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Significance Of Combo Chelation Therapy Over Mono Chelation Therapy In Patients With Thalassemia

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Thalassaemia or "**thalassemia**" is an inherited autosomal recessive blood disease. In thalassemia, the genetic defect results in reduced rate of synthesis of one of the globin chains that make up hemoglobin. Reduced synthesis of one of the globin chains can cause the formation of abnormal hemoglobin molecules, thus causing anemia, the characteristic presenting symptom of the thalassemias.Alpha, beta and delta are different types of thalassemia dependong upon pathophysiology. Both alpha and beta thalassemia include the following two forms:Thalassemia major and Thalassemia minor. Children born with thalessemia major (Cooley's anemia) are normal at birth, but develop severe anemia during the first year of life.Other symptoms can include:bone deformities in the face, fatigue, growth failure, shortness of breath and yellow skin (jaundice). Persons with the minor form of alpha and beta thalassemia have small red blood cells (which are identified by looking at their red blood cells under a microscope), but no symptoms. Treatment for thalassemia major often involves regular blood transfusions and folate supplements. Persons who receive significant numbers of blood transfusions need a treatment called chelation therapy to remove excess iron from the body. Bone marrow transplant may help treat the disease in some patients, especially children.

Two main subtypes thalassemia major (TM) and thalassemia intermedia (TI). TI has a later clinical onset with a milder anemia that does not require transfusions at least during the first few years of life. Nowadays, well-treated TM patients with regular transfusion-chelation therapy showed suppression of the anemia-related disorders in parallel to prolongation of life [1]

Thalassemia intermedia encompass a wide clinical spectrum of beta-thalassemia phenotypes. Some thalassemia intermedia patients are asymptomatic until adult life, whereas others are symptomatic from as young as 2 years of age. A number of clinical complications commonly associated with thalassemia intermedia are rarely seen in thalassemia major, including extramedullary hematopoiesis, leg ulcers, gallstones and thrombophilia. Prevention of these complications, possibly with blood transfusion therapy, is ideal since they may be difficult to manage. Currently, many patients with thalassemia intermedia receive only occasional or no transfusions [2].

Blood product transfusions are a valuable health-care resource. Guidelines for transfusion exist, but variability in their application, particularly in children, remains. The risk factors that threaten transfusion safety are well established, but because their occurrence in children is rare, single-institution studies have limited utility in determining the rates of occurrence. Red blood cells and platelets were the two most frequently transfused products [3]

Blood transfusion in thalassemia is critical for the survival of patients. The hypertransfusion therapy has significantly increased the life expectancy and quality of life in such patients. However, this treatment has also increased the frequency of complications due to iron overload. Despite recent treatment with Desferal® in beta-thalassemia major, the risk of secondary endocrine dysfunction remains high, with hypogonadism being one of the most frequent endocrine complications [4]

Previous studies have shown that the iron overload that results from such therapy in other patient populations is associated with significant morbidity and mortality. In patients

with sickle cell disease, ferritin is a poor marker for accurately assessing iron overload and should not be used to direct long-term chelation therapy. Despite high levels of liver iron, the associated liver injury was not severe [5]

Post transfusionnal iron overload is related to both a degree of RBC units transfused and excess intestinal absorption of Fe related to dyserythopoiesis. This condition is associated with high rates of morbidity and mortality, mainly of cardiac origin. The reference treatment by deferoxamine is strenuous and compliance is poor. Two oral iron chelators, deferiprone and deferasirox, provide potentially useful treatment for iron overload, both agents are relatively well tolerated (mainly deferasirox). They were at least as effective as DFO for decreasing iron burdens in comparative trials, and were associated with improved cardiac outcomes (for deferiprone). A new enthusiastic area for iron chelation with less burdensome treatments is open; however a long term follow up is required before giving up pumps and needles [6]

Iron overload may be prevented or treated with a chelating agent capable of complexing with iron and promoting its excretion. The only iron-chelating agent presently available for clinical use is deferoxamine B, a trihydroxamic acid produced by *Streptomyces pilosus,* with relative specificity for ferric iron [7] Deferoxamine is poorly absorbed orally.[8] and rapidly metabolized in plasma,[9] conferring on the drug its principal drawback: the requirement for prolonged parenteral infusions during which plasma concentrations reach a plateau at 12 hours.[10] The sources of iron chelatable by deferoxamine have been thoroughly reviewed.[11],[10],[12],[13] Iron bound by deferoxamine is rendered virtually inactive metabolically and deferoxamine can prevent or reverse effects of free radical formation and lipid peroxidation in many experimental systems.[14],[15],[16],[17]

Deferoxamine, which has been used since four decades as an iron chelator has limited efficacy due to its demanding therapeutic regimen, leading to poor compliance. Deferasirox, once daily oral iron chelator provides an effective alternative to Deferoxamine in the treatment of transfusional hemosiderosis. Thus, convenient, effective and tolerable chelation therapy with oral Deferasirox is likely to be a significant development in the treatment of transfusional iron overload, due to its ability to provide constant chelation coverage and the potential to improve compliance [18]

Deferoxamine (DFO) appeared to have certain toxic effects on the sensory pathways in some of patients on nightly subcutaneous deferoxamine (DFO) for transfusion-dependent anemia, treatment was stopped in all of these patients to obtain a comprehensive baseline assessment of sensory function. Visual evoked potentials (VEPs) were studied in all the patients having normal ophthalmological examinations. Abnormally prolonged VEP lantecies were found. The VEPs can detect subclinical toxic effects of DFO on the visual system and should be considered as a monitor for patients receiving chronic DFO therapy [19]

Deferiprone (DFP), an orally active iron chelator, emerged from an extensive search for new drugs to treat iron overload. Comparative studies have shown that at comparable doses the efficacy of DFP in removing body iron is similar to that of desferoxamine (DFO). In retrospective and prospective studies, DFP monotherapy was significantly more effective than DFO in the treatment of myocardial siderosis in thalassemia major. DFP can be used in combination with DFO in the management of severe iron overload. This chelation regimen is tolerable and attractive for patients unable to comply with standard DFO infusions or with inadequate response to DFP monotherapy. DFP has a well-known long-term safety profile. Agranulocytosis is the most serious side effect associated with its use, occurring in about 1% of the patients. More common but less serious side effects are gastrointestinal symptoms, arthralgia, zinc deficiency, and fluctuating transaminase levels [20]

The iron chelators deferoxamine (DFO) and deferiprone (L1) have demonstrated their ability to normalize cardiac function in patients

with iron overload-induced cardiac disease. However, conventional chelation with subcutaneous DFO fails to prevent iron deposition in two-thirds of thalassemia major patients, placing them at risk of heart failure and its complications. Deferiprone appears to be more effective in cardiac iron removal. The detection and management of heart complications have improved dramatically over the last 7 years. Non invasive techniques of quantifying iron burden via magnetic resonance imaging (MRI) have been validated. A better understanding of cardiac pathophysiology and improved ability to detect at-risk populations are yielding better outcomes and reduced morbidity. Deferiprone chelation was found to be of statistically significant benefit in upgrading cardiac function and reducing iron accumulation. The use of echocardiography and MRI to closely monitor cardiac functions associated with iron overload complications and mortality has proved quite practical [21]

The benefits of combined chelation therapy with daily deferiprone (DFP) and subcutaneous desferrioxamine (DFO) have been widely reported in literature. We retrospectively evaluated the efficacy of different schedules of combined chelation therapy and the incidence of adverse events. This study showed that the administration of DFO for 5 days a week in combination with daily administration of DFP at 75 mg/Kg seemed to be the most efficacy and rapid method for reducing iron overload at liver and heart level. Furthermore, the use of different schedules of combined DFO and DFP administration was not associated to different incidence of adverse effects between the groups. [22]

Magnetic resonance imaging (MRI)was used to compare the effect of iron chelation on liver, spleen and bone marrow. Patients undergoing combined therapy showed significantly greater reduction (Student's t-test, $p < 0.05$) or less increase (t-test, $p < 0.05$) in iron stores. Combined therapy is more effective than DFO for removing and preventing liver, spleen and bone marrow iron accumulation in beta-thalassemic patients. Magnetic resonance imaging is valuable for organ-specific monitoring of chelation therapy[23]

Report is about the long-term effects of deferasirox 10-30 mg/kg/day on cardiac iron overload in a case series of five patients with transfusion-dependent beta-thalassaemia major who underwent up to 5 years of chelation therapy.T2* MRI showed a decrease from baseline in cardiac iron levels in all patients during treatment with deferasirox Deferasirox chelation treatment regimen was well tolerated and adherence to the regimen was good. In conclusion, this case series suggests that deferasirox may decrease cardiac iron overload and maintain stable LVEF over the long term. [24]

Prospective, multicenter, open-label, single-arm study evaluating response of cardiac and liver iron to deferasirox therapy for 18 months. Monotherapy with deferasirox was effective in patients with mild-to-moderate iron stores but failed to remove cardiac iron in patients with severe hepatic iron burdens. There were two deaths, one from congestive heart failure and one from sepsis. In the twenty-two patients completing the trial [25]

Chronic red blood cell transfusion support in patients with myelodysplastic syndromes (MDS) is often necessary but may cause hemosiderosis and its consequences. The pathophysiologic effects of iron overload relate to increased non-transferrin bound iron generating toxic oxygen free radicals. Studies in patients with MDS and thalassemia major have shown adverse clinical effects of chronic iron overload on cardiac function in patients who underwent polytransfusion. Iron chelation therapy in patients with thalassemia who were effectively chelated has prevented or partially reversed some of these consequences. A small group of patients with MDS who had undergone effective subcutaneous desferrioxamine (DFO) chelation for 1 to 4 years showed substantial hematologic improvements, including transfusion independence. However, because chronic lengthy subcutaneous infusions of DFO in elderly patients have logistic difficulties, this chelation therapy is generally instituted late in

the clinical course. Two oral iron chelators, deferiprone (L1) and deferasirox (ICL670), provide potentially useful treatment for iron overload. This article reviews data indicating that both agents are relatively well tolerated, were at least as effective as DFO for decreasing iron burdens in comparative thalassemia trials, and (for deferiprone) were associated with improved cardiac outcomes. These outcomes could potentially alter the tissue siderosis-associated morbidity of patients with MDS, particularly those with pre-existing cardiac disease. [26]

In patients with thalassemia, neurologic complaints should lead to a high index of suspicion for spinal cord compression from marrow expansion, ectopic bone formation and resultant stenosis. Initial presentation, diagnosis, radiographic findings, surgical treatment and follow-up are reviewed**.** Rapid diagnosis and treatment of such a condition is essential to optimize the chances of recovery. [27]

Lung impairment represents one of the complications of thalassemia major whose clinical picture can remain in subclinical form all life long. Iron overload might be the main factor determining lung impairment, even though a more accurate evaluation is necessary [28]

The iron-related organ dysfunction, hepatitis C, and complications of iron chelation therapy are strongly age-dependent in patients with β-Thalassemia. Endocrinologic complications were common among adults. Among 330 patients who had received deferoxamine chelation therapy, 224 reported no complications. This suggests that treatment of patients with β-Thalassemia major has improved dramatically during the past 40 years [29]

Cardiac disease remains the main cause of death in those patients. In 1995, the oral chelator deferiprone became available for clinical use. We compared the occurrence of cardiac disease in patients treated only with DFO and in those whose therapy was switched to deferiprone during the period of observation, from January 31, 1995, to December 31, 2003. No cardiac events occurred during deferiprone therapy or within at least 18 months after the end of it. In the setting of a natural history study, deferiprone therapy was associated with significantly greater cardiac protection than deferoxamine in patients with thalassemia major. [30]

Prevention of cardiac mortality is the most important beneficial effect of iron chelation therapy. Unfortunately, compliance with the rigorous requirements of daily subcutaneous deferoxamine (DFO) infusions is still a serious limiting factor in treatment success. The development of orally effective iron chelators such as deferiprone and ICL670 is intended to improve compliance. Although total iron excretion with deferiprone is somewhat less than with DFO, deferiprone may have a better cardioprotective effect than DFO due to deferiprone's ability to penetrate cell membranes. Recent clinical studies indicate that oral ICL670 treatment is well tolerated and is as effective as parenteral DFO used at the standard dose of 40 mg/kg of body weight/day. Thus, for the patient with transfusional iron overload in whom results of DFO treatment are unsatisfactory, several orally effective agents are now available to avoid serious organ damage. Finally, combined chelation treatment is emerging as a reasonable alternative to chelator monotherapy. Combining a weak chelator that has a better ability to penetrate cells with a stronger chelator that penetrates cells poorly but has a more efficient urinary excretion may result in improved therapeutic effect through iron shuttling between the two compounds. The efficacy of combined chelation treatment is additive and offers an increased likelihood of success in patients previously failing DFO or deferiprone monotherapy. [31]

Ocular involvement was observed in 58% of patients. Lenticular opacities were the most common ocular finding (44%), followed by decreased visual acuity (33%). An increased occurrence of ocular changes was observed with increase of serum ferritin and serum iron levels as well as with higher number of blood transfusions received. Desferrioxamine seemed

to have a protective influence on retinal pigment epithelium (RPE) mottling. Occurrence of lenticular opacities and RPE degeneration correlated positively with use of desferrioxamine and deferriprone respectively. Follow-up of patients for one year did not reveal any change in ocular status. CONCLUSION: Regular ocular examinations can aid in preventing, delaying or ameliorating the ocular complications of thalassemia. [32]

Transfusion-dependent β-Thalassemia major causes infertility due to iron deposition to endocrine organs after overtransfusion. Very few pregnancies have been reported among such patients after modern therapies. The fertility and pregnancy complications for mothers and newborns includes cardiac failure, endocrine and hepatic functions, viral infections. Pregnancy can be safe for mothers and babies in women started early on intensive treatment [33]

Recent advances in the management of thalassemia have significantly improved life expectancy and quality of life of patients with this hemoglobinopathy, with a consequent increase in their reproductive potential and desire to have children. Among the women with thalassemia major, 91% of the pregnancies resulted in successful delivery of 45 singleton live-born neonates, five sets of twins and one set of triplets. No secondary complications of iron overload developed or worsened during pregnancy. When considering only the singleton pregnancies, the proportion of babies with intrauterine growth retardation did not differ from that reported in the general Italian population. The high prevalence of pre-term births (32.7%) was mostly related to multiple pregnancies and precautionary reasons. Pregnancy was safe in most women with thalassemia major or intermedia. However, women with thalassemia intermedia who had never previously been transfused or who had received only minimal transfusion therapy were at risk of severe alloimmune anemia if blood transfusions were required during pregnancy. [34]

With recent therapeutic advances, thalassemic patients can now reach adulthood and attain reproductive capacity. Endocrine complications due to hemosiderosis and especially hypogonatotropic hypogonadism, which present either with sexual infantilism and primary amenorrhea or with secondary amenorrhea, are common in thalassemic women. These 90 pregnancies resulted in 69 full-term, 12 pre-term, 7 abortions and 2 stillbirths. No severe obstetric complication was observed except for two patients with preeclampsia. One patient with PA who carried the triple pregnancy developed severe cardiac failure, which was successfully treated. Transfusion requirements were increased during pregnancy. Discontinuation of desferrioxamine resulted in elevation of ferritin levels during the second and third trimesters of pregnancy and after delivery. Nine patients who were examined with cardiac echo had a transient increase of ESD and EDD during pregnancy, with return to normal after delivery. Labor was performed by Caesarian section in 26 births (26%) out of the 81 successful pregnancies. These collected data represent the largest number of pregnancies in thalassemic females reported so far and are clearly encouraging for the ultimate improvement of the quality of life in thalassemic patients. [35]

The incidence of fractures in the latest reports was lesser than previously reported. This is a result of better and earlier control of hemoglobin status by improved transfusion techniques, and earlier recognition of the disease. Difficulties arise due to inadequate blood transfusion facilities in developing countries. Majority of the fractures healed within normal union time for a given bone. Permanent deformities and gross limb length discrepancies were uncommon [36]

Impact of iron chelation therapy with deferoxamine (DFO) on patients quality of life were located. A limited number of studies assessed the impact of iron chelation therapy or iron overload on quality of life. All literature suggested a need for easily administered, efficacious and well tolerated oral iron overload treatments, given the impact of

current iron chelation therapy on adherence. Poor adherence to iron chelation therapy was documented to negatively impact survival. the impact of iron chelation therapy on patients with thalassemia, sickle cell disease, and myelodysplastic syndromes is high. quality of life domains affected included: depression; fatigue; dyspnoea; physical functioning; psychological distress; decrease in quality of life during hospitalization[37]

As early diagnosis and treatment of thalassemia are improving the prognosis of pediatric and young adult thalassemia patients, the major cause of illness and mortality has shifted from the problems of hemoglobin-deficient anemia to iron overload associated with chronic blood transfusion therapy. Heart, liver and other organ failure due to iron toxicity is the leading cause of death for thalassemia patients in the developed world. Aggressive monitoring of body iron burden is key to the survival and well-being of a chronically-transfused patient. There are several methods of iron assessment. The easiest, most affordable, least reliable and most common method is a serum ferritin test. So Oral iron chelation therapy improves quality of life.

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