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REVIEW ARTICLE

The challenges of adherence and persistence with iron chelation therapy

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Abstract Due to advances in medical sciences, many chronic diseases that formerly resulted in early death can now be effectively managed with long-term treatment regimens. Patients with potentially fatal anemias, for example, can be treated with ongoing blood transfusions and iron chelation therapy. Ensuring adherence and persistence is challenging, as the benefits of therapy are not perceived immediately. Poor adherence severely compromises the effectiveness of treatment and, therefore, improving compliance in terms of quality of life and health economics is critical. Although adherence to chelation therapy is generally poor, the availability of oral iron chelators may help to improve patient compliance. For chronic conditions such as thalassemia major, even when oral chelation therapy is available, support by an integrated team including a clinical psychologist and nurse specialist working with the treatment center is recommended to achieve optimal results.

Keywords Adherence · Persistence · Iron chelation therapy

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1 Introduction to adherence

Ensuring adherence (the extent to which a patient adheres to their prescribed therapeutic regimen [1]) and persistence (continuing to take the treatment for the prescribed duration [1]) with long-term treatment regimens is challenging. Average adherence among patients with chronic diseases in developed countries is only ~50% [2], thereby compromising the effectiveness of treatment. Interventions to improve adherence would provide a significant positive return on investment through primary prevention of risk factors and secondary prevention of adverse health outcomes. The term 'adherence,' which refers to a voluntary act of subscribing to a point of view, is preferred by many patients to 'compliance', as this term implies an involuntary act of submission to authority. However, the two terms are used interchangeably throughout this review in reference to published data.

2 Iron overload

Anemias such as β-thalassemia and sickle cell disease (SCD) are examples of chronic diseases that require long-term treatment. At one time, patients with these conditions would have died in infancy, but these potentially fatal anemias can now be effectively managed with blood transfusion therapy. Although this approach can improve life expectancy in these and other anemias, such as the myelodysplastic syndromes (MDS), regular transfusions result in ongoing body iron loading. Labile plasma iron (LPI) is a toxic and chelatable form of iron that is produced continually during conditions of iron overload, and has been linked to the development of co-morbidities [3]. There is therefore a need to remove excess iron and

suppress LPI with iron chelation therapy to avoid the serious clinical sequelae associated with iron overload.

3 Approaches to iron chelation therapy

There are currently three iron chelators licensed for the treatment of iron overload. The current reference standard is deferoxamine (DFO; Desferal®; Novartis Pharma AG, Basel, Switzerland), which requires slow subcutaneous infusions over 8–12 h, 5–7 days each week. The burden of this demanding regimen led to the search for more convenient oral chelators. Deferiprone (Ferriprox®; Apotex Inc., Toronto, ON, Canada) is a three-times daily oral chelator approved for the treatment of iron overload in adult patients with β-thalassemia major for whom DFO therapy is contraindicated or inadequate [4, 5]. Deferiprone is often used in combination with DFO, where treatment can be sequential (both chelators are given in any 24-h period) or alternating (only one chelator is administered in any 24-h period). Deferasirox (Exjade®; Novartis Pharma AG, Basel, Switzerland) is the more recent oral chelator and is approved for the treatment of transfusional iron overload in various transfusion-dependent anemias. Because deferasirox has a long half-life of 8–16 h, it only needs to be taken once daily [6].

A limitation of both DFO and deferiprone monotherapy is an inability to constantly control levels of LPI as a result of their relatively short plasma half-lives [3, 7, 8] (Fig. 1a, b). DFO/deferiprone sequential therapy provides more consistent suppression of LPI than monotherapy with either chelator (Fig. 1c). As deferasirox is detectable in the blood within the therapeutic range over a 24-h period, it offers complete chelation coverage with standard dosing and can provide a sustained reduction in LPI [9].

4 Adherence with chelation therapy

A number of studies have demonstrated that patients who comply with chelation therapy have significantly better survival rates than those who do not [10–12]. Poor compliance with chelation therapy will lead to gaps in chelation coverage, during which time LPI levels can increase and cause further tissue damage. The direct capture of LPI with

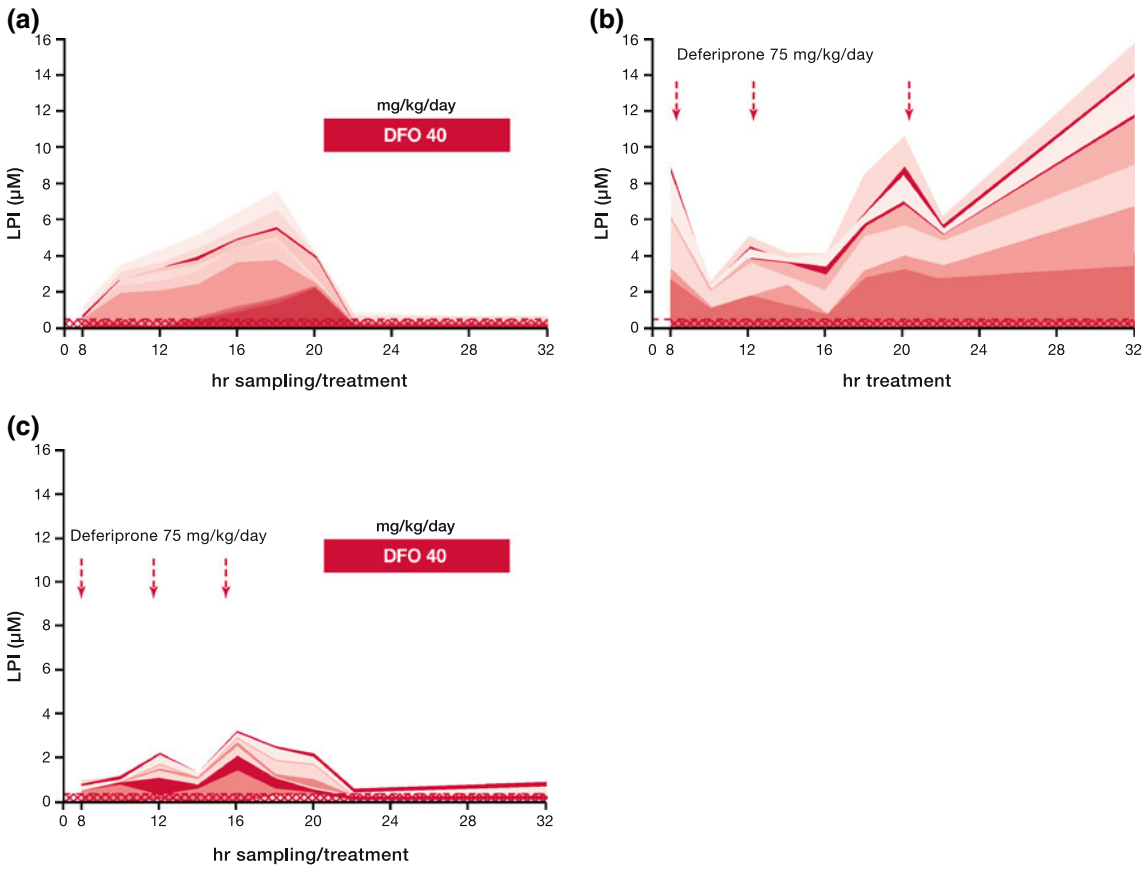

Fig. 1 Suppression of LPI in thalassemia major with **a** DFO monotherapy, **b** deferiprone monotherapy, and **c** DFO/deferiprone sequential therapy [3]. ©2005, Elsevier, with permission. Cabantchik ZI et al. Best Pract Res Clin Haematol. 2005;18:277–87. *Colors* denote individual patient data. *Hatching* denotes 0.4 precision limit

effective chelation therapy may help prevent the adverse consequences of iron overload [3].

Determining the prevalence of non-adherence is therefore important. This is often difficult because of the variety of methods used to measure adherence, none of which is ideal. These include direct markers such as serum ferritin levels and indirect measures such as self-reporting or pill counts. Measurement of serum ferritin levels do not take into account individual differences in medication absorption and blood transfusion rates. In a number of situations, they may also not reflect body iron level (e.g., in chronic disease and ascorbic acid deficiency) [13]. Patient and clinician reporting may be inaccurate and pill counts assume missing pills had been consumed. Electronic methods for measuring compliance such as the Medical Event Monitoring System have been developed [14]; however, this method was found to be no more accurate than pill counts and multiple methods for assessing compliance are strongly recommended. In addition to the variety of methods for assessing chelation adherence, there may be considerable differences in the criteria of good or poor adherence used. This may make it difficult to compare across populations and studies.

4.1 Parenteral therapy: deferoxamine

DFO infusions have a negative impact on patients' quality of life, as the infusions can be troublesome, time-consuming and painful. To maximize compliance, a number of practical interventions can be helpful. The injection site can be varied to decrease the likelihood of local skin reactions, butterfly needles can be used, the infusate should be kept to <10% solution, patients should be properly trained to ensure that subcutaneous, rather than intradermal, infusions are achieved, and ready-made balloon infusors can be provided [15]. A review of published data suggests that compliance with DFO in typical clinical practice is between ~60 and 80% [16]. Non-compliance with DFO also has a substantial negative impact on health economics. One study reported that inadequate compliance had an expected lifetime cost of $33,142 per patient due to management of the iron overload-related complications (e.g., cardiac disease, diabetes, hypogonadism) [16, 17].

4.2 Oral chelation therapy

Oral chelators may improve adherence by alleviating the practical aspects of infusion therapy, which would in turn relieve many of the psychological problems by easing the treatment burden. The oral formulation means that chelators are easier to use, especially for pediatric and adolescent patients for whom compliance is a particular issue [18, 19]. However, as there are no immediate clinical sequelae associated with non-adherence and as it may take months for a patient to feel the benefit of treatment, even adherence with oral chelation is not guaranteed.

4.2.1 *Deferiprone*

A few clinical studies have compared compliance with deferiprone and DFO monotherapy under trial conditions and have noted surprisingly small differences (Fig. 2) [20–22]. One study found that mean compliance improved with deferiprone from 88% at baseline to 98% after 13 months of treatment, whereas compliance with DFO decreased from 94 to 90% after 23 months [23], representing a mean relative change of 14%. To date, there are little published data regarding compliance with DFO/deferiprone combination therapy [24, 25], and the data available are somewhat contradictory and limited by high dropout rates. Adherence is likely to depend on the regimen used: a regimen that reduces the number of days of DFO therapy may improve adherence (e.g., alternate therapy), while a regimen using the standard DFO treatment plus deferiprone may worsen adherence (e.g., sequential therapy). As such, rates of patient adherence with combination therapy require further investigation. Long-term data evaluating adherence with deferiprone monotherapy are not available.

4.2.2 *Deferasirox*

Iron chelation with deferasirox may be beneficial, because it is a once-daily formulation, and it has been shown that regimens requiring fewer pills/tablets [26], or those with a reduced dosing frequency [27], improve compliance.

There are currently limited data directly reporting compliance with deferasirox therapy [28]. However, although patient acceptance of therapy is not the same as adherence, it can provide an indication of 'willingness' to comply. Two deferasirox studies in patients with

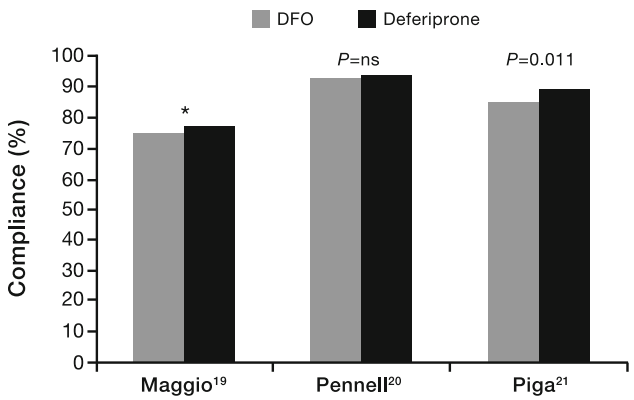

Fig. 2 Compliance with DFO versus deferiprone monotherapy. * *P* value not reported by Maggio; *ns* not significant

β-thalassemia and SCD evaluated actual patient feedback in the form of patient-reported outcomes [29, 30]. Most patients were more satisfied with deferasirox and found it to be more convenient than DFO therapy (Fig. 3). These findings are supported by the impact of chelation therapy on normal daily activities, with less time being lost each month as a result of therapy with deferasirox than with DFO.

The data in Fig. 3 were obtained at baseline and at 1 year in a randomized intervention study. With longer exposure to oral chelation therapy, the high patient acceptance with therapy achieved during 1 year under trial conditions may be more difficult to maintain, as adherence to any regime is generally higher under trial conditions than during regular treatment. Recent data obtained during the extension phases of the study mentioned in Fig. 3 suggest that adherence to deferasirox may fall in some patients after 3–4 years of chelation therapy, a trend that was strongly associated with lack of response to treatment [31]. In this single-center study on 33 patients, long-term trends in myocardial T2* assessments were analyzed for up to 4 years during deferasirox treatment. The proportion of patients failing to comply ≥90% rose from the first to the fourth year, and this correlated with a rise in the proportion of patients showing deterioration in myocardial T2*. Compliance of <90% was associated with lack of response to treatment in the second, third and fourth year of treatment [31]. Hence, adherence to oral chelation cannot be assumed even in controlled trials, as the initial enthusiasm of switching from parenteral therapy may reduce as the regimen becomes less novel. A key role of any thalassemia treatment center remains the early identification of patients with poor adherence by regular inspection of trends in serum ferritin levels, LIC and myocardial T2* measurements. This needs to be followed by appropriate counseling and psychological support if necessary.

A recent study from the Thalassemia Clinical Research Network (TCRN) examined adherence in 79 patients on DFO and 186 on deferasirox from 2007 to 2009. In this study, adherence was defined as percentage of doses administered (patient report) out of those prescribed, obtained from chart review over the last 4 weeks. Self-reported adherence to both DFO (92%) and deferasirox (97%) were surprisingly high. Ninety percent of patients on deferasirox reported at least 90% adherence, compared to 75% with patients on DFO. Adherence to both DFO and deferasirox was highest in children, followed by adolescents and older adults. Switching chelators resulted in increased adherence, regardless of the direction of the switch, although switching from DFO to deferasirox was far more common [28]. The high adherence rate may reflect the method of reporting (self-reporting) to some extent, but also suggests that adherence may be improved by offering patients greater choice in chelation with the ability to switch regimes when adherence decreases.

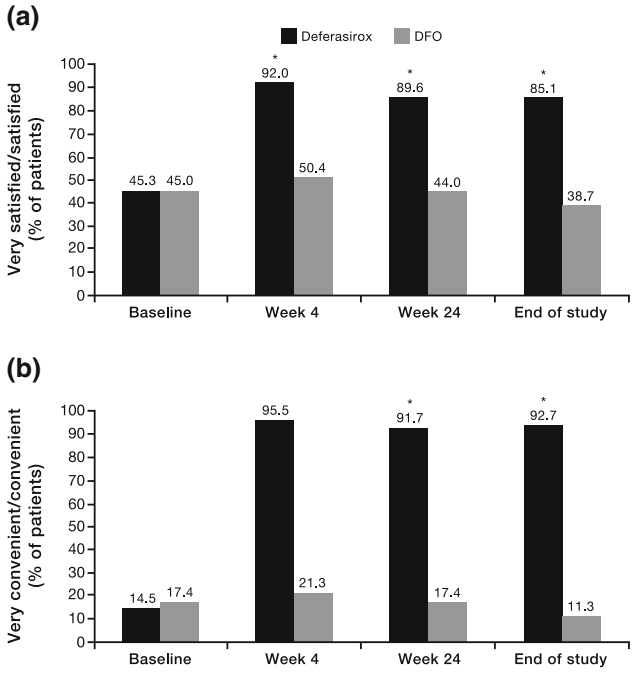

Fig. 3 Overall **a** treatment satisfaction with, and **b** convenience of, deferasirox versus DFO therapy [29]. ©2007, Elsevier, with permission. MD Cappellini et al. Clin Ther. 2007;29:909–17. * $P < 0.001$

5 Factors affecting compliance with chelation therapy

Perhaps the most significant factors associated with non-adherence are those related to regimen/practical aspects of drug administration, as treatment is troublesome, time-consuming and can be painful (hence the hope that oral chelators will improve rates of compliance). Patients may, however, be non-compliant for a number of other reasons (Table 1) [18], such as older age or an absence of shared responsibility for care between the child and caregiver. Some of these factors have been corroborated in a recent systematic review [32]. The recent TCRN study also implicated predictors of lower DFO adherence to be: smoking in the past year; problems with the use of needles (adults only); problems wearing their pump; and fewer transfusions in the past year. Predictors of lower deferasirox adherence were bodily pain and depression [28].

6 Adherence with chelation therapy in specific patient populations

Many patients with β-thalassemia and SCD are children, in whom administration of chelation therapy is largely the

Table 1 Factors affecting compliance with chelation therapy

Regimen and illness	Psychological and social	Demographic	Health system
Subcutaneous infusion over many hours	Motivational state	Age	Extent of integrated care
Frequent treatment	Reluctance to accept need for therapy	Gender	Patient–staff relationship
Time consuming	Negative body image	Educational level	Satisfaction with care
Variety of equipment required	Perceived effect on family and personal relationships	Country of origin	Distance to health care
Restriction of activities	Effect on social activity	Substance use	
Training required	Constant reminder of underlying illness		
Infusion-site pain and adverse effects	Lack of knowledge about disease		
Length of chelation history	Lack of understanding of the consequences of iron overload		
Frequency of hospitalizations	Depression		
Body pain	Mood		
	Self-efficacy		
	Perceived stigma		
	Illness disclosure		
	Chelation beliefs		
	Self-monitoring		
	Risk perception		
	Normative beliefs		
	Memory		

Adapted from Ref. [18]

responsibility of a parent or caregiver. It is therefore essential that the adult, as well as the patient, fully understands the importance of adherence.

Adolescents are a particularly challenging patient group because of their desire to express individuality or independence. For some adolescent patients, a directive by a physician to cooperate with a treatment regimen becomes just another opportunity to assert their independence, which may manifest as non-compliance [19]. Conversely, adolescents are the patients group most likely to benefit from effective chelation therapy.

Most patients with MDS are elderly, a population associated with distinct adherence issues: overuse and abuse, forgetting, and alteration of schedules and doses [33]. Physician expectation of MDS patients adhering to chelation therapy appears to be highly variable [34]. In this survey of 338 European physicians from 27 countries, 28% said that the expected 'non-compliance' to chelation was a strong barrier in initiating iron chelation therapy, while 23% thought that this was a weak barrier. This is partly because data on adherence in patients with MDS are scarce relative to that of thalassemia and sickle disorders; in a satisfaction and adherence survey of oral chelation therapy with deferasirox, using a newly developed patient instrument, MDS patients were only 6% of the subjects evaluated [35]. In this study, patient disease explained the most variance associated with 'never thinking about stopping chelating therapy', (used as the estimate of adherence) in patients with thalassemia, SCD or MDS. Other variables associated with this estimate of adherence were age, perceived effectiveness, low burden and low side effects of iron chelation therapy. Practical issues of tolerability to chelation can also impact on adherence in MDS patients; adherence to parenteral chelation therapy is a particular problem, partly because the introduction of infusion pumps is difficult to adapt to in older patients and also because infusions can lead to bruising in thrombocytopenic MDS patients [36]. With oral deferasirox therapy, gastrointestinal tolerability may impact on adherence. In a large 1-year study of 1,744 patients receiving deferasirox therapy, gastrointestinal side effects, although generally mild, were more common in patients with MDS than in thalassemia patients; for example, diarrhea was reported as a drug-related adverse event in 33% of patients with MDS compared with 8% of thalassemia patients [37]. Discontinuation rates were also more common in the MDS cohort, although only 13% of discontinuations in MDS patients were due to adverse events assessed by investigators to be related to the study drug [38]. Discontinuation of chelation treatment, and by inference adherence, is most likely multifactorial, including the risk of disease progression, pre-existing co-morbidities, use of concomitant medication and the advanced age of patients with MDS. Interestingly however, age was not a major factor affecting tolerability,

as the proportion of patients experiencing drug-related adverse events was 64% in patients aged 16 to <50 years, 65% in patients aged 50 to <65 years, and 67% in patients aged ≥65 years [38]. Thus, both parenteral and oral chelation therapy create practical challenges to adherence in patients with MDS that are greater compared with thalassemia patients.

7 Theory and compliance with chelation therapy

There are a number of theories of medication compliance that could be applied to chelation compliance but, as yet, have not. Most of these highlight psychological and social factors that influence compliance. The *Information, Motivation, Behavioral Skills Model* [39] suggests that compliance is dependent on: (1) accurate *information* about the condition and its treatment; (2) *motivation* to comply, which consists of (a) beliefs about the consequences of compliance and the importance of these outcomes, (b) social norms and the importance of complying with these norms and (3) *behavioral skills* required for compliance.

The *Medication Adherence Model* [40] also suggests that there are three key elements to medication compliance. *Purposeful action* refers to the degree to which individuals' intentionally decide to take medications based on perceived need, effectiveness and safety. *Patterned behavior* refers to the degree to which individuals initiate and establish a habit of taking medications through access, routine and remembering. *Feedback* refers to the extent to which information, facts, prompts or events influence compliance.

These models have sometimes been criticized for being rather static. There may be different determinants of compliance at the initiation of chelation therapy than during maintenance of therapy (or at times of stress vs. other times). However, there has been little work examining chelation compliance over time. In addition, there may be different determinants at different ages/stages of life and theoretical models have been accused of downplaying non-health motivations for non-compliance, the role of dynamic affect and non-individual level factors.

8 Improving patient adherence

A number of techniques can be used to improve adherence with chelation therapy (Fig. 4). A selection of these will be discussed below.

Establishing a multidisciplinary team approach (physicians, nurses, psychologists and patient counselors) with an interactive relationship with a patient who is involved with their treatment decisions may be of benefit, as it is essential that the patient understands the risks of iron overload and

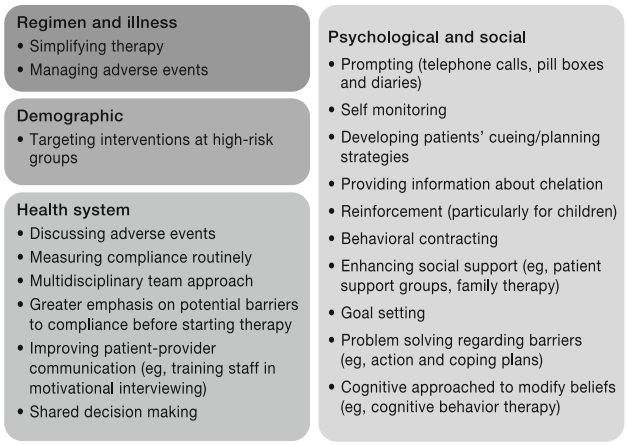

Fig. 4 Interventions to improve compliance

accepts the need for chelation therapy. Simplifying therapy may help, as evidenced by data showing improved compliance with once-daily dosing or fewer tablets/pills [26, 27]. Routinely assessing adherence and checking pill counts (in the case of deferiprone and deferasirox) at each visit may also have value. Similarly, a telephone call reminding the patient of the need to take their chelation therapy and openly discussing any existing barriers may improve compliance. It may also be advantageous for the physician to discuss potential adverse events with a patient before initiating chelation therapy. If the patient does experience problems, they will be aware that these events are normal and, in most cases, can be effectively managed even if they continue treatment.

9 Conclusions

Iron overload requires lifelong chelation therapy and patient attitude toward adherence will change over time. Although adherence with DFO infusions is generally poor, the availability of oral iron chelators may help to improve patient compliance. Investing time, effort and resources in strategies to improve adherence will result in significant long-term benefits, as the success of chelation therapy, in terms of reduced morbidity and improved survival, is dependent upon good adherence.

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