

## **The Non-Responder**

**Prof. John B. Porter MA, MD, FRCP, FRCPath**

The term, non-responder, needs clarification. Non-response can be defined as either the failure to balance transfusional iron input with excretion or the failure to excrete more iron than transfusional iron input. It may also be defined as the failure to decrease serum ferritin/LIC or to control serum ferritin/LIC to target levels. Although not covered in this presentation, non-response is increasingly being defined in terms of failure to control myocardial iron as well. In determining response, it is important to note that the average change in a measure of response in a given group of patients is not sufficient to predict the probability of response in an individual. To predict individual probability of response, the proportion of patients responding to a particular regimen must be known.

Dosage, transfusion rate, and iron stores must be taken into consideration in determining the reason for non-response to chelation therapy. For example, desferrioxamine (DFO) 35 mg/kg, the dose used in several comparative studies, is unlikely to result in negative iron balance unless the transfusion rate is low. In addition, as iron load falls, chelation becomes less efficient, requiring increased dosage to achieve a previous response rate. Response to deferiprone (DFP) is also linked to both the transfusion rate and the degree of LIC. At lower LIC (<1500 µg/g wet wt), approximately 24% of patients receiving 75 mg/kg achieve negative iron balance, compared to 50% with higher LIC (>1500 µg/g wet wt). Starting ferritin levels also influence response to DFP, with ferritin levels declining significantly in response to treatment in patients having initial ferritin levels higher than 2500 ng/mL, but not in patients with lower starting ferritins.

The determination of response to chelation with DFP is also influenced by the parameter used to measure it. In a study of patients receiving DFP 70 mg/kg, 17% were considered non-responders when response was based on serum ferritin, whereas 70% were deemed non-responsive when response was based on LIC. Similarly, in another study, 43% of patients receiving DFP had a decrease in ferritin, but only 24% had a decrease in LIC and

spleen iron stores. Thus, in determining response in patients receiving DFP, it is important to keep in mind that ferritin changes may not fully reflect iron balance.

Response to deferasirox (DFX) is also a function of dose and transfusion rate. In addition, studies suggest that in some non-responders with good compliance to DFX, patient variability in absorption of drug may result in sub-optimal response. When this is the case, dividing the daily dose in half and administering it BID may resolve this problem. There is also a disconnect in the relationship of serum ferritin and LIC that may influence determination of response to DFX. Studies indicate that when there is no change in ferritin, there is a fall in LIC of about 4-7mg/g d wt. Thus, when body iron falls, there may be a decrease in LIC (negative iron balance) without a significant change in ferritin. Ferritin may also increase in the absence of a positive trend in LIC.

Several reasons for the differences observed between chelators in terms of response as measured by serum ferritin have been suggested. With DFO, iron removal is approximately equal in hepatocytes and macrophages; thus, changes in ferritin reflect changes in both LIC and reticuloendothelial (RE) iron. In contrast, DFP removes iron preferentially from RE cells compared with hepatocytes; therefore, response may be reflected in ferritin but not in LIC. The reverse is the case with DFX, which removes iron preferentially from hepatocytes compared with RE cells, resulting in a fall in LIC with a possible lag in ferritin. As a practical consequence of the differences in serum ferritin/LIC associated with the different chelators, clinicians need to assess the manner in which they determine non-response to insure that they are using the correct measure.

In addition to questioning patients concerning adherence (prescribed dose and frequency), other actions that can be taken when faced with a patient who is non-responsive to chelation therapy include determining the patient's current transfusional iron loading rate; considering the use of an additional measure of response, such as changes in LIC; and checking to see whether administration of drug is optimal (e.g., in terms of timing of oral medications relative to food, etc). In some cases, increasing the

dose, if it can be done safely, may result in increased response. In others, response may be increased by switching to an alternative chelator.