

Brief Review of Studies on Oral Martial Therapy Compared to the Administration of Intravenous Iron in Nephrology and Dialysis

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Anemia is a frequent and early complication of Chronic Kidney Disease (CKD), and its prevalence increases with the worsening of renal function, involving over 50% of patients in predialysis (stage 4 - 5) and practically almost 100% of patients in hemodialysis [1]. The anemic state depends on an inadequate production of erythropoietin, however a fundamental importance is represented by the alterations of the martial state or due to an iron deficiency, as a consequence of inadequate intestinal absorption, or due to reduced bioavailability, linked to the systemic inflammatory state, characteristic of these patients or for uremic toxicity [2]. The administration of oral or intravenous iron and erythropoietin (Epo) is a key element for the correction of anemia both in patients with CKD and in patients on chronic hemodialysis [3,4]. The martial therapy, administered orally is preferred in patients in the conservative phase, but presents frequent side effects especially of gastrointestinal type. In contrast, hemodialysis patients use almost exclusively the intravenous route that can promote even serious allergic phenomena, and can lead to an increase in the systemic inflammation with consequent functional anemia due to a reduced use of the iron by the marrow [3,4]. The possibility of having a particular oral iron preparation, the liposomal iron, based on ferric pyrophosphate carried within a phospholipid membrane, appears to have a lower incidence of gastrointestinal side effects, without increasing the inflammation of the patient [5]. Ionic iron absorption takes place predominantly in duodenal level and is mediated by specific carriers: ionic iron enters the intestinal cells by means of a divalent metal transporter. The transition to the blood stream is then mediated by ferroportin at the basolateral membrane of the enterocyte; in normal conditions only 15-

20% of the administered iron is absorbed [10,11]. The sophisticated technology of natural phospholipids mounting makes the highly bioavailable iron, well tolerated and rapidly absorbed. The presence of liposomal wrapper, in fact, protecting the iron by contact with the gastric mucosa avoids the pro-oxidant effect of free iron. Liposomal protection allows the micro-nutrient to overcome harmless the gastric environment to be absorbed directly in the small intestine and not only in duodenum. Liposome technology delivery corresponds, in our body, to the transport of various substances from the chylomicrons. These vehicles are few crowded natural and voluminous lipoproteins that represent the mode of transport of dietary fats from the intestine to the various tissues. This similarity between liposomes and chylomicrons enables liposomal molecules to exploit same metabolic pathways that the body usually enacts to chylomicrons. In the intestinal lumen, the liposome is absorbed directly from M cells (enterocytes) that originate from the lymphatic system and are located on all the small intestine. Then the liposome is incorporated for endocytosis by macrophages and through the lymphatic stream reaches, intact hepatocytes [8,13]. Within the hepatocytes, liposomes are opened by lysosomal enzymes, making iron available to the organism. So in patients with conservative CKD oral iron administration is preferred, but sometimes for intestinal malabsorption or the appearance of side effects, such as abdominal pain, gastralgia, nausea, vomiting, diarrhea, we are forced to pass to the administration via intravenous [6]. As mentioned early, in patients on chronic hemodialysis, intravenous iron during dialysis session, is preferred for practical reasons. However, allergic phenomena may occur up to severe anaphylactic reactions, potential cytotoxicity, hepatic disease with iron

accumulation in various forms of hemochromatosis, an increased risk of developing cirrhosis with levels of ferritin > 1000 ng / ml and an increase in the systemic inflammation with a decrease in antioxidant defenses [7]. The increased production of inflammatory markers, such as CRP, IL-6, TNF-alpha, promotes the release of hepcidin, a protein produced by the liver that acts by binding to another protein, called ferroportin, which regulates the escape of iron from cells, blocking the passage of iron from cells to blood resulting in functional iron deficiency, so-called inflammatory anemia [8,9,15]. Furthermore, recently they have been emphasized the medico-legal issues related to intravenous iron administration: a recent note dated 25 October 2013 from the Italian Medicines Agency (AIFA) (www.agenzia.droga.gov.it) underlined the risk of intravenous administration with potentially fatal reactions, especially in patients with known allergies and in patients with inflammatory diseases, including the immune system, as well as in patients with asthma, eczema, atopic allergies [1, 10]. Therefore, according to these notes, hemodialysis patients undergoing intravenous therapy should be monitored closely during and at least 30 minutes after administration in the presence of a doctor, in addition to the nursing staff, and all this could create organizational problems of considerable complexity especially if such indications should be extended to the Dialysis Centers for limited and / or decentralized assistance, where the presence of the doctor is notoriously circumscribed at times that do not cover all the dialysis sessions of the day. Although on one hand, among the various preparations, iron gluconate and carboxymaltose seem to be the one with fewer side effects, the Work Group KDIGO 2012 did not show a definite benefit of the intravenous route compared to the oral [1]. On the other hand, as already mentioned, the use of old oral iron compounds has not had much development until now due to their low efficacy and to the gastroenteric side effects linked to the compound which usually contains iron sulphate, which can be used only for a limited range of patients, certainly not affected by Chronic Renal Insufficiency, since in these patients gastritis and gastralgia are constant [6]. So recently, the possibility of having a particular oral iron preparation, the liposomal iron, based on ferric pyrophosphate carried within a phospholipid membrane, showed a lower incidence of gastrointestinal side effects, thanks to the

liposomal microencapsulation, for which iron does not come into contact with mucous membranes with better intestinal absorption bypassing the block induced by hepcidin, moreover the absorbed pyrophosphate iron has a greater affinity for the transferrin and is directly transferred to the bone marrow [5]. In this regard we have conducted a study [12], on a small number of patients in chronic daily home hemodialysis (8 pts) and on a group in conservative therapy with chronic renal failure Stage 3b-4 (16pts) who were on treatment for sideropenic anemia: all pts belonging to the two groups had been earlier treated for at least 6 months, with carboxymaltose iron iv (500 mg/month) and after they were passed to oral liposomal iron. The protocol lasted 6 months for home hemodialysis pts and 12 months for CKD pts. The study showed the equivalent efficacy of oral liposomal iron, compared to intravenous iron, with the maintenance and in many cases favoring the increment of hemoglobin values and reducing or keeping the same Erythropoietin dosages. These results confirmed previously performed nephrological works including a previous our work performed in 10 patients on three weekly dialysis treatment [10-14]. Differently from the precedent study the oral iron period was compared to an iv gluconate iron period. The period (3months) of liposomal iron intake showed a significant increase in terms of Hb concentration, transferrin saturation and a significant decrease regarding CRP values and weekly consumption of Epo. While the returning to iv gluconate iron administration period showed a significant reduction of Hb, a significant increase in the weekly consumption of Epo and increase of CRP. The conclusion of these two our studies [12, 14] was that liposomal iron seems to be a valid alternative to intravenous iron therapy (iron gluconate or carboxymaltose). A particularly interesting aspect of these studies is the reduction of PCR: statistically significant in the first experience and not statistically significant in the second experience of these two different works. This positive effect is explained by a lower activation / production of inflammatory markers that increase with the use of intravenous iron through the production of the species of reactive oxygen that exacerbate systemic inflammation, with decreased antioxidant defenses and increased TNF and IL-6 release [15]. The absence of these inflammation effects in the case of the use of liposomal iron, also explains the maintenance of weekly doses of

erythropoietin, recalling that 7 patients out of 16 in conservative therapy, throughout the period of observation, did not use erythropoietin and this has certainly contributed to a reduction in the costs of managing the anemia of patients in conservative treatment with chronic renal failure and in dialysis schedule [12]. Another argument in favor of liposomal iron is the reliability of oral iron also on the appearance of its intestinal absorption in an almost constant percentage (20%) compared to the intravenously administered iron of which the percentage of use is not certain, with an amount that it certainly precipitates at the tissue level, once the transferrin is saturated. In conclusion, our experience and that of many other authors demonstrates the possibility of replacing intravenous iron administration with liposomal oral iron, well tolerated, effective, and with significant economic savings in maintaining or reducing periodic doses of erythropoietin. Furthermore, we would like to underline the important relapse also on the medico-legal level, due to the lower clinical risk in the use of liposomal oral iron compared to intravenous iron.

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