An analytical view of the BJH publication of ‘a clinician's view of voxelotor’

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LETTER TO THE EDITOR

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In the recent correspondence by Osunkwo et al. voxelotor is praised as an important advance for patients with sickle cell disease (SCD).[1] Voxelotor inhibits sickle haemoglobin polymerization by increasing its affinity for oxygen. It has been approved by the Food and Drug Administration and the European Medicines Agency for treatment of children and adults with SCD mainly based on the recently published three-arm randomized placebo-controlled trial (RCT) of two voxelotor doses (1500 mg, 900 mg) (HOPE trial).[2] This study met its primary end-point in the 1500 mg voxelotor dose, which was an increase in haemoglobin concentration from baseline by more than 10 g per litre. Some secondary end-points were also met, namely reduction in some markers of haemolysis. A trend of reduced incidence in painful vaso-occlusive crisis (VOC) frequency (a difference of 0.43 VOC per person per year or a 13% decrease) was observed and maintained with longer follow-up.[3] Osunkwo et al. base their views on the available RCT data, post-hoc analysis of HOPE, case reports and expert opinion and argue that voxelotor is a safe option for patients four years and older and that it should be used where available. Even though voxelotor is an exciting new development for SCD, we offer a critical view of the statements made by the authors.

It is well established that a lower haemoglobin concentration due to a higher haemolytic rate is prognostic for specific SCD-related complications such as pulmonary hypertension and leg ulcers, whereas a lower haemolytic rate with a higher haemoglobin concentration is prognostic for complications such as VOC and avascular necrosis.[4] Whether a *volexotor-induced haemoglobin increment* will lead to an alteration of clinical manifestations in SCD, an improvement in quality of life and/or survival, and thus can be considered a surrogate end-point for clinically meaningful outcome, remains to be established. An increase in haemoglobin by hydroxyurea (hydroxycarbamide) is an established surrogate for clinical benefit. With hydroxyurea, along with increasing the fetal haemoglobin percentage, other changes occur (e.g., increased mean corpuscular volume) that likely contribute to its clinically relevant benefits. It remains to be seen whether long-term voxelotor treatment increases for example avascular necrosis, a complication related to the more vaso-occlusive phenotype which may take years to develop. Even though short-term data suggest safety, as stated by Osunkwo et al, careful long-term follow-up remains of utmost importance.

In HOPE (where >63% of patients were on hydroxyurea), the modest effect on VOC frequency was not statistically significant.[2,3] Nonetheless, several references are made by Osunkwo et al. to the reduction of VOC frequency in patients on voxelotor and, referring to a retrospective study of patients prescribed voxelotor, state '…large dataset of patients with SCD aged 12 years or older (n = 3128) showed that rates of transfusions vaso-occlusive crises were significantly lower after voxelotor initiation ($p < 0.001$)'.[1,5] However, VOC frequency (notoriously variable per patient in time) was documented in a selected subset of 1034 patients.[5] The reduced transfusion rate was documented in 190 selected patients.[5] The mean follow-up period in this study was only 3.9 months.[5] With RCT data available and considering inherent limitations of a retrospective registry study, the statement as made can be misleading.

Voxelotor is priced at approximately $123 per 500 mg tablet in the United States (https://www.goodrx.com/voxelotor) and one year of treatment at the recommended daily 1500 mg dose thus carries an estimated cost of $134.600 per annum. Pertaining to VOC, this translates to approximately $313.000 annually to avert one VOC per year. Sickle cell patients mostly live in countries with relatively limited resources, necessitating medical interventions that are readily accessible, safe to use and affordable. Such exorbitant pricing of voxelotor will render the drug unaffordable for most societies. Therefore, efficacy, as detected in optimal clinical trial conditions, will unlikely translate to real-world effectiveness as solely based on price (the efficacy–effectiveness gap).[6]

Pharmaceutical industry (Pharma) sponsorship of RCTs occurs increasingly. In the field of oncology, for example, it parallels the increasing use of surrogate end-points that mostly do not predict living better and/or living longer, the only outcomes that matter to patients.[7,8] The probability of achieving positive results in RCTs are greater when studying surrogate end-points, resulting in many, often costly, treatments of marginal (if any) benefit reaching the market.[8] This leads to unrealistic expectations of both patients and physicians and unjust spending of valuable health care resources with large revenue for Pharma.[8,9] One contributing factor thereto is financial conflicts of interest (FCI) of researchers,

opinion leaders, editors of medical journals, patient advocacy organizations and drug regulatory agencies among others with Pharma.[10] The HOPE trial was Pharma-sponsored with a surrogate end-point as the primary outcome measure, with involvement of the sponsor in study design, data analysis, interpretation and writing of the manuscript.[2] Seventeen of the 22 listed primary authors had a registered FCI with the trial sponsor. All authors of the letter by Osunkwo et al. have a FCI with the manufacturer of voxelotor, two of whom were investigators in the HOPE trial, and writing assistance was provided to the authors of this letter by a medical writer funded by the sponsor.[1] Providing insight into registered FCI is of importance as it is increasingly clear that FCI influences key opinion leaders, guideline authors and authors of editorials to move the needle to unduly favourable views of the concerned interventions.[10,11] 'A clinician's view on voxelotor' is based largely on expert opinion by authors with registered Pharma FCI arguing for implementation of an expensive new drug for which a durable impact on clinical disease-related manifestations as well as long-term safety data in large patient cohorts remain to be demonstrated. These views may contribute to unjust expectations of both patients and physicians based upon current data. This could negatively impact willingness to placebo-controlled trial participation (which is needed for further delineation of voxelotor in the SCD-related treatment landscape), and even strain the physician–patient relationship when those aware of the current limitations of voxelotor evidence are reluctant to prescribe.[12]

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REFERENCES

1. Osunkwo I, Anderson A, Brown RC, Shah N, Estepp JH. A clinician's view of voxelotor. Br J Haematol. 2022;199(4):616–8.
2. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. N Engl J Med. 2019;381(6):509–19.
3. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8(5):e323–e33.
4. Kavanagh PL, Fasipe TA, Wun T. Sickle cell disease: a review. JAMA. 2022;328(1):57–68.
5. Shah N, Lipato T, Alvarez O, Delea T, Lonshteyn A, Weycker D, et al. Real-world effectiveness of voxelotor for treating sickle cell disease in the US: a large claims data analysis. Expert Rev Hematol. 2022;15:167–73.
6. Templeton AJ, Booth CM, Tannock IF. Informing patients about expected outcomes: the efficacy-effectiveness gap. J Clin Oncol. 2020;38:1651–4.
7. Del Paggio JC, Berry JS, Hopman WM, Eisenhauer EA, Prasad V, Gyawali B, et al. Evolution of the randomized clinical trial in the era of precision oncology. JAMA Oncol. 2021;7(5):728–34.
8. Schnog JB, Samson MJ, Gans ROB, Duits AJ. An urgent call to raise the bar in oncology. Br J Cancer. 2021;125(11):1477–85.
9. Meyers DE, Meyers BS, Chisamore TM, Wright K, Gyawali B, Prasad V, et al. Trends in drug revenue among major pharmaceutical companies: a 2010-2019 cohort study. Cancer. 2022;128(2):311–6.
10. Schnog JB, Samson MJ, Duits AJ. Financiële belangen en oncologische geneesmiddelen [financial conflict of interest and anti-cancer drugs: why the NTVG's stance to exclude pharma-advertisement is of importance.]. Ned Tijdschr Geneeskd. 2022;166:D6738.
11. Sharma S, Booth CM, Eisenhauer EA, Gyawali B. Do editorialists with industry-related conflicts of interest write unduly favorable editorials for cancer drugs in top journals? J Natl Compr Canc Netw. 2021;19:jnccn20459. https://doi.org/10.6004/jnccn.2021.7016
12. Schnog JB, Samson MJ, Duits AJ. Contemporary oncology trials, drug approvals and the physician-patient relationship. Lancet Reg Public Health Am. 2022;11:100247. https://doi.org/10.1016/j.lana.2022.100247