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Original Article

Comparative efficacy, safety, and cost of iron chelation monotherapy *vs.* combination therapy in pediatric β-thalassemia major: a single-center retrospective study

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Abstract

Background Iron chelation therapy is used to maintain iron balance in β-thalassemia major patients who undergo repeated blood transfusions.

Objective To compare the efficacy, safety, and cost of iron chelation combination regimens [deferiprone (DFP) + deferoxamine (DFO) or DFP + deferasirox (DFX])] *vs.* high-dose DFP monotherapy (≥ 90 mg/kg/day) in pediatric β-thalassemia major patients.

Methods This cross-sectional, retrospective study was done at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Retrospective data was obtained from electronic medical records of pediatric β-thalassemia major patients with serum ferritin of ≥ 2,500 ng/mL and/or transferrin saturation of ≥ 60%, who received either combination or monotherapy iron chelation agents. Outcome effectiveness was determined by the reduction of serum ferritin level of at least 80%. Safety was analyzed descriptively. A pharmacoeconomic analysis was performed based on clinical outcomes consisting of effectiveness and direct medical costs.

Results At the end of the study, serum ferritin was reduced in 34.7% of the combination therapy group and 27.5% of the monotherapy group, however there was no significant difference between the two treatments (P=0.391). Nine (19.5%) patients on combination therapy and 17 (21.2%) patients on monotherapy had adverse drug reaction (ADR), with the most frequently reported ADR was elevated transaminase enzyme levels. Cost minimization analysis revealed that monotherapy for 6 months was IDR 13,556,592.64 less expensive than combination therapy (IDR 44,498,732.07); whereas monotherapy for 12 months was IDR 20,162,836.10 less expensive than combination therapy (IDR 78,877,661.12).

Conclusion Combination regimens are as effective as monotherapy regimens in reducing serum ferritin in pediatric β-thalassemia major patients. There is no differences of ADR between combination or monotherapy. The average cost per patient is less expensive with monotherapy compared to combination therapy. **[Paediatr Indones. 2022;62:91-7; DOI: 10.14238/pi62.1.2022.91-7**].

Keywords: *thalassemia; children; iron overload; chelation agents; cost*

Thalassemia is a hereditary anemia caused by impaired hemoglobin production. Compared to other hemoglobin disorders, thalassemia is the most common. The *World Bank* showed that 7% of the world's population are carriers of thalassemia. Every year, approximately 300,000-500,000 infants are born with severe hemoglobin abnormalities, of whom 50,000-100,000 have β-thalassemia; and about 80% of β-thalassemia live in developing countries. In Indonesia, the frequency of the thalassemia trait is considered high, as it is one of the countries identified as part of the thalassemia belt. Epidemiologic studies in Indonesia showed a rate of genetically β-thalassemia of 3-10%.[1] The *Indonesian Pediatric Association Hematology-Oncology Work Group Unit* reported that the number of thalassemia patients throughout Indonesia was 10,555 through mid-March 2019. The total number of patients recorded by the end of 2017 at the Center of Thalassemia, Department of Maternal and Child Health, Dr. Cipto Mangunkusumo

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Hospital, Jakarta, Indonesia, was 1,612. About 600-700 patients came for routine transfusions per day, with an average of 60 new patients per month.[2]

Routine blood transfusion is the primary supportive therapy for thalassemia patients, with the aim of improving the anemia and maintaining a hemoglobin level of 9-10 gram/dL. This therapy also suppresses the ineffective erythropoiesis process, in turn preventing bone deformities and hepatosplenomegaly.[3] However, repeated blood transfusions may create a new problem, in which excess iron is absorbed by and accumulates in the tissues (hemosiderosis). Iron deposits occur in vital organs such as the liver, heart, and endocrine system.[3] Iron build-up triggers free reactive oxygen species (ROS), which oxidize lipid membranes, and ultimately result in cellular damage and death manifested as heart failure, liver cirrhosis, growth inhibition, and other endocrine abnormalities.[4] Iron chelation is done to maintain safe levels in the body and stabilize the accumulation rate resulting from the transfusion by increasing iron excretion through urine and feces.[3] Chelation therapy should begin approximately one year after receiving chronic transfusions, or after 10-20 transfusions, or when the serum ferritin level reaches 1,000 ng/mL, and/or transferrin saturation is ≥ 60%.[3,5] The selection of iron chelation therapy to be administered should be made by the physician and the patient together. Choice of therapy involves numerous factors such as the excess level of iron, the age of the patient, medication tolerability, and the cost of therapy. Many patients already have high iron accumulation in their system such that a single chelation therapy may not be sufficient to induce iron stability, thus a combination of two iron chelation therapies may be necessary.[5]

Iron chelation combination therapy and monotherapy have important roles in lowering very high levels of serum ferritin and preventing complications related to the iron build-up. In addition, studies evaluating the two regimens are still limited in Indonesia. As such, we aimed to compare effectiveness, safety, and cost of combination therapy (DFP + DFX or DFO + DFP) versus high dose monotherapy (DFP 90-100 mg/kg/day) in pediatric β-thalassemia major patients at Cipto Mangunkusumo Hospital, Indonesia from 2014 to 2018.

Methods

This observational study with retrospective cross-sectional design was done using electronic medical record data from the Department of Maternal & Child Health Center at Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, from December 2018 to April 2019, after obtaining ethical approval from Universitas Indonesia Faculty of Medicine. Subjects were pediatric β-thalassemia major outpatients who came to Cipto Mangunkusumo General Hospital for treatment from 2014 to 2018. Inclusion criteria were age 5 to 18 years, diagnosed with β-thalassemia major, serum ferritin ≥2,500 ng/mL and/or transferrin saturation ≥60%, serum ferritin examinations recorded for 6 or 12 months, as well as use of DFP (75 mg/kgBW/day) + DFO (30-60 mg/kgBW/day) or DFP (75 mg/kgBW/day) + DFX (20-40 mg/kgBW/day) combination or monotherapy of high dose DFP 90-100 mg/kg/day for 6 or 12 months. Combination therapy could be either simultaneous therapy (used of 2 iron chelators on the same day) or alternate therapy (used of 2 iron chelators on the different day). Exclusion criteria were incomplete medical records or supporting data that could not be evaluated. Iron chelation therapy was considered effective when there was a reduction of the serum ferritin of ≥500 ng/mL after 6 or 12 months of therapy. The minimum required sample size was calculated to be 80 subjects per group, based on hypothesis testing for the proportion of two independent groups.

Subjects were selected by consecutive sampling. Data obtained from patients' medical records comprised of characteristics/demographic data (name, age, gender, body weight, medical record ID number), variant of thalassemia, transfusion frequency, accompanying diseases (chronic hepatitis B, C and HIV-AIDS), iron profiles (serum ferritin and transferrin saturation), therapy effectiveness, and adverse drug reactions. Administration cost data during the period were obtained from financial records and the managerial information system unit.

Baseline characteristic data were presented as descriptive statistics. Chi-square test was used to analyze therapy effectiveness differences and adverse drug reactions. Numerical data were analyzed using Mann-Whitney test or T-test. The results were considered significant for P values <0.05. Quantitative

data were processed and analyzed using the *SPSS (Statistical Product and Service Solutions) version 20.0* software.

Results

Of 337 medical records collected, 126 patients met the inclusion criteria and 211 were excluded due to age > 18 years, incomplete data, use of DFX monotherapy, use of DFP monotherapy at a dosage of <90 mg/kg/day, diagnosis of non-thalassemia major, or use of DFO+DFX combination (**Figure 1** and **Table 1**).

After 6 or 12 months of therapy, 38 of the 126 (30.2%) subjects had a decrease in serum ferritin level of ≥500 ng/mL. There was no significant difference between monotherapy and combination therapy in terms of effectiveness (**Table 2**). Analysis of the effectiveness of alternating- *vs*. simultaneous-combination therapies revealed that simultaneous combination was more effective at reducing serum ferritin compared to alternating combination therapy (RR 0.351; 95%CI 0.180 to 0.683; P=0.015) (**Table 3**). In addition, we also compared the use of monotherapy with simultaneous and alternating combination therapy (**Table 4**), which showed that the simultaneous combination therapy was more effective in reducing ferritin serum as compared to the monotherapy.

From the 126 subjects, 26 (20.6%) experienced adverse drug reactions, with some experiencing more than one adverse reaction (**Table 5**). Of the 126 subjects, 3 (2.4%) had comorbid diseases. One (0.8% of all subjects) subject in the combination group had chronic hepatitis C. In the monotherapy group, 1 (0.8%) subject had chronic hepatitis B and 1 (0.8%) had chronic hepatitis C. None of the subjects had HIV-AIDS.

The costs of treatment were gleaned from data collected directly from the electronic health records (EHR), according to the respective periods. The cost components included were doctor visits, laboratory fees, iron chelation, and transfusions. In the combination therapy group, the cost analysis was performed only on the DFP + DFX therapy due to frequently used of those combination. Cost minimization analysis was carried out in this study because there was no significant difference in terms of effectiveness between the combination and monotherapy groups. A discount was calculated using the following formula: (x/ (1+r) t) where x=cost, r=discount rate (3%). Discounting needed to be performed if the cost and outcomes accumulated in several years. Our study used a 5 years period hence we performed discounting. The minimization analysis revealed the higher percentage cost of DFP+DFX therapy over DFP monotherapy to be:

$$\frac{44.498.732,07 - 30.942.139,43}{44.498.732,07} \times 100\% = 30.46\% \text{ (6 months costs)}$$

$$\frac{78.877.611,12 - 58.714.775,02}{78.877.661,12} \times 100\% = 25.56\% \text{ (12 months costs)}$$

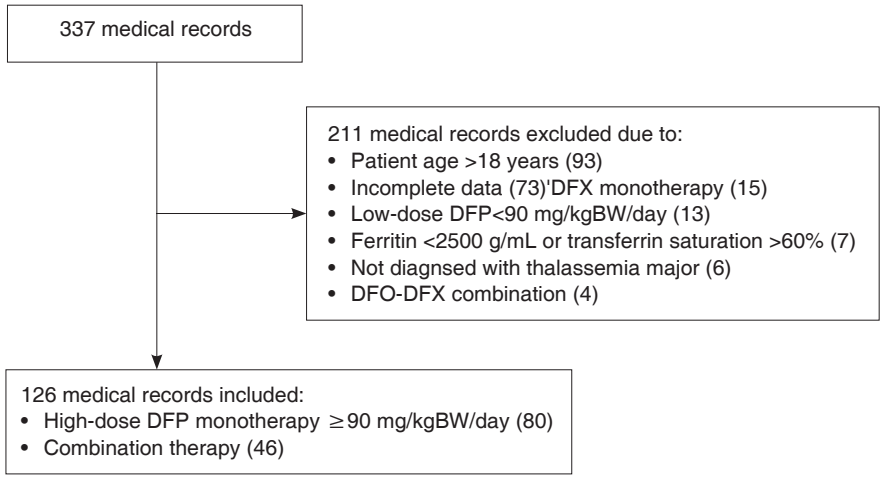

Figure 1. Selection flow chart

Table 1. Baseline characteristics of subjects

Characteristics	Combination therapy (n=46)	High-dose DFP monotherapy (n=80)
Sex, n (%)		
Male	20 (43.5)	45 (56.3)
Female	26 (56.5)	35 (43.7)
Median age, years	14 (5-18)	13 (6-17)
Variants of thalassemia		
β-homozygote	28 (60.9)	39 (48.7)
β-HbE	18 (39.1)	41 (51.3)
Frequency of transfusions		
< 2-weeks interval	4 (8.7)	4 (5)
2 to ≤ 3-weeks interval	19 (41.3)	17 (21.2)
3 to ≤ 4-weeks interval	19 (41.3)	48 (60.0)
> 4-weeks interval	4 (8.7)	11 (13.8)
Iron profiles		
Median serum ferritin (range), ng/mL	4787 (1198-10,658)	3270 (1630-9,282)
Median transferrin saturation (range), %	86 (31-102)	90.5 (17-100)
Comorbid diseases		
Chronic hepatitis B	0 (0)	1 (1.25)
Chronic hepatitis C	1 (2.2)	1 (1.25)
HIV – AIDS	0 (0)	0 (0)
Drug combination		
DFP+DFO	22 (17.5)	
DFP+DFX	24 (19.0)	
Type of combination		
Simultaneous	8 (17.4)	
Alternating	38 (82.6)	

Table 2. Analysis of regimen type and effectiveness

Regimen	Effectiveness		RR (95% CI)	P value
	Yes	No		
Combination therapies, n (%)	16 (34.8)	30 (65.2)	0.791 (0.464 to 1.346)	0.391
Monotherapy, n (%)	22 (27.5)	58 (72.5)		

Table 3. Analysis of effectiveness in simultaneous vs. alternating combinations

Combination regimen	Effectiveness		RR (95% CI)	P value
	Yes	No		
Simultaneous, n (%)	6 (75.0)	2 (25.0)	0.351 (0.180 to 0.683)	0.015*
Alternating, n (%)	10 (26.3)	28 (73.7)		

Table 4. Analysis of monotherapy *vs.* simultaneous combination, and monotherapy *vs.* alternating combination therapy

Regimen	Effectiveness		RR (95% CI)	P value
	Yes	No		
Monotherapy, n (%)	22 (27.5)	58 (72.5)		
Simultaneous combination, n (%)	6 (75)	2 (25)	0.37 (0.22 to 0.63)	0.012*
Alternating combination, n (%)	10 (26.3)	28 (73.7)	1.05 (0.55 to 1.98)	0.892

From the above calculations, the average cost of the DFP monotherapy regimen with dosage ≥ 90 mg/kg/day for 6 months after a 3% discount was IDR 13,556,592.64 or 30.46% less compared to the combination regimen cost. For 12 months of use, the average cost of the DFP monotherapy regimen after a 3% discount was IDR 20,162,886.10 or 25.56% less compared to the combination regimen (**Table 6**).

Discussion

After 6 or 12 months of intervention, treatment was effective in 16 (34.8%) subjects in the combination group *vs.* 22 (27.5%) subjects in the DFP monotherapy group, indicating similar effectiveness in reducing serum ferritin level (P=0.391). In contrast, a previous study showed a more significant serum ferritin reduction for the DFP+DFX combination group (P=0.008), compared to the monotherapy group.[6] Another study also reported a significant difference between the DFO+DFP combination and DFO monotherapy groups in the reduction of the serum ferritin (P<0.001) after a 12-month intervention.[7] Moreover, a study reported reduced mean serum ferritin after a one-year intervention in two combination regimens (DFO+DFP and DFP+DFX), even though the differences were not statistically significant (P=0.301 and P=0.218) compared to a monotherapy group.[8] Some conditions that may have contributed to the differences include low adherence to taking medication and limited drug supply, possibly leading to inappropriate drug dosage. Furthermore, serum ferritin is strongly influenced by inflammation, acute infection, physical trauma, and liver disease, none of which were evaluated.[9]

Of the 46 subjects in the combination group, 8 subjects used simultaneous chelation, and 6 of 8 (75%) experienced a reduction of serum ferritin of ≥500 ng/mL after 6- or 12-months of therapy. In the alternating chelation group, the therapy was effective in 10 of 38 subjects (26.3%). In addition, we found that the simultaneous combination was more effective in the lowering serum ferritin compared to the monotherapy regimen (P=0.012) as well as compared to the alternating combination regimen (P=0.015). Simultaneous chelation combination was likely more effective due to the added chelation intensity of two chelators as well as the longer duration of chelator administration compared to the alternating chelation combination.

The most common adverse drug reaction in this study was elevated transaminase enzyme [12 (9.5%) subjects], in 8 monotherapy subjects and 4 combination subjects. A previous study noted ALT elevation in 6 of 12 (50%) subjects who received DFP monotherapy at a dosage of 100 mg/kg/day.[12] Another study found that the elevated transaminase enzymes occurred in both combination groups, but it was not severe and returned to normal within 2 months without any intervention.[8] Digestive tract symptoms, such as vomiting, nausea,

Table 5. Adverse drug reactions

Variables	Combination therapy (n=46)	Monotherapy (n=80)
Digestive tract symptoms,* n (%)	3 (6.5)	5 (6.3)
Elevated transaminase enzymes, n (%)	4 (8.7)	8 (10)
Neutropenia, n (%)	1 (2.2)	2 (2.5)
Arthralgia, n (%)	4 (8.7)	3 (3.8)

*Digestive tract symptoms included nausea, vomiting, and diarrhea

Table 6. Comparisons of the treatment cost components for durations of 6 and 12 months in mean IDR

Cost components	Duration 6 months		Duration 12 months	
	DFP-DFX combination (n=6)	High-dose monotherapy (n=32)	DFP-DFX combination (n=17)	High-dose monotherapy (n=48)
Doctor visits	600,000	625,312.50	1,526,470.59	1,198,750
Lab costs	630,250	540,218.75	815,176.47	689,452.08
Medications	32,196,733.33	17,211,800	48,213,030.65	31,072,388.33
Transfusions	14,406,666.67	15,113,937.50	35,294,470.59	30,283,687.50
Total costs	47,833,650	33,397,409.38	86,201,265.94	63,244,277.92
Total costs after 3.0% discount	44,498,732.07	30,942,139.43	78,877,661.12	58,714,775.02

and diarrhea, was another side effect which appeared in 8 (6.3%) subjects, occurring in slightly more monotherapy subjects. A previous study reported that digestive tract symptoms occurred in 19 of 29 subjects (66%) in the DFP group. The symptoms were light and usually disappeared within the average time of 3 days without any adjustment of the dosage or discontinuation of therapy.[11] Another study reported that this side effect occurred in 12.5% and 20.88% of the DFP+DFX and DFO+DFP combination groups, respectively; discontinuation of therapy was unnecessary in both groups.[8] In addition, a study reported that mild nausea occurred in 3 of 12 high-dose DFP subjects in the first month, discontinuation of therapy was not required.[12] In our study, iron chelator agent-induced digestive tract symptoms did not lead to treatment interruption. In addition, neutropenia occurred in 3 (2.4%) subjects, which led to temporary DFP treatment discontinuation for approximately 2 weeks. A previous study also reported that 2 of 16 patients given DFP at 100 mg/kgBW/day experienced neutropenia. One patient had to discontinue the DFP until the laboratory results returned to normal, and the other patient had the DFP dosage reduced to 75 mg/kgBW/day.[12] Another study noted that 2 of 6 (33%) subjects with neutropenia had to discontinue therapy.[5] However, a study reported that none of their subjects experienced neutropenia.[6]

An iron-chelator pharmacoeconomic study analyzed the cost effectiveness of DFP and DFX in thalassemia major patients at the Regional General Hospital in Tangerang, West Java, Indonesia. According to this study, the effectiveness of DFX in reducing ferritin serum (1164 ng/mL) was higher than DFP (692 ng/mL). The total median cost of DFX (IDR 76,610,618.69) was higher than that of DFP (IDR 51,869,965.64). However, the cost effectiveness ratio (CER) for DFX (IDR 65,816.68/effectivity) was lower than that for DFP (IDR 74,956.60/effectivity).[13]

An Italian study on the analysis of cost effectiveness and utilization of the cost for three types of iron chelators, from the payer point of view. The authors concluded that DFP was the most cost effective in Italy for β-thalassemia major patients and its use could result in cost savings for the health services system. With regards to quality-adjusted life-year (QALY), DFO had higher QALY than DFX, but with higher total cost.[15]

A limitation of this study was that collecting patient data was very dependent on the accuracy of medical record recording and the accuracy of the hospital information system. Another limitation was that we used retrospective data from patients who were treated in only one hospital in 2014-2018. Therefore, the results of the pharmacoeconomic study only apply to that hospital and cannot be generalized to other health centers. In addition, the cost analysis was performed only on the DFP + DFX therapy, because this combination was the most frequently used

In conclusion, there is no statistically significant difference in the effectiveness of serum ferritin reduction between the combination and monotherapy regimens. However, serum ferritin is significantly more reduced in the simultaneous combination regimen compared to monotherapy, and compared to the alternating combination. There is no significant difference in adverse effects between the combination and monotherapy groups. The average monotherapy cost per patient (after 3% discount) is IDR 13,556,592.64 or 30.46% lower for 6 months and IDR 20,162,836.10 or 25.56% lower for 12 months than the average costs of the combination regimen.

Conflict of interest

None declared.

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References

1. Direktorat Pencegahan dan Pengendalian Penyakit Tidak Menular, Direktorat Jenderal Pencegahan dan Pengendalian Penyakit, Kementrian Kesehatan Republik Indonesia. Thalassemia. [cited 2018 April 4]. Available from: http://p2ptm.kemkes.go.id/informasi-p2ptm/thalassemia.
2. Unit Kerja Kelompok Hematologi-Onkologi Ikatan Dokter Anak Indonesia. judul slide. Power point slides presented at (nama acara) on (tgl bulan tahun). [cited 2019 Mar 19]

3. Gatot D, Amalia P, Sari TT, Chozie NA. Pendekatan mutakhir kelasi besi pada thalassemia. Sari Pediatri. 2007;8:78-84.
4. Trinchero A, Marchetti M, Giaccherini C, Tartari CJ, Russo L, Falanga A. Platelet haemostatic properties in β-thalassaemia: the effect of blood transfusion. Blood Transfus. 2017;15:413-21. DOI: 10.2450/2016.0033-16.
5. Karami H, Kosaryan M, Amree AH, Darvishi-Khezri H, Mousavi M. Combination iron chelation therapy with deferiprone and deferasirox in iron-overloaded patients with transfusion-dependent β-thalassemia major. Clin Pract. 2017;7:912. DOI: 10.4081/cp.2017.912.
6. Gomber S, Jain P, Sharma S, Narang M. Comparative efficacy and safety of oral iron chelators and their novel combination in children with thalassemia. Indian Pediatr. 2016;53:207-10. DOI: 10.1007/s13312-016-0821-4.
7. Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, *et al*. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. J Cardiovasc Magn Reson. 2008;10:12. DOI: 10.1186/1532-429X-10-12.
8. Elalfy MS, Adly AM, Wali Y, Tony S, Samir A, Elhenawy YI. Efficacy and safety of a novel combination of two oral chelators deferasirox/deferiprone over deferoxamine/deferiprone in severely iron overloaded young beta thalassemia major patients. Eur J Haematol. 2015;95:411-20. DOI: 10.1111/ejh.12507.
9. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: Past, present and future. Biochim Biophys Acta. 2010;1800:760-9. DOI: 10.1016/j.bbagen.2010.03.011.
10. Totadri S, Bansal D, Bhatia P, Attri SV, Trehan A, Marwaha RK. The deferiprone and deferasirox combination is efficacious in iron overloaded patients with β-thalassemia major: a prospective, single center, open-label study. Pediatr Blood Cancer. 2015;62:1592-6. DOI: 10.1016/j.bbagen.2010.03.011.
11. Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, *et al.* Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood. 2006;107:3738-44. DOI: 10.1182/blood-2005-07-2948.
12. Taher A, Sheikh-Taha M, Sharara A, Inati A, Koussa S, Ellis G, et al. Safety and effectiveness of 100 mg/kg/day deferiprone in patients with thalassemia major: a two-year study. Acta Haematol. 2005;114:146-9. DOI: 10.1159/000087888.
13. Chairunissa HG, Sauriasari R, Rizkyani NA. Cost-effectiveness analysis of deferoprone and deferasirox on thalassemia-major patients in Tangerang District Hospital, Indonesia. J Young Pharm. 2018;10:s128-31. DOI:10.5530/jyp.2018.2s.26.
14. Xia S, Zhang W, Huang L, Jiang H. Comparative efficacy and safety of deferoxamine, deferiprone and deferasirox on severe thalassemia: a meta-analysis of 16 randomized controlled trials. PLoS One. 2013;8:e82662. DOI:10.1371/journal.pone.0082662.
15. Pepe A, Rossi G, Bentley A, Putti MC, Frizziero L, D'Ascola DG, *et al.* Cost-utility analysis of three iron chelators used in monotherapy for the treatment of chronic iron overload in B-thalassaemia major patients: an Italian perspective. Clin Drug Investig. 2017;37:453-64. DOI: 10.1007/s40261-017-0496-1.