data; ŁS and TS provided FC-MRD data; KZ and PB performed statistical analyses; JK and TS coordinated acquisition of samples and clinical data; BSZ and RJ designed and created figures; PVV supervised sWGS analyses; AEK supervised MLPA analyses; MD supervised the study and MW was in charge of overall direction; BSZ and MD wrote the manuscript; all authors approved the manuscript.

ORCID

Bronisława Szarzyńska-Zawadzka [ID] https://orcid.org/0000-0002-2879-1671

Bronisława Szarzyńska-Zawadzka[1] [ID]

Joachim B. Kunz[2,3,4]

Łukasz Sędek[5]

Maria Kosmalska[1]

Katarzyna Zdon[6]

Przemysław Biecek[6]

Obul R. Bandapalli[2,3,4]

Monika Kraszewska-Hamilton[1†]

Roman Jaksik[7]

Monika Drobna[1]

Jerzy R. Kowalczyk[8]

Tomasz Szczepański[9]

Pieter Van Vlierberghe[10,11]

Andreas E. Kulozik[2,3,4]

Michał Witt[1]

Małgorzata Dawidowska[1]

[1]*Institute of Human Genetics, Polish Academy of Sciences, Poznań, Poland*

[2]*Department of Pediatric Oncology, Hematology, and Immunology and Hopp Children's Cancer Center (KiTZ), University of Heidelberg, Heidelberg, Germany*

[3]*Molecular Medicine Partnership Unit, European Molecular Biology Laboratory, University of Heidelberg, Heidelberg, Germany*

[4]*German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany*

[5]*Department of Microbiology and Immunology, Medical University of Silesia, Katowice, Poland*

[6]*Faculty of Mathematics and Information Science, Warsaw University of Technology, Warsaw, Poland*

[7]*Silesian University of Technology, Gliwice, Poland*

[8]*Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Lublin, Poland*

[9]*Department of Pediatric Hematology and Oncology, Zabrze, Medical University of Silesia, Katowice, Poland*

[10]*Department of Biomolecular Medicine, Ghent University, Ghent, Belgium*

[11]*Cancer Research Institute Ghent (CRIG), Ghent, Belgium*

Correspondence

Małgorzata Dawidowska, Institute of Human Genetics, Polish Academy of Sciences, Strzeszyńska 32, 60-479 Poznań, Poland.
Email: malgorzata.dawidowska@igcz.poznan.pl

[†]*Present address: Imperial Innovations, London, United Kingdom, 52 Princes Gate, Exhibition Road, London SW7 2PG*

This article was published online on 24 January 2019. An error was subsequently identified. This notice is included in the online and print versions to indicate that both have been corrected 25 February 2019.

REFERENCES

1. Maddalena P, Francesca GM, Daniela S, et al. The presence of mutated and deleted PTEN is associated with an increased risk of relapse in childhood T cell acute lymphoblastic leukaemia treated with AIEOP-BFM ALL protocols. *Br J Haematol*. 2018;182(5):705-711.
2. Tesio M, Trinquand A, Ballerini P, et al. Age-related clinical and biological features of PTEN abnormalities in T-cell acute lymphoblastic leukaemia. *Leukemia*. 2017;31(12):2594-2600.
3. Bandapalli OR, Zimmermann M, Kox C, et al. NOTCH1 activation clinically antagonizes the unfavorable effect of PTEN inactivation in BFM-treated children with precursor T-cell acute lymphoblastic leukemia. *Haematologica*. 2013;98(6):928-936.
4. Jenkinson S, Kirkwood AA, Goulden N, Vora A, Linch DC, Gale RE. Impact of PTEN abnormalities on outcome in pediatric patients with T-cell acute lymphoblastic leukemia treated on the MRC UKALL2003 trial. *Leukemia*. 2016;30(1):39-47.
5. Basso G, Veltroni M, Valsecchi MG, et al. Risk of relapse of childhood acute lymphoblastic leukemia is predicted by flow Cytometric measurement of residual disease on day 15 bone marrow. *J Clin Oncol*. 2009;27(31):5168-5174.
6. Petit A, Trinquand A, Chevret S, et al. Oncogenetic mutations combined with MRD improve outcome prediction in pediatric T-cell acute lymphoblastic leukemia. *Blood*. 2018;131(3):289-300.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Influence of patient-reported outcomes on the treatment effect of deferasirox film-coated and dispersible tablet formulations in the ECLIPSE trial: A post hoc mediation analysis

To the Editor:

Deferasirox dispersible tablets (DT), a once-daily, oral iron chelator, were approved by the US Food and Drug Administration in 2005. Deferasirox

TABLE 1 Multiple mediators of the effect of treatment group (FCT vs DT) on absolute change in serum ferritin levels from baseline at the end of treatment, overall and by subgroup

Mediators	Overall population				DT non-naïve patients				Patients with thalassemia				DT non-naïve patients with thalassemia			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	PM[b] (%)	P	PM[b] (%)	P	PM[b] (%)	P	PM[b] (%)	P	PM[b] (%)	P	PM[b] (%)	P	PM[b] (%)	P	PM[b] (%)	P
Adherence, assessed by average adherence PRO score	36.0	0.041*	66.6	0.012*	62.6	0.014*	62.6	0.014*	34.4	0.084	45.0	0.090	65.1	0.014*	68.1	0.025*
Adherence, assessed by average adherence PRO score + other PRO scores[c]	58.0	0.049*	77.0	0.020*	94.3	0.012*	94.3	0.012*	36.2	0.1626	56.1	0.125	68.9	0.050	66.1	0.093
Adherence, assessed by average adherence PRO score + other PRO scores[c] and severe GI-related AEs	58.4	0.060	90.1	0.014*	—[d]	—	—[d]	—	36.8	0.1472	69.5	0.074	75.7	0.032*	85.1	0.044*

Abbreviations: AE, adverse event; DT, dispersible tablet; FCT, film-coated tablet; GI, gastrointestinal; PM, proportion mediated; PRO, patient-reported outcome.

*P < 0.05.

[a]Models adjusted for age, sex, race, underlying disease, level of iron overload severity at baseline, average planned dose and number of blood transfusions while on treatment.

[b]PM calculated as the ratio of the indirect effect (effect through the mediator) to the total effect (effect both through and not through the mediator).

[c]Satisfaction, concerns and palatability scores.

[d]PM calculated to be >100%; in instances with multiple mediators, because of the interaction between them, the PM may be calculated to be >100%.

DT is typically dispersed in water or juice (20-30 mg/kg/day) and taken on an empty stomach ≥30 minutes before a meal.[1] For patients to receive the maximum therapeutic benefit from chelation therapy, adherence to the prescribed dosing regimen is essential. Treatment satisfaction can affect adherence and, thus, its ultimate effectiveness.[2] Deferasirox DT has been associated with better patient satisfaction and adherence (>80%), as well as lower impact on daily activities, than the previous standard iron chelator, deferoxamine.[3,4] However, barriers to optimal adherence exist, including the need to take medication on an empty stomach, palatability, and gastrointestinal (GI)-related side effects.

ECLIPSE was a 24-week, open-label, randomized study (NCT02125877) of DT and a new film-coated tablet (FCT) formulation of deferasirox (which can be taken with a light meal) among 173 iron chelation-naïve and -experienced patients with transfusion-dependent thalassemia or myelodysplastic syndromes.[5] ECLIPSE showed that the safety profile of the two formulations were comparable, with FCT recipients experiencing fewer severe GI-related adverse events (AEs). Although not a study endpoint, serum ferritin was monitored to guide dosing. FCT patients had a higher median reduction in serum ferritin from baseline (−350.0 [FCT] vs −85.5 ng/mL [DT]) to study end, suggesting a possible association between deferasirox formulation and observed efficacy. Furthermore, FCT patients had more favorable patient-reported outcomes (PROs) than DT recipients, reporting better adherence, satisfaction, and palatability, and fewer concerns about iron chelation therapy, as assessed using modified Satisfaction with Iron Chelation Therapy and palatability questionnaires. One explanatory factor of the observed difference in serum ferritin reduction could be better treatment adherence among FCT patients. The objective of this post hoc analysis was to estimate the proportion of the observed difference in serum ferritin reduction between the two formulations mediated by PROs, with a focus on patient-reported adherence. We assessed the proportion mediated (PM) by PROs in the overall population, as well as in subgroups with prior DT use ("DT non-naïve"), with thalassemia only, and in DT non-naïve patients with thalassaemia.

The mediation analysis was based on a method outlined previously.[6] Average PROs were calculated by taking the average of all available PRO domain scores over the treatment period for each patient. Three mediation frameworks with incremental increases in the number of mediators were considered: (i) average PRO adherence domain score; (ii) all average PRO domain scores (adherence, satisfaction, concerns, palatability); and (iii) all average PRO scores and frequency of severe GI-related AEs (Supporting Information Figure S1).

Univariate and multivariate generalized linear models, with and without the mediator variables of interest as predictors, were used to model the association between treatment (FCT or DT) and change in serum ferritin from baseline to end of treatment. The multivariate models included the covariates age, sex, race, underlying disease, prior use of iron chelation therapy, level of iron overload severity at baseline, average planned dose, and number of blood transfusions while on treatment. The models without the mediator(s) of interest provided an estimate of the total association between treatment and change in serum ferritin, ie the association between both *through* and *not through* the mediator(s). The models with the mediator(s) of interest provided an estimate of the association between treatment and serum ferritin

change *not through* the mediator(s). Results are reported as PM, ie the proportion of the total association between exposure and outcomes that is operationalized *through* the mediator(s) of interest, calculated as one minus the ratio of the association that does *not* go through the mediator, divided by the total association. Analytical variables were log transformed or square-root transformed for normality, as required.

A total of 154 patients had at least one PRO assessment over the study period and were included in the analyses. Among these patients, the average patient-reported adherence score mediated 66.6% ($P = 0.012$) of the association between treatment and change in serum ferritin (Table 1). Patient-reported adherence, satisfaction, concerns, palatability scores, and frequency of severe GI-related AEs together mediated 90.1% of the association ($P = 0.014$). In DT non-naïve patients, the PM by patient-reported adherence was 62.6% ($P = 0.014$), and by patient-reported adherence and other PRO scores was 94.3% ($P = 0.012$). In the DT non-naïve with thalassemia and thalassemia subgroups, similar trends were observed (Table 1).

In summary, these analyses found that PRO scores, specifically adherence, represent important mediators of the observed difference in serum ferritin reduction between the two treatment groups.

The PM was greatest among patients with prior experience with DT. One explanation, supported by a previous comparative analysis of iron chelation therapies,[3] is that patients with prior experience with DT have a reference frame for comparing the new FCT formulation with the standard formulation, and are better able to appreciate attributes of the new formulation.

This analysis is subject to several limitations. During ECLIPSE, a larger proportion of FCT patients received a higher-than-recommended dose or were not dose adjusted during management of AEs, which could have contributed to the observed serum ferritin reduction.[5] In addition, serum ferritin levels in the deferasirox FCT arm were higher than in the DT arm at baseline (2983 vs 2485 ng/mL). Furthermore, these results may not be generalizable outside the context of ECLIPSE because of the stringent inclusion/exclusion criteria. Although multivariate models were used to adjust for baseline covariates, the effect estimates between treatment group and serum ferritin reduction should be interpreted as associations, and the estimates of mediation by PROs should be interpreted as statistical mediation and not necessarily as causal.

In conclusion, this post hoc analysis supports the importance of considering PROs in determining the efficacy of chelation therapy for iron overload. Owing to its better palatability and ease of use, deferasirox FCT may be a superior therapy to DT for some patients with iron overload by increasing adherence to therapy.

AUTHOR CONTRIBUTIONS

ATT, RO, SP, AK, KB, and JBP served as investigators in the ECLIPSE trial, enrolling patients. VH, JH, and AB contributed to the interpretation and reporting of this analysis. PB and MSD conducted the analysis for this study. All authors contributed to data interpretation, reviewed, and provided their comments on this manuscript, and approved the final version.

PREVIOUS PRESENTATION

A synopsis of the current research was submitted for presentation at the European Hematology Association Congress in Madrid, Spain, 22-25 June 2017, at the Thalassemia International Federation congress in Thessaloniki, Greece, 17-19 November 2017, and at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Prague, Czech Republic, 22-26 August 2018.

DATA SHARING

Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. This trial data availability is in accordance with the criteria and process described on www.clinicalstudydatarequest.com.

ORCID

Ali T. Taher https://orcid.org/0000-0001-8515-2238
Raffaella Origa https://orcid.org/0000-0002-2346-9616
Mei Sheng Duh https://orcid.org/0000-0001-5035-6687

Ali T. Taher[1] 🆔

Raffaella Origa[2] 🆔

Silverio Perrotta[3]

Alexandra Kouraklis[4]

Khawla Belhoul[5]

Vicky Huang[6]

Jackie Han[6]

Andreas Bruederle[7]

Priyanka Bobbili[8]

Mei Sheng Duh[8] 🆔

John B. Porter[9]

[1]Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

[2]Ospedale Pediatrico Microcitemico 'A Cao', University of Cagliari, Cagliari, Italy

[3]Dipartimento della Donna, del Bambino e della Chirurgia Generale e Specialistica, Universita degli Studi della Campania 'Luigi Vanvitelli', Naples, Italy

[4]Hematology Division, Department of Internal Medicine, University of Patras Medical School, Patras, Greece

[5]Dubai Thalassemia Center, Dubai Health Authority Thalassemia Center, Dubai, United Arab Emirates

[6]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

[7]Novartis Pharma AG, Basel, Switzerland

[8]Analysis Group, Boston, Massachusetts

[9]Department of Haematology, University College London, London, United Kingdom

Correspondence

Ali T. Taher, American University of Beirut Medical Center, Beirut, Lebanon.
Email: ataher@aub.edu.lb

REFERENCES

1. Novartis Pharmaceuticals. EXJADE® (deferasirox) US Prescribing Information. 2018. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/exjade.pdf.

2. Escudero-Vilaplana V, Garcia-Gonzalez X, Osorio-Prendes S, Romero-Jimenez RM, Sanjurjo-Saez M. Impact of medication adherence on the effectiveness of deferasirox for the treatment of transfusional iron overload in myelodysplastic syndrome. *J Clin Pharm Ther*. 2016; 41:59-63.

3. Cappellini MD, Bejaoui M, Agaoglu L, et al. Prospective evaluation of patient-reported outcomes during treatment with deferasirox or deferoxamine for iron overload in patients with β-thalassemia. *Clin Ther*. 2007;29:909-917.

4. Taher A, Al Jefri A, Elalfy M, et al. Improved treatment satisfaction and convenience with deferasirox in iron-overloaded patients with thalassaemia: results from the ESCALATOR trial. *Acta Haematol*. 2010;123: 220-225.

5. Taher AT, Origa R, Perrotta S, et al. New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: results of the randomized, Phase II ECLIPSE study. *Am J Hematol*. 2017;92:420-428.

6. Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. *Stat Med*. 1997;16: 1515-1527.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Calculator-free point-of-care prognostication in myelodysplastic syndromes

To the Editor:

Contemporary prognostication in primary myelodysplastic syndromes (MDSs) began with the 1997 publication of the International Prognostic Scoring System (IPSS).[1] The particular model was subsequently revised in 2012 (IPSS-R). Both IPSS and IPSS-R employ multiple categories of bone marrow (BM) blast percentage, karyotype and cytopenias. BM blast categories in IPSS include <5%, 5%-10%, 11%-20% and 21%-29% and in IPSS-R ≤ 2%, >2 and <5%, 5%-10% and >10%. Cytogenetic risk groups in IPSS include good (normal, -Y, 20q-, 5q-), poor (chromosome 7 anomalies or complex karyotype with ≥3 abnormalities) and intermediate (all other abnormalities) and in IPSS-R very good (-Y, 11q-), good (normal, 5q-, 20q-, 12p- or two abnormalities including 5q-), intermediate (+8, 7q-, i[17q], +19, +21, other single abnormalities, independent clones, two abnormalities not including 5q- or −7/7q-), poor (−7, inv,[3] del(3q), two abnormalities including −7/7q-, complex karyotype with ≥3 abnormalities) and very poor (complex karyotype with ≥4 abnormalities). Cytopenias in IPSS included hemoglobin <10 g/dL, platelets <100 × 10⁹/l and absolute neutrophil count (ANC) <1.8 × 10⁹/l and in IPSS-R multiple categories of anemia (hemoglobin 8 to <10 g/dL and <8 g/dL), thrombocytopenia (platelets <50 × 10⁹/l and 50 to <100 × 10⁹/l) and neutropenia (ANC <0.8 × 10⁹/l).

IPSS and IPSS-R and more contemporary risk models for MDS[2] are generally not easily applicable in routine office practice where immediate access to risk model components and the extra time needed to refer to an online calculator are difficult to secure. With the exception of allogeneic hematopoietic stem cell transplant (HCT), current treatment in MDS has not affected survival, in a substantial manner.[3] In other words, the primary purpose of prognostication in MDS is currently to determine whether or not HCT should be considered sooner than later. The question then becomes whether or not one needs a sophisticated and complex prognostic system in order to deliver optimal care or whether that can be accomplished by a simpler and more practical prognostic model.

The three variables of interest for the current study were selected based on their consistent prognostic value in MDS. Karyotype and BM blast percentage are generally accepted as the most important prognostic determinants in MDS. However, the current IPSS-R system for classifying cytogenetic and BM blast percentage risk levels is too cumbersome for application in routine clinical practice. Also, in a large