Adv Ther. 2008;25(8):725–742.
DOI:10.1007/s12325-008-0085-z

REVIEW

Iron Chelation Therapy: Clinical Effectiveness, Economic Burden and Quality of Life in Patients with Iron Overload

Krista A Payne
United BioSource Corporation, Montreal, Quebec, Canada

Diana Rofail
Mapi Values, Bollington, Cheshire, UK

Jean-François Baladi
Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

Muriel Viala
Mapi Values, Lyon, France

Linda Abetz
Mapi Values, Bollington, Cheshire, UK

Marie-Pierre Desrosiers
United BioSource Corporation, Montreal, Quebec, Canada

Noreen Lordan
United BioSource Corporation, Concord, Massachusetts, USA

Khajak Ishak
Irina Proskorovsky
United BioSource Corporation, Montreal, Quebec, Canada

Address correspondence to: Krista A Payne, United BioSource Corporation, 185 Dorval Ave, Suite 500, Montreal, Quebec, H9S 5J9 Canada. Email: krista.payne@unitedbiosource.com

ABSTRACT

Introduction: This study of UK patients examines clinical, health-related quality of life (HRQOL) and economic outcomes associated with iron chelation therapy (ICT). Desferrioxamine (DFO) (Desferal®; Novartis, Switzerland) and Deferiprone (Ferriprox®; Apotex, Canada) are ICTs used to treat iron overload. DFO requires 8- to 12-hour infusions a minimum of five times per week. Deferiprone is administered in an oral daily regimen. Although pharmacologically efficacious, clinical effectiveness of ICT within the real-world setting is yet to be fully elucidated.

Methods: A naturalistic cohort study of 60 patients (beta-thalassaemia, n=40; sickle cell disease, n=14; myelodysplastic syndromes, n=6; 63% female) receiving ICT in four UK treatment centres was conducted. Serum ferritin level data were abstracted from medical charts. Compliance, HRQOL, satisfaction and resource utilisation data were collected from interviews. Maximum ICT costs were estimated using the resource utilisation data associated with DFO.

Results: Mean serum ferritin levels, generally, remained elevated despite ICT. Compliance was suboptimal and HRQOL scores were lower than population norms. The total estimated mean weighted annual per-patient cost of DFO treatment was approximately £19,000. DFO-related equipment, DFO drug, and home healthcare were estimated to account for 43%, 19% and 24% of costs, respectively. Other more minor components of total annual costs were for in-patient infusions, ICT home delivery services and monitoring costs.

Conclusion: Generally, patients are not achieving target serum ferritin thresholds despite chronic treatment for iron overload. ICT appears to negatively impact HRQOL; compliance with ICT is poor; and, in the case of DFO, treatment costs well exceed the cost of DFO alone. These results suggest that current ICT in the real-world setting is suboptimal with respect to various clinical, HRQOL and economic outcomes.

Keywords: clinical effectiveness; economic burden; health-related quality of life; ICT; iron overload

INTRODUCTION

Patients with haematological disorders such as thalassaemia, sickle cell disease and myelodysplastic syndromes (MDS) attend hospital outpatient appointments to receive regular blood transfusions. A consequence of frequent blood transfusions is excess iron or iron overload, which cannot be excreted naturally. This leads to tissue damage and fibrosis.[1,2] Furthermore, although in the short-term iron overload does not cause visible symptoms to the patient, in the long-term if iron overload is not treated, many patients experience cardiac complications – a main cause of death in this population. Desferrioxamine (DFO; Desferal®, Novartis, Switzerland), an iron chelation therapy (ICT), is the standard life-long treatment for patients with iron overload due to chronic transfusions.[3] DFO is self-administered by the patient at home by subcutaneous infusion over 8 to 12 hours, 5 to 7 days per week, either overnight or during the day.[4] Although effective, DFO is associated with bothersome local site reactions including bumps, rashes, bruises and infections.[5,6] Other side effects experienced by patients administered DFO include neutropenia, haematological toxicity, shortness of breath, headaches and dizziness.[7]

In addition to these side effects, the DFO treatment regimen can also negatively impact aspects of patients' health-related quality of life (HRQOL).[4,8] A recent literature review revealed that few studies have focused on HRQOL in patients with iron overload.[9] In those that did, the results showed that for patients receiving ICT, HRQOL could be impaired in the following domains: depression,[10] fatigue, dyspnoea, physical functioning and psychological distress.[11]

Although less burdensome, the oral formulation of ICT, deferiprone (Ferriprox®, Apotex, Canada), has been shown to be less effective at lowering hepatic iron than subcutaneous DFO.[12,13] Side effects including arthropathy and neutropenia, which require strict monitoring during therapy, can also be experienced by patients receiving deferiprone.[14]

To better understand the potential impact of novel treatments for iron overload, it is important to understand the clinical effectiveness, HRQOL and economic impact of current ICT. The main objectives of the study described in this paper, which was conducted in a UK cohort were to assess:

- Clinical effectiveness of current ICT in the usual care environment
- HRQOL of patients with thalassaemia, sickle cell disease and MDS prescribed ICT, by comparing the Medical Outcomes Study Short Form Health Survey (SF-36) and Child Health Questionnaire (CHQ-PF50) responses against UK norms
- Patient satisfaction and compliance with ICT therapy
- Total annual costs of ICT using DFO.

MATERIALS AND METHODS

Study Design

The design and methods of this binational hybrid chart review and single patient interview study are reported else-

where in greater detail.[14] In this UK cohort, 60 patients with thalassaemia (n=40), sickle cell disease (n=14) and MDS (n=6) currently receiving ICT at four UK study sites (St Thomas' Hospital, London; The Royal Bournemouth Hospital, Dorset; The Whittington Hospital, London; King's College Hospital and GKT School of Medicine, London) were invited to participate in one study visit. A small number (n<75) of patients was considered acceptable due to the low prevalence of such disorders.[15,16] Furthermore, a comparable control group was not feasible given that the aim was to establish health and economic outcomes within a real-world setting using a naturalistic study design.[15,16]

UK central ethics review board approval was obtained. Upon receipt of informed patient consent, clinical data from the medical charts of subjects were abstracted retrospectively. In addition, sociodemographic, HRQOL, treatment satisfaction, compliance and 30-day retrospective resource utilisation data were collected from an interview with each subject. Using a secure internet site, anonymised data were then entered into a study database by site study staff that would normally have access to the subjects' medical records.

Effectiveness of ICT

To evaluate the effectiveness of ICT, all documented serum ferritin level test results and adverse events from the subjects' first and most recent years of ICT were abstracted retrospectively from the medical charts. During the study visit, subjects were asked if they had missed any prescribed doses of ICT over the previous 7-day period. If the subject reported that the ICT was not taken as prescribed, the number of missed doses was recorded and entered into the study database. Subjects were also asked if they had experienced any adverse events during the previous 30 days. Adverse events specifically queried were site irritation or soreness, nausea, breathing problems, ringing in the ears, temporary hearing loss, decreased night vision, blurred vision, fever, diarrhoea, abdominal pain, decreased appetite, headache and/or joint pain.

HRQOL

Adult patients undergoing ICT completed the SF-36,[17] and parents of children (age 5–17 years) undergoing ICT completed the CHQ-PF50. Both of these HRQOL instruments have been shown to be reliable, valid and responsive in a number of populations, and are frequently used to measure HRQOL.

Patients also completed the 'Satisfaction with ICT' instrument,[18] which is currently being validated. All HRQOL and satisfaction analyses were based on the overall adult sample and included all treatments.

The SF-36 comprises 36-items yielding a profile of eight concepts: Physical Functioning; Role Limitations – Physical; Bodily Pain; General Health; Vitality; Social Functioning; Role Limitations – Emotional; and Mental Health. The SF-36 also has a Physical Component and a Mental Component Summary Score.

The SF-36 data were then transformed into the SF-6D, a descriptive profile of

health states. Each health state is composed of six statements, one from each dimension, starting with Physical Functioning and ending in Vitality. A total of 9000 possible health states are defined in this way.[19]

Utilities were also estimated for the UK population using published algorithms developed by Brazier et al.[19] to transform SF-36 scores into utility-based scores. Utility scores are a measure of health outcome which assigns to each time period a weight ranging from 0 to 1, corresponding to the HRQOL during that period.[20] Utility scores can range between 1 (perfect health) and 0 (worst possible health as measured by the SF-6D).

The CHQ-PF50 measures HRQOL in children as reported by the parent. The parent form (for parents of children aged 5–17 years) contains 50 items yielding 12 domains: Physical Functioning; Role/Social Limitations – Physical; Bodily Pain; General Health; Role/Social Limitations – Emotional/Behavioural; Mental Health; Behaviour; Self-Esteem; Parent Impact – Time; Parent Impact – Emotional; Family Activities; and Family Cohesion. The CHQ-PF50 also contains two summary scores: the Physical Summary Scale and the Psychosocial Summary Scale.

Treatment Satisfaction with ICT

All participants 10 years of age and older completed a 28-item self-administered 'Satisfaction with ICT' questionnaire comprising four domains: the Perceived Effectiveness domain, which measures participants' perceptions of the clinical benefit; the Burden of ICT domain, which assesses the impact of ICT on daytime and evening activities, sleep and loss of independence; the Acceptance of ICT domain, which evaluates participants' perceptions of convenience (or inconvenience) of ICT, satisfaction with the mode of administration, and the extent to which benefits of treatment meet expectations; and the Side Effects of ICT domain, which assesses pain, side effects, and the potential negative impact of treatment on the body. Scores range from 1 to 5 where 1 represents 'very dissatisfied' and 5 represents 'very satisfied'.

Annual Costs of ICT

To identify prior studies reporting costs of infused ICT, a literature review was undertaken (EMB reviews, Scirus and Ovid Medline [1996–2005], PubMed [1995–2005]), using the following keywords (including MeSH terms): thalassaemia, sickle cell disease, myelodysplastic syndromes, cost, iron chelation, Desferal, desferrioxamine, deferiprone, L1, resource use, and reimbursement. Only four studies were identified that contained data related to the costs of infused ICT.[21–24]

On the basis of the literature, a single composite list of cost variables (such as drug, equipment, monitoring toxic effects, and psychotherapist) was created to serve as the basis for the health economics component of the case report form. Frequency of use and unit cost data for each of these variables were identified from the literature, this study, administrative databases, and medical supply catalogues. To estimate

the maximum total cost burden of ICT, only the cost of treatment with DFO was estimated given that deferiprone does not require equipment or infusions because it is an oral formulation. Data sources are presented in the results section alongside cost estimates. All costs are reported in 2007 GBP (£).

RESULTS

Demographic Characteristics

The demographic characteristics of the sixty participants are summarised in Table 1. Participants were mostly female (female, *n*=38; male, *n*=22).

At the time of the study visit, 29 (48%) participants were being treated with DFO, 18 (30%) with deferiprone, and 13 (22%) were on a combination of both. Mean duration of therapy was 4.9±4.0 years. The mean dose and prescribed regimen for DFO monotherapy was 34.9±13.1mg/ kg, 4.4±1.3 times/week. For deferiprone monotherapy, the mean total daily dose was 82.3±13.1 mg/kg with a mean total number of doses of 7.0±0.0 times/week. For patients on combination therapy, the mean DFO dose was 50.9±24.6 mg/kg, prescribed 3.2±1.6 times/week; and the mean total daily dose of deferiprone was 71.6±17.6 mg/kg with a mean of 8.0± 3.9 doses/week.

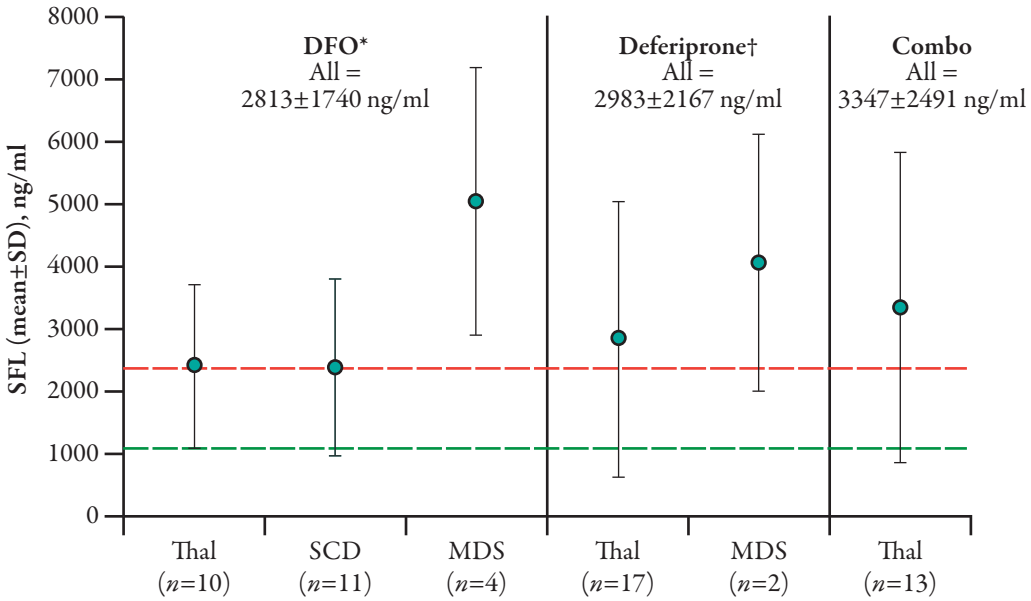
Table 1. Demographic characteristics of study sample.

	n (%)
All patients	60 (100)
Age	
6–10 years	2 (3)
11–18 years	9 (15)
≥19 years	49 (82)
Gender	
Female	38 (63)
Male	22 (37)
Disease	
Thalassaemia	40 (67)
Sickle cell disease	14 (23)
Myelodysplastic syndromes	6 (10)
Employment status	
Unemployed	31 (52)
Retired	6 (10)
Part-time	7 (12)
Full-time	16 (27)

Effectiveness of ICT

Despite ongoing ICT, serum ferritin levels remained very high over the mean duration of ICT treatment. In DFO-treated subjects, for whom serum ferritin test results were available, mean serum ferritin levels over the initial and most recent years of ICT were 3013±1370 ng/ml (*n*=8) and 2813±1740 ng/ml (*n*=25), respectively. These data were not available from the initial year of ICT for subjects on combination, and were unavailable for all but one subject on deferiprone. In the most recent year of ICT, mean serum ferritin levels for combination and deferiprone subjects were 3347±2491 ng/ml (*n*=13) and 2983±2167 ng/ml (*n*=19), respectively (Figure 1).

Figure 1. Mean serum ferritin levels (most recent year of ICT).



*Does not include three patients for whom the initial year of ICT equals the most recent year of ICT.
†One patient started the year on deferiprone and switched to DFO.
DFO=desferrioxamine; ICT=iron chelation therapy; MDS=myelodysplastic syndromes; SCD=sickle cell disease; SD=standard deviation; SFL=serum ferritin level; Thal=thalassaemia.

In general, mean serum ferritin levels of patients receiving ICT were much higher than 1000 ng/ml (Figure 1, green line) and in many patients, levels were higher than 2500 ng/ml (Figure 1, red line).

During the interview, non-compliance with ICT during the previous 7 days was assessed and 17 of 58 (30%) subjects missed at least two doses during this time period. In addition to non-compliance, a notable number of adverse events to ICT over the previous 30 days were observed in this study cohort (Table 2). Site soreness (n=20) was the most common adverse event in patients taking DFO; site soreness (n=6) and irritation (n=6) were the most common adverse events in patients taking combination; joint pain (n=3) was the most common adverse event in patients taking deferiprone. Of the 23 DFO patients who reported adverse events, 35% of these (n=8) also reported that adverse events resulted in missed doses during the previous 30 days (mean number of missed doses per patient, 4.1±2.7). Eight of 19 patients (42%) who reported missing at least one dose of DFO over this same period, did so because of adverse events. Trends were similar in patients on combination therapy at the time of the study visit. Two of eight (25%) patients in the combination group reporting adverse events also re-

Table 2. ICT-related adverse events.

Adverse event (AE)	Desferrioxamine*† (*n*=29)	Deferiprone* (*n*=18)	Combination (*n*=13)
≥1 AE‡	23 (79)	4 (22)	8 (62)
Site irritation	17 (74)	NA*	6 (75)
Site soreness	20 (87)	NA*	6 (75)
Nausea	3 (13)	1 (25)	3 (38)
Breathing problems	0 (0)	NA*	0 (0)
Ringing in the ears	4 (17)	NA*	0 (0)
Temporary hearing loss	0 (0)	NA*	0 (0)
Decreased night vision	1 (4)	NA*	1 (13)
Blurred vision	2 (9)	NA*	0 (0)
Diarrhoea	3 (13)	0 (0)	2 (25)
Fever	2 (9)	NA*	0 (0)
Abdominal pain	7 (30)	1 (25)	2 (25)
Decrease in appetite	NA§	1 (25)	4 (50)
Headache	NA§	2 (50)	2 (25)
Joint pain	NA§	3 (75)	5 (63)

*Monotherapy AE.
†Only one of the patients experiencing an AE reported associated resource utilisation (2 doctor visits, 1 nurse visit, 1 A&E visit, 1 admission to the hospital).
‡Patients who experienced at least one AE in relation to ICT in the previous 30 days.
§AE not queried for the type of therapy.
ICT=iron chelation therapy; NA=not applicable.

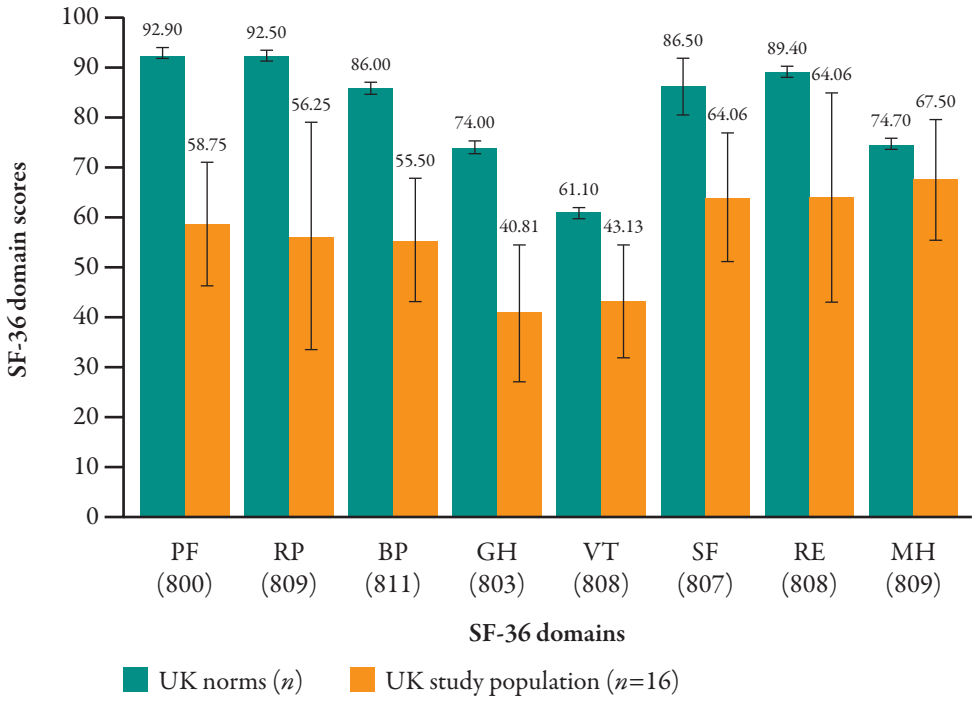
ported that these resulted in missed doses (mean number of missed doses in previous 30 days, 2.5±0.7).

HRQOL

SF-36 Domain and Summary Scores

Forty-nine participants older than 18 years of age completed the SF-36 questionnaire. Mean SF-36 domain scores for males on ICT ranged from 40.81 for General Health to 67.50 for Mental Health. Compared with age- and gender-matched norms,[25] study participants scored lower on all SF-36 scales. Specifically, point differences between UK male norms and the UK men on ICT in our study sample (*n*=16) indicated a decrement ranging from 7.2 for the Mental Health domain to 36.25 for the Role Limitations – Physical domain (Figure 2).

Figure 2. UK male study participants (mean age, 31.78 years) scored lower on all SF-36 domains compared with age-matched norms.



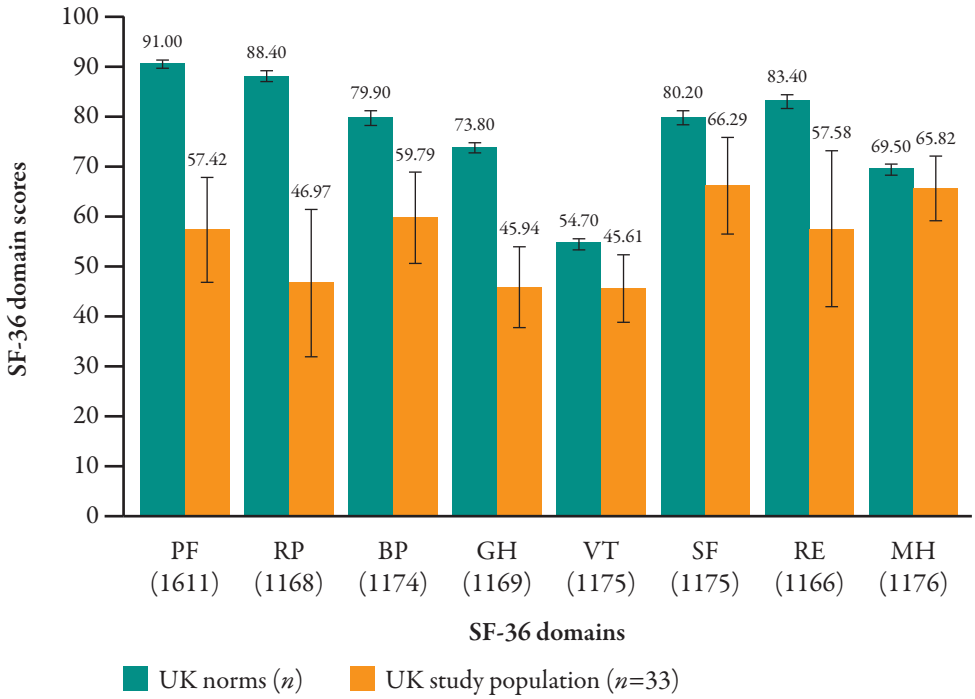
BP=Bodily Pain; GH=General Health; MH=Mental Health; PF=Physical Functioning; RE=Role – Emotional; RP=Role – Physical; SF=Social Functioning; VT=Vitality.

The mean SF-36 domain scores for females on ICT in our study ranged from 45.61 for Vitality to 66.29 for Social Functioning. Compared with age- and gender-matched norms,[25] study participants (n=33) scored lower on all SF-36 scales. Specifically, decrements ranged from 3.68 for the Mental Health domain to 41.43 points for Role Limitations – Physical (Figure 3).

The mean SF-36 summary scores for males were 38.23 for the Physical Component Summary scale and 44.93 for the Mental Component Summary scale, well below the norm of 50. Compared with age-matched norms (n=768), male study participants (n=16) scored lower on both SF-36 summary scales (decrements of 6.17 for the Mental Component Summary and 14.47 for the Physical Component Summary).

SF-36 summary scores for females in the UK on ICT were 38.39 for the Physical Component Summary and 45.45 for the Mental Component Summary. Compared with age-matched norms (n=1107), female study participants (n=33) scored lower on both SF-36 summary scales (dec-

Figure 3. UK female study participants (mean age, 33.97 years) scored lower on all SF-36 domains compared with age-matched norms.



BP=Bodily Pain; GH=General Health; MH=Mental Health; PF=Physical Functioning; RE=Role – Emotional; RP=Role – Physical; SF=Social Functioning; VT=Vitality.

rements of 3.55 for the Mental Component Summary and 11.91 for the Physical Component Summary).

SF-6D Utilities

A mean utility score of 0.66 (n=49; min=0.37, max=0.95) was generated for UK study participants on ICT, which is lower than that for patients who are receiving dialysis for chronic kidney disease, who have a utility score of 0.72 (n=38),[26] and lower than that of age-matched norms (0.81, n=361).[27]

CHQ-PF50 Domain and Summary Scores

CHQ-PF50 HRQOL data revealed similar results to the SF-36 scores. The CHQ-PF50 was completed by parents of all children aged 18 years or younger (n=11). UK mean CHQ-PF50 domain scores ranged from 46.59 for the General Health domain to 85.91 for the Family Cohesion domain. Compared with US age-matched norms,[28] UK study participants scored lower on all CHQ-PF50 scales (reduced point differences ranged

Table 3. Estimated mean weighted annual per-patient cost associated with infused ICT drug, equipment and monitoring.

Cost component	Data sources*	Mean annual weighted cost, £†
DFO drug	‡	3671§
Home delivery	‡	297
Infusions in healthcare setting	‡	1595
Home healthcare	24	4411
EquipmentΔ		
Pump (purchased)	29‡	212
Elastomeric balloon infusor	30‡	7336
Portacath	‡	101¶
Disposables#	29, 31–33‡	343
Equipment total		**7992**
Monitoring		
Serum ferritin level	‡	79
Audiology	23, 34‡	203
Ophthalmology	23, 34	108
Skeletal survey	23, 34	18
Psychotherapy visits	23, 34	138
Adverse events	34‡	169
Monitoring total		**715**
Total cost		**18,681**

*Data sources for resource utilisation profiles and unit costs.

†Cost weighted by percentage of patients using resource and for DFO, by patient age. Costs are reported in GBP 2007 (£) using UK medical inflation indices.[34]

‡Source: study data.

§The mean weighted annual cost reflecting actual patient-reported compliance is £3671. Cost increases to £4421 when 100% compliance is assumed.

ΔUnit costs provided by equipment supply companies.

¶Includes annual weighted cost for a portacath, needles for a portacath, and the surgery for the portacath implant.

#Includes syringes, needles, infusion sets, tape, alcohol pads, gauze, sharp bins and batteries.

DFO=desferrioxamine; ICT=iron chelation therapy.

from 5.58 for Mental Health to 30.99 for Family Activities) except for Family Cohesion, Behaviour and Self-Esteem domains.

CHQ-PF50 summary scores were 37.19 for the Physical Summary Scale and 46.05 for the Psychosocial Summary Scale. Compared with US age-matched norms, UK study participants scored lower on both CHQ-PF50 summary scales (decrements were 4.75 for the Psychosocial Summary Scale and 16.41 for the Physical Summary Scale).

'Satisfaction with ICT' Scores

The 'Satisfaction with ICT' questionnaire was completed by all patients over 10 years of age (n=58). Mean scores for the Satisfaction with ICT domains were highest for Perceived Effectiveness of ICT (4.36) followed by Burden of ICT (3.52), and then Acceptance of ICT (3.28). Side Effects of ICT was the lowest mean score (3.14).

When mean satisfaction scores were plotted against ratings of an overall satisfaction question, patients in the 'satisfied' group scored the highest for Perceived Effectiveness and Acceptance of ICT, but also had the lowest mean scores for Burden and Side Effects of ICT.

Annual Costs of ICT (DFO)

The total estimated mean weighted annual per-patient cost of DFO treatment was approximately £19,000 (Table 3). DFO-related equipment, DFO drug, and home healthcare, were estimated to account for 43%, 19% and 24% of costs, respectively. The largest component of the total annual cost was equipment, estimated to be £7992. The estimated annual cost of DFO was £3671. If compliance was assumed to be 100%, mean weighted drug costs would increase to £4421. Home healthcare was the next most significant contributor of cost, totalling £4411. Other more minor components of total annual costs were for in-patient infusions (£1595), ICT home delivery services (£297) and monitoring costs (£715).

DISCUSSION

Overall, data from this study suggest that current ICT in the real-world setting is suboptimal with respect to various health and economic outcomes. Patients are not achieving their target serum ferritin thresholds despite chronic treatment for iron overload, ICT appears to negatively impact their HRQOL, and compliance to ICT is poor. Also, in the case of DFO, treatment costs well exceed the cost of DFO alone.

Despite an average of approximately 5 years of ICT, mean serum ferritin levels in most subjects remained above 2500 ng/ml – a level considered elevated and associated with cardiovascular disease[35–37] and mortality.[37] Improved outcomes are typically associated with serum ferritin levels below 1000 ng/ml.[38]

Adverse events associated with ICT during the 30 days prior to the study visit were fairly common, with local reactions such as irritation and soreness at the infusion site, the most frequently reported (approximately 75% of subjects). Two other

studies have reported similar findings. In the first study,[39] of the 89% of subjects reporting adverse events, the most common were redness, itching and pain. In the other study[40] the most common side effects of ICT were pain, tenderness, itching, erythema, swelling and a burning sensation at the infusion site.

Given the burdensome DFO regimen of 8- to 12-hour infusions 5 to 7 times per week and the prevalence of bothersome side effects of current ICT it is not surprising that compliance was generally poor.[41] Consistent with these studies, a significant number of subjects in this UK cohort also reported that they had not taken their ICT as prescribed. More than half of the subjects reported that at least one dose was missed in the previous 7 days, while 40%–50% of subjects (depending on their regimen) reported missing at least two doses over this same period. The association between ICT-related adverse events and non-compliance observed in this study is also consistent with the findings of other earlier studies.[42,43]

Patients with thalassaemia, sickle cell disease, and MDS currently undergoing ICT had much lower HRQOL scores compared with population norms, and in particular for the General Health, Role Limitations – Physical, and Physical Functioning domains of the SF-36. The difference between the SF-36 domain study scores and the population norms were often 3 to 5 units. Therefore, these results are clinically meaningful and significant,[44,45] and infer that changes need to be made to ICT treatment for patients with iron overload.

The CHQ-PF50 data revealed similar results, with participants scoring lower on all CHQ-PF50 domains compared with US population norms, except for Family Cohesion, Behaviour and Self-Esteem domains.

The findings that HRQOL is compromised in patients with ICT are in line with previous studies.[39] Furthermore, given that patients on dialysis have a utility score of 0.72, it can be inferred that a utility score of 0.66 for patients receiving ICT is very low, indicating a relatively poor health state.[26]

Overall mean satisfaction scores showed that patients were satisfied with the perceived effectiveness of their ICT but less with the burden of ICT, and side effects of ICT. As a score of 5 represents 'very satisfied' for all items in a domain, a mean of 3.5 or more suggests that most patients were rather satisfied with most or all of the items in the domain. Specific questions regarding satisfaction with ICT elicited more critical responses, as is generally the case.[46] Consistent with this finding, a closer examination of mean satisfaction scores plotted against ratings of an overall satisfaction question from the 'Satisfaction with ICT' questionnaire, demonstrated that patients identified as 'satisfied' were perhaps not as satisfied with ICT as overall scores first indicated.

Based on a more comprehensive costing assessment than has been reported previously, the total annual cost of infused ICT estimated in this study is significant and much higher than the cost of DFO alone. Among the four published studies we identified,[21–24] only one[22] reported the

mean annual ICT per-patient cost, which was estimated to range from $12,719 to $24,845 (USD 1998), but only the costs associated with DFO and home healthcare services were included. In another of these studies,[24] the lifetime cost of DFO was estimated to be about $63,000 (USD 1996). Three of the studies[21,23,24] presented lifetime treatment costs of beta-thalassaemia, but in two of these[21,23] it was not possible to disaggregate the cost of DFO treatment from that of the treatment for underlying disease. In the US implementation of this study, which was conducted concurrently using a standard protocol and case report form,[28] total annual ICT treatment costs were estimated to be about US$30,000. However, it is difficult to relate current cost estimates to those reported in the literature, given the small number of previously published studies and variability in study designs. Furthermore, to simplify the methodology, only the per-patient cost of annual treatment with DFO was estimated. Given the need for infusion-related equipment and supplies, it is possible that the DFO cost could represent an upper limit to ICT cost estimates.

Some additional limitations of this study deserve comment. These results do not distinguish the impact of ICT from that of the underlying condition and the adverse events reported may be a consequence of ICT and the patient's condition. Further research could evaluate outcomes related to the patients' conditions. In particular, since the HRQOL of iron-overloaded patients is already poor, studies could explore HRQOL scores between patients defined as 'well' versus those who are ill with frequent hospital or doctor visits. Alternatively, HRQOL scores of iron-overloaded patients could be compared with those of other patients with chronic conditions rather than UK population norms.

Further studies could also investigate the number of red blood cell transfusions the patients received during therapy, and the extent to which HRQOL is related to compliance.

Finally, some caution is necessary in the interpretation of these results given that sample sizes were small. A high degree of variability was observed across all study outcomes, thus studies with larger sample sizes may provide greater certainty of results.

CONCLUSION

This study provides some evidence that ICT in the real-world setting is suboptimal with respect to various clinical, HRQOL and economic outcomes. Overall, study subjects had not achieved target serum ferritin thresholds despite chronic treatment for iron overload with ICT. Observed compliance to ICT was generally poor, and treatment appeared to negatively impact the HRQOL of subjects. Total estimated annual DFO cost per patient was substantial (≈£19,000). The largest estimated components of total annual cost were those related to equipment and the medication itself, followed by home healthcare costs. Novel treatments for ICT which are more tolerable, less burdensome and less costly are warranted.

ACKNOWLEDGEMENTS

This manuscript was supported by a grant from Novartis Pharmaceuticals Corporation, USA. The authors give thanks to the clinicians who have assisted in the conduct of this study. In particular, we thank the Principal Investigators and their research staff: Dr Iheanyi Okpala, Dr Baba Inusa, St Thomas' Hospital; Dr Sally Killick, The Royal Bournemouth Hospital; Dr James Malone-Lee, The Whittington Hospital; and Dr Swee Lay Thein, King's College Hospital and GKT School of Medicine.

Competing Interests

Authors Krista Payne, Marie-Pierre Desrosiers, Noreen Lordan, Khajak Ishak and Irina Proskorovsky are employees of United BioSource Corporation, a consultancy that has also received grants for other, unrelated research from Novartis Pharmaceuticals Corporation.

Diana Rofail works as a Senior Project Manager in the Questionnaire Development and Validation unit of Mapi Values. She has acted as an advisor for various pharmaceutical companies regarding their clinical trials and patient-reported outcomes.

Jean-François Baladi is employed by Novartis Pharmaceuticals Corporation and owns stocks and/or stock options.

Muriel Viala works as a Statistician in the Questionnaire and Validation unit of Mapi Values. She has acted as an advisor for various pharmaceutical companies regarding their clinical trials and patient-reported outcomes.

Linda Abetz works as a Director of the Questionnaire and Validation unit of Mapi Values. She has acted as an advisor for various pharmaceutical companies regarding their clinical trials and patient-reported outcomes.

REFERENCES

1. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood.* 1997;89:739–761.
2. Harvard Medical School. Effects of iron overload: hemochromatosis, tranfusional iron overload. 2006. Available at: http://sickle.bwh.harvard.edu/index.html. Accessed June 2008.
3. Gabutti V, Piga A. Results of long-term iron-chelating therapy. *Acta Haematol.* 1996;95:26–36.
4. Vidler V. Compliance with iron chelation therapy in beta thalassaemia. *Paediatr Nurs.* 1998;10:17–18.
5. Rebulla P. Transfusion reactions in thalassemia. A survey from the Cooleycare programme. The Cooleycare Cooperative Group. *Haematologica.* 1990;75(suppl 5): 122–127.
6. Giardina PJ, Grady RW. Chelation therapy in beta-thalassemia: an optimistic update. *Semin Hematol.* 2001;38:360–366.
7. Alymara V, Bourantas D, Chaidos A, et al. Effectiveness and safety of combined iron-chelation therapy with deferoxamine and deferiprone. *Hematol J.* 2004;5:475–479.
8. Shumaker SA, Berzon RA. *The International Assessment of HRQL. Theory, Translations, Measurement and Analysis.* Oxford: Rapid Communications; 1995.

9. Abetz L, Baladi JF, Jones P, Rofail D. The impact of iron overload and its treatment on quality of life: results from a literature review. *Health Qual Life Outcomes.* 2006;4:73.

10. Hasan SP, Hashmi S, Alhassen M, et al. Depression in sickle cell disease. *J Natl Med Assoc.* 2003;95:533–537.

11. Kornblith AB, Herndon JE, Silverman LR, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. *J Clin Oncol.* 2002;20:2441–2452.

12. Olivieri N, Brittenham GM, McLaren CE, et al. Long-term safety and effectivness of iron chelation therapy with deferiprone for thalassemia major. *N Engl J Med.* 1998;339:417–423.

13. Caro JJ, Huybrechts K, Green TC. Estimates of the effect on hepatic iron of oral deferiprone compared to subcutaneous desferrioxamine for treatment of iron overload in thalassaemia major: a systematic review. *BMC Blood Disord.* 2002;2:4.

14. Payne KA, Desrosiers MP, Caro JJ, et al. Clinical and economic burden of infused iron chelation therapy (ICT) in the United States. *Transfusion.* 2007;47:1820–1829.

15. Serjeant GR. Sickle-cell disease. *Lancet.* 1997;350:725–730.

16. Cazzola M, Malcovati L. Myelodysplastic syndromes – coping with ineffective hematopoiesis. *N Engl J Med.* 2005;352:536–538.

17. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30:473–483.

18. Rofail D, Abetz L, Viala M, et al. Satisfaction and adherence in patients with iron overload receiving iron chelation therapy as assessed by a newly developed questionnaire. *Value Health.* 2008; Jul 11. Epub ahead of print.

19. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. *J Clin Epidemiol.* 1998;51:1115–1128.

20. Gold MR, Siegel JE, Russell LB, Weistein MC. *Cost Effectiveness in Health and Medicine.* Oxford: Oxford University Press; 1996.

21. Zeuner D, Ades A, Karnon J, et al. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. *NHS Health Technol Assess Prog.* 1999;3:1–186.

22. Wayne A, Schoenike S, Pegelow C, et al. Financial analysis of chronic transfusion for stroke prevention in sickle cell disease. *Blood.* 2000;96:2367–2369.

23. Karnon J, Zeuner D, Brown J, et al. Lifetime treatment cost of beta-thalassemia major. *Clin Lab Haem.* 1992;21:377–385.

24. Ginsberg G, Tulchinsky T, Filon D, et al. Cost-benefit analysis of a national thalassemia prevention programme in Israel. *J Med Screen.* 1998;5:120–126.

25. Jenkinson C, Stewart-Brown S, Petersen S. *Assessment and Evaluation of the SF36 Version II.* Health Services Research Unit: University of Oxford; 2006. Available at: www.hsru.ox.ac.uk/sf36v2.htm. Accessed 9 February 2006.

26. Gorodetskaya I, Zenios S, McCulloch CE, et al. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney Int.* 2005;68:2801–2808.

27. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ.* 2001;21:271–292.

28. Landgraf JM, Abetz L, Ware JE. *The Child Health Questionnaire (CHQ): a User's Manual.* 2nd ed. Boston, MA: The Health Institute; 1996.

29. Medi-Scot web site. Available at: www.medi-scot.co.uk. Accessed 18 September 2006.

30. Medicines and Healthcare Products Regulatory Agency. Market survey. Non-electrically powered dispoable infusion devices. Report 05055. September 2005. Available at: www.pasa.nhs.uk/evaluation/docs/general_medical/Report_05055 pdf. Accessed 23 October 2006.

31. Williams Medical Supplies. Available at: www wmsplc.co.uk. Accessed 18 September 2006.

32. Modell B. Guidelines for the control of haemoglobin disorders. *Report of the Sixth Annual Meeting of the WHO Working Group on Haemoglobinopathies, Cagliari, Sardinia, 8–9 April 1989.* Geneva: World Health Organization; 2004.

33. Chan GC, Ng DM, Fong DY, et al. Comparison of subcutaneous infusion needles for transfusion-dependent thalassemia patients by the intrapersonal cross-over assessment model. *Am J Hematol.* 2004;76:398–404.

34. Curtis L, Netten A. *Unit Costs of Health and Social Care 2005.* The University of Kent, Personal Social Services Research Unit 202.

35. Olivieri NF, Nathan DG, MacMillan JH, et al. Survival in medically treated patients with homozygous beta thalassemia. *N Engl J Med.* 1994;331:574–578.

36. Telfer PT, Prestcott E, Holden S, et al. Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassaemia major. *Br J Haematol.* 2000;110:971–977.

37. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica.* 2004;89:1187–1193.

38. Thalassemia International Federation web site. Guidelines for Clinical Management of Thalassemia. 2000. Available at: www.thalassaemia.org.cy/MyData/Books/Clinical_%20Management_Thalassaemia.pdf. Accessed June 2008.

39. Arboretti R, Tognoni G, Alberti D. Italian Collaborative Group on Thalassarmia. Pharmacosurveillance and quality of care of thalassaemic patients. A large scale epidemiological survey. *Eur J Clin Pharmacol.* 2001;56:915–922.

40. Taher A, Sheikh-Taha M, Koussa S, et al. Comparison between deferoxamine and deferiprone (L1) in iron-loaded thalassemia patients. *Eur J Haematol.* 2001;67:30–34.

41. Caro JJ, Ward A, Green TC, et al. Impact of thalassemia major on patients and their families. *Acta Haematol.* 2002;107:150–157.

42. Ward A, Caro JJ, Green TC, et al. An international survey of patients with thalassemia major and their views about sustaining life-long desferrioxamine use. *BMC Clin Pharmacol.* 2002;2:3.

43. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR. Complications of beta-thalassemia major in North America. *Blood.* 2004;104:34–39.

44. Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum.* 2000;43:1478–1487.

45. Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics.* 1999;15: 141–155.

46. Williams JJ, Calnan M. Convergence and divergence: assessing criteria of consumer satisfaction across general practice, dental, and hospital care settings. *Soc Sci Med.* 1991;33:707–716.