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Perspective

# Iron chelators or therapeutic modulators of iron overload: Are we anywhere near ideal one?

Iron overload is an important cause of mortality and morbidity in chronic transfusion-dependent states commonly exemplified by transfusion-dependent beta-thalassaemia syndromes [including non-transfusion-dependent (NTD) thalassaemia intermedia] as well as transfusion-dependent myelodysplastic syndromes (MDS). Hence, therapeutic iron chelation is indicated in these conditions[1-5]. There seems to be an increasing interest for different iron chelators and labile iron pool for patients with thalassaemia syndromes (thalassaemia major and thalassaemia intermedia) and transfusion-dependent MDS with respect to their efficacy, tolerability, safety, cost and long-term side effects. Several studies have been published recently on this topic[1-9]. Di Maggio and Maggio[4] evaluated 10 trials on various iron chelators singly or in combination for iron overloaded transfusion-dependent beta-thalassaemia major. Longitudinal changes in liver iron concentrations using different chelation regimens were discussed well by Vitrano *et al*[1]. There is a need for better chelators while search for optimum chelation regimen combining different chelators continues. Adding amlodipine to inhibit iron uptake by heart is another idea[3] as heart failure is one of the key serious complications in iron-loaded beta-thalassaemia major patients.

Di Maggio and Maggio[4] reviewed 10 different combination of three iron chelators in the market singly or in combination of two either given simultaneously or alternately in different trials. However, no data were given for trials evaluating three-drug combination or a combination of two oral drugs (deferasirox and deferiprone) though the use of two oral drug combination alternately has been used for hard to chelate patients[10].

Deferiprone as an iron chelator still does not have wide acceptance in the developed countries outside restricted indications in MDS and myocardial iron overload in combination with deferoxamine[6]. Iron deposition in multitransfused beta-thalassaemia patients produces clinical effects in mainly three organ systems, *i.e*. heart, liver and endocrine glands. Iron deposition-related mortality in transfusion-dependent beta-thalassaemia patients mostly occurs due to cardiac iron overload or iron overload in the liver[4]. In spite of all the intense chelation regimens, a significant number of transfusion-dependent beta-thalassaemia patients develop endocrine deficiency[11], showing that present chelation therapy is inadequate particularly with regard to recovery of endocrine gland function. The most effective, deferoxamine has to be given by long hours of subcutaneous injection[10]. The other two *i.e.* deferasirox and deferiprone have side effects such as agranulocytosis, hepatitis, renal disturbances, gastric intolerance, retinal and auditory toxicity and olfactory disturbances and these may not produce desired level of tissue iron in iron-overloaded state despite adequately intense therapy in some patients underscoring the need for more effective and safe iron chelators for clinical use[4,6,10].

Iron overload has multiple effects on thalassaemia patients. Oxidation damage to red cells due to labile non-transferrin bound iron (NTBI) damages the red cell membrane and shortens transfused red cells lifespan. This increases the transfusion requirement as well as iron overload[12]. It has damaging effects on mitochondria[13] that produce progressive mutation in mitochondrial genes in MDS[14] and affect DNA stability in the cell[15]. Iron overload also directly suppresses haemopoiesis[16]. Although mitochondrial mutation in thalassaemia major has not been studied extensively[17], considering the mechanism of action of NTBI and its ability to cause mutation, mitochondria are likely to be vulnerable to DNA damage in this disease. Hence, we need better iron chelators and should probably start early chelation in these patients.

Iron metabolism is controlled by a master hormone called hepcidin secreted from the liver when liver and tissues sense higher levels of iron in the body. Secretion of hepcidin is negatively regulated by matriptase 2 (also called TMPRSS6) which on activation through a chain of reactions leads to increased transcription and translation of hepcidin. Hepcidin inhibits absorption of iron from intestine and egress of iron from macrophage and other stores by catabolizing the iron transporter ferroportin[18]. Hence, matriptase 2 inhibitor or long-acting hepcidin mimetics can cause negative iron balance by preventing its absorption or its transport out of the cell rather than reducing iron overload by chelation. Second-generation TMPRSS6 antisense oligonucleotides were tested in animal model either singly or in combination with other available iron chelators such as deferiprone with good and synergistic reduction of iron overload and limited toxicity[19]. This product will now be taken up for phased clinical trials. Similarly, several chemical inhibitors of matriptase 2 have been synthesized and will undergo safety studies[20]. Small molecule peptides called minihepcidins which are orally bioavailable, have also been synthesized and effectively tested on animals successfully[21]. Small molecules with isoflavone structure (*i.e*., genistein) have been shown to stimulate hepcidin synthesis from liver[22] and can possibly be used to reduce iron levels in the iron-loaded state. Both these classes of compounds tend to reduce hepatic iron overload in preference to iron in other organs and may be especially useful for NTD thalassaemia intermedia where hepatic iron overload is a major challenge. However, no human trial with these compounds has been conducted as yet.

None of the 10 trials described[4] evaluated serial NTBI or labile free iron serially in their patients. This needs to be included in all future trials.

Hydroxyurea, a commonly used medicine for sickle cell disease and myeloproliferative disorders, was evaluated by us both in transfusion-dependent thalassaemia major and non-transfusion or minimally transfusion-dependent thalassaemia intermedia patients[23-25]. The reason for considering hydroxyurea as an iron chelator was due to its reported cytotoxicity because of inhibition of ribonucleotide reductase by iron chelation. Its chemical structure has a bidentate iron binding site[26].

Hydroxyurea synergistically works with both orally active iron chelators, has very good cardiac iron removing potential and strongly suppresses NTBI iron levels. It is equally potent in iron removal as deferasirox at a dose level without causing myelosuppression at the dose ranges used. It also reduced iron overload by reducing transfusion requirement in 30 per cent of thalassaemia major patients[25]. Whether hydroxyurea or some of its future analogues will form another class of iron chelators needs to be seen.

Iron chelation is increasingly being considered for many different conditions such as *Plasmodium falciparum* infection[27] or drug-resistant bacterial infections[28] or malignancies[29]. Drug-resistant bacteria producing carbapenemase and metallobetalactamase (NDM1) can now be countered by an antibiotic where an iron (and other metal) chelating catechol nucleus has been coupled to cephalosporin moiety[28]. Similarly, iron chelators are being explored to treat various malignancies[29]. It has been revealed that chelation of iron from proper cellular compartments can alter actions of various signal transduction mechanisms involved in cell growth, mitosis, apoptosis, autophagy and metastasis by involving [phosphatidyl inositol 3-kinase/protein kinase B (PI3-K)/ AKT, c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), $p^{38}$ mitogen-activated protein kinase (p38MAPK), signal transducer and activator of transcription 3 (STAT3), Wnt (Wingless/ Integrated)] transforming growth factor-β (TGF-β), *etc*[30]. Hence, one iron chelator may not fit all the bills. Different iron chelators may remove iron from different compartment of cells or tissues with different efficiency and may have differential toxicity and utility for different diseases. It has been found that efficiency of iron chelation depends on lipid solubility of the drug, but highly lipid-soluble iron chelators also increase the toxicity of the drug as seen in case of moderately lipid-soluble SP-420, a desferrithiocin analogue which was withdrawn from the trial because of nephrotoxicity[31]. Iron chelator has also been used to reduce daunorubicin toxicity on the heart using a heart directed iron chelator dexrazoxane[32]. However, one of the interesting ways to reduce toxicity and develop efficiency of the iron chelator is by developing metabolically programmable iron chelators[33] where the compound is designed in such a way that after reaching the tissue and chelating iron, the compound is metabolically transformed into more polar compound hence quickly excreted from the body.

It is hoped that many more novel molecules or combination of molecules or repurposing of old

molecules singly or in combination for removal of iron with novel mechanism of action or prevention of gastrointestinal absorption of iron will be developed in the future. These may improve iron chelation and overall improvement of health in multitransfused thalassaemia major and other patients in the future.

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**Kanjaksha Ghosh[1] & Kinjalka Ghosh[2,*]**
[1]Surat Raktadan Kendra & Research Centre, Surat 395 002, Gujarat & [2]Department of Biochemistry, Tata Memorial Hospital, Mumbai 400 012, Maharashtra, India
[*]*For correspondence*: kanjakshaghosh@hotmail.com

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