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ORAL IRON CHELATOR: DEFERIPRONE

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1. INTRODUCTION:

Patients who require multiple blood transfusions, such as patients with b-thalassemia major or those with oncohematologic malignancies, develop iron overload that in time becomes responsible for organ damage and dysfunction. Iron chelation therapy is, therefore, necessary to prevent or decrease the iron burden [1]. Since its introduction, more than three decades ago, the iron chelating agent desferrioxamine mesylate (DFO) has dramatically reduced the mortality and improved the quality of life in regularly transfused patients. However, since desferrioxamine must be administered chronically by subcutaneous continuous infusion through a battery-operated portable pump, the patients' compliance can be severely strained. Currently, deferoxamine is the only chelator for which there is strong evidence of reversal of iron-induced heart failure. Unfortunately, poor compliance with deferoxamine occurs even in this serious clinical situation and consistently leads to death.

Over the last two decades, research efforts in the field of iron chelation have been directed towards the developmentof an oral chelator that would liberate thalassemic patients from daily continuous infusions of deferoxamine. Although many chelators have been identified,only a few have demonstrated a satisfactory oral bioavailability. Deferiprone—also known as L1, Ferriprox (Apotex, Toronto, Canada), and CP20 Kelfer (Cipla, India) — is one of a series 3-hydroxy-pyrid-4-ones synthesized and tested as iron chelators in Professor R. Hider'slaboratories at the University of Essex in the early 1980s [2].

Deferasirox (ICL670, Exjade) belongs to a new class of oral tridentate chelator, N-substituted bis-hydroxyphenyltriazoles. Deferasirox, the result of a concerted discovery program, underwent extensive safety testing and clinical trials including preclinical studies, initial phase 1 and iron balance studies, phase 2 efficacy studies in adult and pediatric thalassemia patients, patients with a variety of anemias or unable/noncompliant with DFO, and the phase 3 clinical trial. With a plasma half-life of 8 to 16 hours, once-daily dosing permits circulating drug at all times to scavenge non–transferrin-bound "labile plasma iron," the chemical species responsible for tissue damage in iron-overloaded subjects, by means of toxic oxygen intermediaries. Deferasirox-iron complexes are excreted in the stool. Based on the study results, the United States Food and Drug Administration (FDA) approved the drug for transfusional iron overload for patients older than 2 years of age in November 2005 [3]. The drug is still under regulatory review in Europe. Deferasirox is an oral alternative to the injectable iron chelator deferoxamine for patients with transfusion-associated iron overload. It appears effective and well tolerated based on limited published data and the use of surrogate markers, but no outcome studies (morbidity/mortality) is available. Additional study results are necessary to fully assess efficacy in comparison with deferoxamine, but it is reasonable to assume that its efficacy is similar to deferoxamine based on the available data and the fact that acceptance and compliance with the oral dosage form may be better than with the injectable formulation required for deferoxamine therapy[4].

In Malaysia, Ferriprox and Kelfar are currently registered by the National Pharmaceutical Bureau.

2. OJECTIVE/ OBJECTIVES

To determine the safety, adverse events and effectiveness of the oral chelator deferiprone: ferriprox from Apotex, Canada; and kelfer from Cipla, India with regards to treatment for thalasemia.

3. TECHNICAL FEATURES

Ferriprox contains deferiprone, a bidendate chelating agent that chelates trivalent iron cations (Fe^{3+}) in a 3:1 (deferiprone:iron) ratio, 3 molecules of deferiprone are required to fill the 6 binding sites of iron. In Europe, deferiprone is licensed for the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate. Indications differ somewhat in other countries such as Turkey and Australia in which the chelator is licensed. Deferiprone is generally administered 3 times daily, and most of the chelator-induced iron excretion is found in the urine [5]

Progress on the drug was curtailed in 1993 by Ciba-Geigy due to the toxic effects observed in non-clinical studies. The main toxic effect of the drug was bone marrow suppression that was observed in all non-iron loaded animal species, which were investigated. In contrast, the status of deferiprone was also reviewed at this time by clinical investigators from the International Study Group on Oral Iron Chelators, which clearly recommended expansion of the clinical evaluation (Hershko, 1993). Since then, a number of further studies have been undertaken on the drug, and its development has been re-instated by Apotex due to the effectiveness of chelation achieved in humans. The Department of Health in India in December 1994 approved the clinical use of another formulation of deferiprone, called Kelfer®. The marketing authorisation holder is Cipla. Ferriprox is given orally as 25-mg/kg body weights, three times a day for a total daily dose of 75-mg/kg body weights. Dosage per kilogram body weight should be calculated to the nearest half tablet. Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions. There are limited data available on the use of Ferriprox in children between 6 and 10 years of age, and no data on use of Ferriprox in children under 6 years of age [6]

The European Union granted marketing approval for deferiprone in 1999 under the “exceptional circumstances” policy that requires further studies. Deferiprone achieved full marketing authorization in Europe in April 2002 after the sponsor fulfilled its specific obligations for additional studies. Nevertheless, some workers consider that deferiprone, because of its variable efficacy and potential side effects, should not be widely used outside clinical trials, even as second-line therapy to deferoxamine.

Deferiprone is rapidly absorbed and has a peak plasma level usually within 45 to 60 minutes of ingestion. Food reduces the rate of absorption but not the amount of drug absorbed. Deferiprone forms a 3:1 chelator/iron complex that is excreted together with free drug in the urine. More than 90% of the free drug is eliminated from plasma in most patients within 5 to 6 hours of ingestion [2].

Deferiprone is indicated in transfusion hemosiderosis, especially in cases of thalassemia, other hemolytic anemias, aplastic anemia and myelodysplastic syndromes, acute iron poisoning, siderosis associated with liver cirrhosis and for diagnosis of iron-storage diseases. Recommended dose of Deferiprone is 75 mg/kg/day in 2-3 divided doses. The only contraindication mentioned is hypersensitivity to deferiprone. Its use is not recommended in children below two years of age. Blood count monitoring is recommended every 3-4 weeks and if platelet counts fall less than 1 lac/µl and Absolute Neutrophil Count (ANC) less than 1000/µl the drug should be discontinued. The daily dose of deferiprone was 75-mg/kg body weight administered 3 times a day [7].

4. SEARCH METHODS

PUBMED, OVID and MEDLINE via EBSCO were searched using the keywords deferiprone , ferriprox, kelfar, deferiprone safety, deferiprone effectiveness and efficacy, deferiprone adverse events either singly or in combination, with the limits to human study, year of publication from 2003 – 2006. In addition websites for existing HTA agency, society websites and cross-referencing of the articles retrieved were also carried out accordingly to the topic.

5. RESULTS AND DISCUSSION

5.1 SAFETY

Most studies of deferiprone (ferriprox or kelfar) have found fluctuations in alanine aminotransferase (ALT) levels, particularly in the first months of treatment. Agranulocytosis has generally been considered the most serious side effect of deferiprone Arthralgia was one of the earliest reported side effects of deferiprone. Large joints, especially the knees, are most affected. The incidence of arthralgia was 20% of the 82 patients in the International study 30 but only 3.9% in a much larger Italian study [2]. The most serious undesirable effect of Ferriprox treatment reported in clinical trials is agranulocytosis. The mechanism of Ferriprox-induced agranulocytosis and of milder forms of neutropenia is unknown.

In deferiprone manufactured by Apotex (Ferriprox) , adverse events occurred less frequently after the first year of therapy, and no new drug-related complications were identified Gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, were the most frequently reported deferiprone related adverse events. In general, these events were reported early in the first year of therapy and uncommonly thereafter. Joint problems were associated with the use of deferiprone in 15% of the patients and rarely required discontinuation of therapy. Unlike gastrointestinal problems, episodes of joint problems occurred throughout the study period. A large survey of patients with thalassemia receiving deferoxamine found drug-related arthralgia and myalgia in 13% of patients. These findings suggest that problems on the joints may be related to the underlying disease or may be generally associated with iron chelation [5].

In a study conducted based on the medical records of ‘Thalassemia Day Care Centre’ of Kalawati Saran Children’s Hospital, New Delhi and cleared by the ethical committee of the hospital, forty-four patients with transfusion dependant thalassemia major, age 25 months to 72 months, using kelfar, the usual adverse advents occurring were gastrointestinal symptoms, reddish urine, and arthropathy {four patients (9.1%) reported joint pains but none had joint swelling}. Joint symptoms have been related to severity of iron overload. Two of the study case

(4.51%) had neutropenia and there were 20 patients (45.45%) with thrombocytopenia defined as platelet count less than 1.5 lac/µl [7].

5.2 EFFECTIVENESS

The efficacy of deferiprone has been determined by the amount of iron excreted in urine within 24 hours in response to the drug. In longer-term studies, the efficacy of deferiprone has been determined by changes in the body iron burden, assessed by trends in serum ferritin, liver iron and most recently in cardiac iron assessed by magnetic resonance imaging (MRI). Clinical parameters have also been used, for example, changes in liver and cardiac function as well as the prevention of new complications of iron overload, such as the endocrine system. The results of studies using serial serum ferritin and liver iron estimations have been summarized [2]. It is recognized that it would be difficult to perform a new prospective, randomized, comparative study in view of the limited number of patients. In addition, new oral iron chelators are under development and only a second line indication has been applied for [6].

The effectiveness of deferiprone has been assessed by many parameters. To name a few: A. Victor Hoffbrand et al stated that the effectiveness of deferiprone has been assessed by iron excretion, serum ferritin, serum nontransferrin-bound iron, liver iron and cardiac iron. Liver iron concentration could be measured biochemically by superconducting quantum-interference device (SQUID) and magnetic resonance imaging (MRI). A more recent study found that assessment of T2* by MRI is a promising method for the early diagnosis of myocardial iron overload. [2]

6. CONCLUSION

Many patients are successfully chelated at a dose of deferiprone 75 mg/kg/day(for both feriprox and kelfar). Some patients may need higher doses (up to 100 mg/kg), or combination therapy of deferiprone every day and desferrioxamine on several days each week. Recent data suggest that deferiprone may be superior to desferrioxamine at protecting the heart from iron overload [2-3]
Side-effects of deferiprone (both ferriprox and kelfar) —agranulocytosis, neutropenia, gastrointestinal symptoms, arthropathy, transient changes in liver enzymes, and zinc deficiency—are now well recognized.
Patients with thalassemia major and other transfusion dependent disorders who are able to successfully control iron overload at a safe level with deferoxamine should be encouraged to continue with this approach to chelation therapy. Treatment with deferiprone should be carefully considered for patients unable to use deferoxamine or for patients with an unsatisfactory response to deferoxamine as judged by liver iron and serum ferritin measurements or evidence of cardiac iron overload or iron-induced cardiac dysfunction. At a dose of deferiprone of 75 mg/kg per day, iron stores may decrease in some patients, remain stable in others, and increase in some others. Thus, careful monitoring of iron stores, preferably by measurement of tissue iron and of cardiac function, is important during treatment with deferiprone, as it is with deferoxamine. Enhanced iron excretion can be obtained at higher doses of deferiprone or by combining deferiprone and deferoxamine therapy. Early studies of combined therapy are particularly encouraging, but these approaches have not undergone rigorous long-term testing for complications.

Although we have focused on the use of deferiprone (either ferriprox or kelfer) for thalassemia major, deferiprone may also have an important role in the treatment of patients with thalassemia intermedia and of patients with other anemias who accumulate iron at lower rates than do those with thalassemia major. As with any drug recently introduced to clinical practice, further studies of the risks and benefits associated with deferiprone therapy should take place, and all patients receiving the drug should be closely monitored. This is due to the fact that for deferiprone manufactured by Apotex (ferriprox), adverse events do occur and more research data on the use of kelfar is warranted.

7. REFERENCES

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8. APPENDICES

9.1. Appendix I- Levels of evidence scale

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to fair	Small sample RCT
4		Non-randomized controlled prospective trial
5	Fair	Non-randomized controlled prospective trial with historical control
6	Fair	Cohort studies
7	Fair	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT (CAHTA), SPAIN