion-dependent beta-thalassemia

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Introduction

Abnormal hemoglobin, also referred to as "hemoglobinopathy," is a relatively common condition prevalent among 7% of the global population[1]. Major causes of common hemoglobinopathies include beta-thalassemia and sickle cell disease. Unfortunately, a definitive cure has not been found yet for several of these blood disorders. Consequently, the patients become blood transfusion-dependent relatively early in their lives, becoming vulnerable to the dangerous side effects of chronic iron overload due to the need of repeated blood transfusions[1].

A 2008 World Health Organization (WHO) report estimated that each year more than 40 000 babies are born with beta-thalassemia, of which approximately 25 500 suffer with transfusion-dependent beta-thalassemia (TBT). In addition, approximately 1.5% of individuals worldwide carry beta-thalassemia. Southeast Asia and the Eastern Mediterranean region have relatively high beta-thalassemia prevalence and carrier rates. But given the recent surge in immigration to the USA and Europe, it could potentially be on the rise there as well[2]. These statistics indicate an increasing global burden in the general population due to increasing prevalence in addition to needs of continuous blood transfusions and prolonged follow-ups.

The lack of physiologic mechanisms to remove excess iron in the body renders transfusion-dependent patients prone to the development of transfusional hemosiderosis, which in turn can result in deposition of iron into heart muscle cells. Excess deposition can in turn lead to adverse effects on cardiac function such as cardiac arrythmia and cardiomyopathy[3].

Currently, three oral iron chelators have been in use for the management of transfusional iron overload in adults, including deferiprone, deferasirox, and deferoxamine[1]. Deferiprone is approved in over 60 countries for the treatment of transfusional iron overload in adult and pediatric patients. Deferiprone tablets are available for treatment in children aged 8 years and older in the USA, and patients aged 3 years and older can use an oral solution[3]. Recently, further trials have been conducted for its use in infants and children.

Deferiprone's mechanism of specifically targeting surplus iron for its removal makes it a cornerstone in the treatment of iron overload due to frequent blood transfusions. Mechanism of action has been shown in Fig. 1. Children under 10 with transfusion-dependent anemia and iron overload often benefit from deferiprone's well-tolerated oral form. Despite its efficacy in efficiently reducing excess iron, the necessity for further long-term safety and efficacy studies especially in young children is emphasized. In the realm of infants reliant on transfusions, deferiprone stands out due to its promising iron-chelating abilities[4].

Methods

Data for this Review were identified by searches of PubMed, Google Scholar, and references from relevant articles using the search terms "deferiprone," "iron chelation," "transfusion," "iron overload," "hemoglobinopathies," and "thalassemia." Only randomized controlled trials (RCTs) published in English between 2010 and 2023 were included.

Results

A total of three RCTs were included in this review, and 521 patients of pediatric population were included in the studies. A total of 480 children had beta-thalassemia, 27 had sickle cell disease, 5 had thalassemia drepanocytosis, and 6 had other hemoglobinopathies. Few limitations of the included trials are small sample size, lack of inclusion of several doses ranging from minimum to maximum approved doses to determine an optimum dose, and long-term effects of the iron chelation therapies on individuals.

First, the START trial (a prospective, multicenter, randomized, double-blind, placebo-controlled trial) showed great promise for the use of early-start deferiprone in infants and children with TBT. The trial showed promising results with an iron load lower than the current serum ferritin (SF) threshold before initiation of chelation therapy significantly more compared to placebo, 66% compared to 38%, respectively. Furthermore,

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the deferiprone group exhibited statistically superior results in various secondary outcomes. These included a longer time to reach the SF iron overload threshold, a faster time to reach a transferrin saturation (TSAT) value ≥60%, and a higher mean TSAT compared to the placebo group.

No life-threatening complications or deaths were observed in the study; therefore, the safety profile was satisfactory. Adverse effects observed included pyrexia being the most common followed by nasopharyngitis (34%), decreased neutrophil count (28%), and gastroenteritis (16%), etc. There was also no statistical difference seen in growth parameters (weight and height *Z*-scores), creatinine, and prolactin in children of both groups, highlighting deferiprone safety in growing children[5].

In another trial, the DEEP-2 study,[1] (a phase 3 non-inferiority trial), the effectiveness and safety of deferiprone and deferasirox were directly compared in pediatric patients with hemoglobinopathies that require transfusions. The trial successfully demonstrated the non-inferiority of deferiprone compared to deferasirox, with a similar proportion of patients achieving treatment success in both groups. Furthermore, there were no discernible variations between the two groups in terms of serious adverse events or side effects related to the medication.

In another trial,[6] the efficacy of early-start deferiprone was compared with delayed chelation therapy. In current clinical practice, chelation therapy in patients with transfusion-dependent hemoglobinopathy is usually delayed until SF levels reach ≥1000 µg/L[7]. This is done to minimize the risk of iron depletion observed with deferoxamine[8,9]. However, this delayed therapy leads to iron accumulation in various organs of the body,[10,11] increasing the risk for iron overload in future transfusions. The trial's findings showed that early start of deferiprone therapy at 50 mg/kg/day significantly delays the onset of iron overload symptoms in young children with newly diagnosed transfusion-dependent thalassemia, which would otherwise occur after 5–10 blood transfusions. Additionally, no serious side effects such as agranulocytosis, neutropenia, or arthralgia were observed in this particular trial.

Discussion

In the above trials, deferiprone clearly demonstrates significant effectiveness in reducing body iron levels comparable to the therapies currently in use with minimal side effects. Deferoxamine, administered through subcutaneous or intravenous infusion, is well-regarded for its efficacy in iron chelation therapy. In contrast, deferasirox, an oral iron chelator, is recognized for its convenient administration compared to deferoxamine[12]. Deferiprone's oral administration provides advantages for infants averse to injections, while deferoxamine typically involves subcutaneous or intravenous routes, demanding cautious administration in infants[13].

Despite these considerations, deferiprone stands out as an iron chelator with comparatively minimal side effects. The observed neutropenia, gastrointestinal issues, and joint problems associated with deferiprone, while existing, are generally well-tolerated, and there is no evidence suggesting a significant increase in mortality or severe adverse events compared to its alternatives.

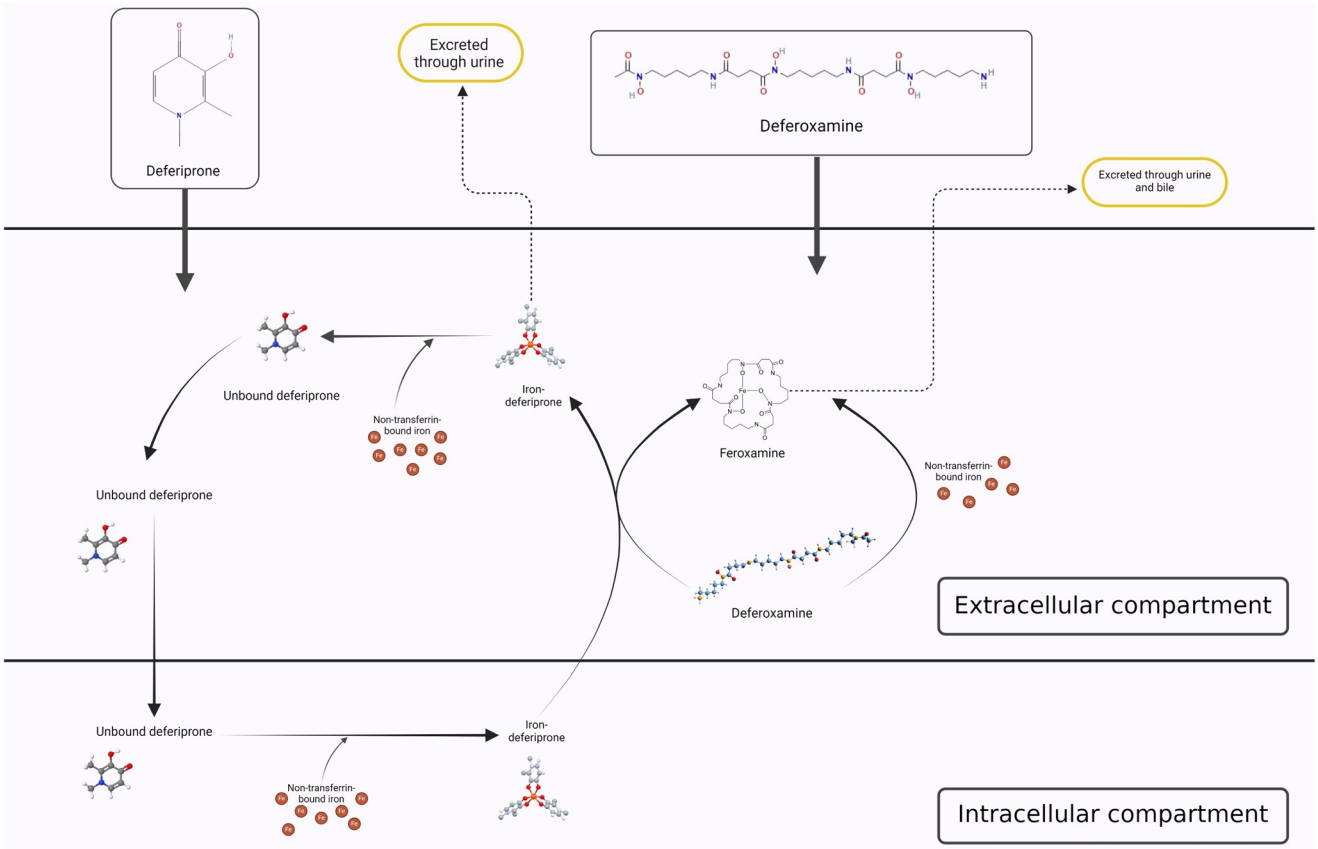

Figure 1. Deferiprone mechanism of action.

Challenges in iron chelation therapies

Iron chelation therapy is essential for managing iron overload in beta-thalassemia patients, but it presents several challenges that need to be addressed to optimize treatment outcomes. Patient compliance is among the most common challenge faced by physicians when treating beta-thalassemia patients. As the iron chelation therapy comprises of complex regimens often requiring multiple daily doses or prolonged subcutaneous infusions, which can be burdensome for patients.[14]

Adverse effects such as gastrointestinal disturbances, joint pain, and skin reactions can also deter patients from adhering to their prescribed regimen. Long-term use of some chelators can cause toxicity in several organs such as the liver, kidneys, and auditory and ocular systems. Certain chelators can also lead to neutropenia or agranulocytosis, increasing the risk of infections. Nausea, vomiting, and abdominal pain are common side effects that can affect patient compliance. Furthermore, it can cause heavy metal toxicities as well[15].

Variable response is also seen due to genetic differences which can lead to differences in drug metabolism and response to chelation therapy. Additionally, disease severity of iron overload and the underlying thalassemia genotype can influence the effectiveness of chelation therapy[16].

Strategies to improve compliance and minimize adverse effects

Several strategies can be used to work on these challenges and provide relief to these patients effectively. First, providing comprehensive education about the importance of chelation therapy, its benefits, and how to manage side effects can empower patients. In addition, developing chelators with longer half-lives that require less frequent dosing can enhance compliance. For example, long-acting oral formulations or depot injections could reduce the treatment burden. Using a combination of chelators with complementary pharmacokinetic profiles can improve efficacy and reduce the required doses of each drug, potentially minimizing side effects.

Advances in genes research can potentially now make it possible to identify genetic markers that predict response to chelation therapy can help tailor treatments to individual patients, optimizing efficacy and reducing adverse effects. On the other hand, regular monitoring of biomarkers such as SF, liver iron concentration, and hepcidin levels can provide adjustments in chelation therapy to maintain optimal iron levels with minimal toxicity and adverse effects. Developing chelators that specifically target iron-loaded tissues or cells can enhance efficacy and reduce systemic toxicity. Nanoparticle-based delivery systems are a promising area of research. Designing chelators that can bind both free and protein-bound iron may offer more comprehensive iron clearance with fewer side effects.

Routine monitoring for early signs of organ toxicity, cytopenias, and other adverse effects allows for timely intervention and dose adjustments. Moreover, utilizing magnetic resonance imaging (MRI)-based techniques to noninvasively measure liver and cardiac iron concentrations can provide accurate assessments of iron overload and guide chelation therapy adjustments.

By addressing these challenges through a combination of education, support, personalized medicine, novel therapies, and comprehensive care, the management of iron overload in beta-thalassemia patients can be significantly improved.

Risks of misdiagnosis and complications

To diagnose iron deficiency anemia (IDA) in a patient with no underlying malignancy or inflammation, the test with highest specificity is detection of ferritin levels, which would be <30 µg/L[17]. As it is an acute-phase reactant, ferritin levels vary in the body, and its sole use for detection of iron overload or iron deficiency states can result in misdiagnosis and potential inadequate treatment. Literature shows that iron overload can precipitate malignancy formation in postmenopausal women; therefore, adequate diagnosis and treatment of iron overload must be sought. Transferrin is also an acute-phase reactant which decreases in iron overload and increases in iron deficiency, and is therefore a more reliable marker for IDA. In one study, the transferrin levels were measured in multiple patient populations, one of which were patients with iron overload[17]. The difference in transferrin levels for this patient population was significant for both cancer-related anemia and functional iron deficiency.

In addition, the differentiation between a case of pure IDA versus beta-thalassemia can be challenging, and although multiple indices such as Mentzer index have been formulated, correct diagnosis of either condition can prove to be a dillemma. In one study, the use of Laser-assisted Optical Rotational Cell Analyzer (LoRRca) ektacytometer has allowed the additional use of osmotic gradient ektacytometry (OGE), which can detect the osmotic gradient, cell hydration, and deformability of red blood cells. All parameters of the Osmoscan curve were shown to be statistically significant between IDA and beta-thalassemia except one. This study provides evidence in favor of the use of LoRRca and OGE for diagnosis IDA or beta-thalassemia[18].

Other recent studies (up to date) and research developments

Other emerging chelators such as ferroportin inhibitors are being investigated for their promising effects seen in recent studies. Ferroportin inhibitors, which block iron export from cells, are a new class of iron chelators. Ferroportin inhibitors act by reducing iron absorption and promoting the retention of iron within enterocytes and macrophages, thus decreasing systemic iron levels[19]. Additionally, deferasirox advancements have been made with new formulations of deferasirox, such as film-coated tablets, have been developed to improve gastrointestinal tolerance and patient adherence. These formulations have shown comparable efficacy to traditional forms but with fewer gastrointestinal side effects[20].

The application of combination therapies is another area under investigation for the treatment of this disorder. A recent clinical trial has investigated the combination of deferasirox and deferiprone, showing that this combination can be more effective in reducing liver and cardiac iron compared to monotherapy. This approach leverages the complementary mechanisms of action of both chelators[1]. Furthermore, triple chelation therapy has also been studied in exploring the efficacy of combining all three major chelators (deferoxamine, deferiprone, and deferasirox) in patients with severe iron overload, showing potential as well for more rapid and effective iron removal[21].

Gene therapy and gene editing are novel treatments being applied to various diseases with the aim of curing patients. Clinical trials are currently underway for beta-thalassemia

patients as well, exploring the potential of these advanced therapies. First, the CRISPR/Cas9 therapy is being ransacked in ongoing clinical trials to edit the *HBB* gene mutation in beta-thalassemia patients. The trials have shown encouraging results. Early-phase trials have demonstrated the potential to increase hemoglobin production and reduce the need for transfusions, thereby mitigating iron overload[22].

Another gene therapy, which introduces a functional beta-globin gene into the patient's hematopoietic stem cells, has shown promise in recent studies. Patients treated with LentiGlobin BB305 have achieved transfusion independence, reducing iron overload and the need for chelation therapy[23].

Hepcidin Mimetics and Modulators are another alternative being investigated as they play an important role in iron metabolism. Rusfertide, a hepcidin mimetic, is currently in clinical trials and has shown promising results in regulating iron homeostasis. By mimicking the action of hepcidin, rusfertide can decrease iron absorption and mobilization, effectively reducing iron overload in polycythemia vera patients and could potentially be able to treat beta-thalassemia patients with further research[24]. Synthetic mini-hepcidins are also being developed to treat iron overload. These small peptides have demonstrated efficacy in preclinical studies in mice by increasing hepcidin activity, leading to reduced iron absorption and improved iron homeostasis[25].

Noninvasive monitoring including new MRI techniques, such as T2* and R2* imaging, offer more precise quantification of iron in the liver and heart. These methods provide a noninvasive and accurate assessment of iron overload, enabling better monitoring and adjustment of chelation therapy[26].

Recent studies have identified novel biomarkers, such as serum hepcidin and erythroferrone levels, which can provide insights into iron metabolism and guide personalized chelation therapy[27].

Personalized medicine approaches are a relatively new approach to handle this ailment. Advances in pharmacogenomics are helping to tailor chelation therapy based on individual genetic profiles. Research has identified genetic variants that affect chelator metabolism and efficacy, enabling more personalized and effective treatment plans. Moreover, implementing TDM for chelation therapy allows for precise dose adjustments based on drug levels in the blood, optimizing efficacy and minimizing toxicity[28].

Therefore, the field of iron chelation therapy for beta-thalassemia is evolving rapidly, with significant advancements in chelator development, combination therapies, gene therapy, hepcidin modulation, and personalized medicine. Recent studies underscore the importance of patient-centered care and the use of advanced monitoring techniques to optimize treatment outcomes. By staying abreast of these developments, health-care providers can offer the most effective and up-to-date care for beta-thalassemia patients, ultimately improving their quality of life and long-term health outcomes.

Conclusion

In conclusion, deferiprone emerges as a promising solution for effectively managing iron overload in infants undergoing transfusions. Its oral administration and favorable safety profile position it as a viable option for addressing excess iron in this vulnerable population. However, careful consideration of its benefits and potential risks by health-care professionals, coupled with close monitoring during transfusion therapy, is crucial. Further investigations and clinical trials are imperative to comprehensively grasp deferiprone's long-term effectiveness and safety in this patient group. This ongoing pursuit will refine treatment approaches, enhance outcomes, and ultimately benefit pediatric patients with transfusion-dependent conditions.

Ethical approval

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Consent

Not applicable.

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Author contribution

M.T. and M.H.A.: conceptualization, methodology, writing – review and editing; S.H.: writing – original draft; Z.S.R., H.S., and M.A.H.: writing – review and editing; A.U.Q.U.: writing – review and editing.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

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Provenance and peer review

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Data availability statement

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BioRender.com was used to create Fig. 1.

References

[1] 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:e469–e478.
[2] Kattamis A, Forni GL, Aydinok Y, *et al*. Changing patterns in the epidemiology of β-thalassemia. Eur J Haematol 2020;105:692–703.
[3] Cianciulli P. Iron chelation therapy in thalassemia syndromes. Mediterr J Hematol Infect Dis 2009;1:e2009034.
[4] Belmont A, Kwiatkowski JL. Deferiprone for the treatment of transfusional iron overload in thalassemia. Expert Rev Hematol 2017;10: 493–503.
[5] Elalfy MS, Hamdy M, Adly A, *et al*. Efficacy and safety of early-start deferiprone in infants and young children with transfusion-dependent beta thalassemia: evidence for iron shuttling to transferrin in a randomized, double-blind, placebo-controlled, clinical trial (START). Am J Hematol 2023;98:1415–24.
[6] Elalfy MS, Adly A, Awad H, *et al*. Safety and efficacy of early start of iron chelation therapy with deferiprone in young children newly diagnosed with transfusion-dependent thalassemia: a randomized controlled trial. Am J Hematol 2018;93:262–68.
[7] Hider RC, Hoffbrand AV. The role of deferiprone in iron chelation. N Engl J Med 2018;379:2140–50.
[8] Efficacy and possible adverse effects of the oral iron chelator l,2-dimethyl-3-hydroxypyrid-4-one (L1) in thalassemia major—ScienceDirect. Accessed February 3, 2024. https://www.sciencedirect.com/science/article/pii/S0006497120705641?pes=vor
[9] De Sanctis V, Pinamonti A, Di Palma A, *et al*. Growth and development in thalassaemia major patients with severe bone lesions due to desferrioxamine. Eur J Pediatr 1996;155:368–72.
[10] American Journal of Hematology. Blood Research Journal. Wiley Online Library. Accessed February 3, 2024. https://onlinelibrary.wiley.com/doi/10.1002/ajh.23543
[11] Berdoukas V, Chouliaras G, Moraitis P, *et al*. The efficacy of iron chelator regimes in reducing cardiac and hepatic iron in patients with thalassaemia major: a clinical observational study. J Cardiovasc Magn Reson 2009;11:20.
[12] Waheed N, Ali S, Butt MA. Comparison of deferiprone and deferrioxamine for the treatment of transfusional iron overload in children with beta thalassemia major. J Ayub Med Coll Abbottabad 2014;26:297–300.
[13] Kontoghiorghes GJ. The vital role played by deferiprone in the transition of thalassaemia from a fatal to a chronic disease and challenges in its repurposing for use in non-iron-loaded diseases. Pharmaceuticals (Basel) 2023;16:1016.
[14] Eziefula C, Shah FT, Anie KA. Promoting adherence to iron chelation treatment in beta-thalassemia patients. Patient Prefer Adherence 2022;16: 1423–37.
[15] Entezari S, Haghi SM, Norouzkhani N, *et al*. Iron chelators in treatment of iron overload. J Toxicol 2022;2022:4911205.
[16] Madian AG, Wheeler HE, Jones RB, *et al*. Relating human genetic variation to variation in drug responses. Trends Genet 2012;28:487–95.
[17] Ivanova TI, Klabukov ID, Krikunova LI, *et al*. Prognostic value of serum transferrin analysis in patients with ovarian cancer and cancer-related functional iron deficiency: a retrospective case-control study. J Clin Med 2022;11:7377.
[18] Krishnevskaya E, Payán-Pernía S, Hernández-Rodríguez I, *et al*. Distinguishing iron deficiency from beta-thalassemia trait by new generation ektacytometry. Int J Lab Hematol 2021;43:e58–e60.
[19] Bayır H, Dixon SJ, Tyurina YY, *et al*. Ferroptotic mechanisms and therapeutic targeting of iron metabolism and lipid peroxidation in the kidney. Nat Rev Nephrol 2023;19:315–36.
[20] Taher AT, Origa R, Perrotta S, *et al*. New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: results of the randomized, phase II ECLIPSE study. Am J Hematol 2017;92:420–28.
[21] Kontoghiorghe CN, Kontoghiorghes GJ. Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes. Drug Des Devel Ther 2016;10:465–81.
[22] Zhang S, Wang Y, Mao D, *et al*. Current trends of clinical trials involving CRISPR/Cas systems. Front Med (Lausanne) 2023;10:1292452.
[23] Rattananon P, Anurathapan U, Bhukhai K, *et al*. The future of gene therapy for transfusion-dependent beta-thalassemia: the power of the lentiviral vector for genetically modified hematopoietic stem cells. Front Pharmacol 2021;12:730873.
[24] Handa S, Ginzburg Y, Hoffman R, *et al*. Hepcidin mimetics in polycythemia vera: resolving the irony of iron deficiency and erythrocytosis. Curr Opin Hematol 2023;30:45–52.
[25] Preza GC, Ruchala P, Pinon R, *et al*. Minihepcidins are rationally designed small peptides that mimic hepcidin activity in mice and may be useful for the treatment of iron overload. J Clin Invest 2011;121:4880–88.
[26] Hernando D, Levin YS, Sirlin CB, *et al*. Quantification of liver iron with MRI: state of the art and remaining challenges. J Magn Reson Imaging 2014;40:1003–21.
[27] Kowdley KV, Gochanour EM, Sundaram V, *et al*. Hepcidin signaling in health and disease: ironing out the details. Hepatol Commun 2021;5:723–35.
[28] Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. Fertil Steril 2018;109:952–63.