The efficacy of voxelotor, 900 mg in patients with sickle cell anemia: a meta-analysis of the randomized controlled trial

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Sickle cell anemia (SCA) is an autosomal recessive disease caused by a mutation in the gene that codes the β-globin chain of hemoglobin. The abnormal hemoglobin (hemoglobin S) can polymerize when deoxygenated, changing the physical properties of the red cells (which deform to a sickle shape, hence the name) and damaging cell membranes.[1] Sickle cell anemia can lead to a variety of signs and symptoms namely vaso-occlusive attacks (presenting as pain, tissue hypoxia, necrosis, and organ damage), acute chest syndrome, hemolytic crisis, and primary and secondary stroke.[2,3] Acute and chronic manifestations increase with age and these complications lead to early mortality. Approximately 100,000 individuals are affected by sickle SCA within the United States alone and the condition dramatically decreases life expectancy by about 30 years.[4]

Voxelotor (GBT440) is a first-in-class, oral, once-daily drug (Global Blood Product, San Francisco, CA) that binds to the α-chain of hemoglobin S (HbS), which is known to interrupt HbS polymerization.[5-7] This study aimed to conduct a meta-analysis of the efficacy of voxelotor 900 mg in patients with SCA.

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[8], The review protocol was registered in the International Register of Prospective Systematic Reviews (PROSPERO), under the registration number: CRD42020147796. We performed a literature search through ClinicalTrials.gov, Cochrane CENTRAL, Conference Abstracts, Google Scholar, Ovid Medline, Scopus, Web of Science, and Wiley Online Library from 2010 through July 25, 2019 (See Appendix 1.). Details of the method can be found at the PROSPERO database.[9] Based on the prespecified inclusion and exclusion criteria, 2 randomized controlled trials[10,11] involving a total of 204 patients were included.

The primary outcome measured was hemoglobin change, as assessed in a highly similar fashion in both trials. There was a significant difference between voxelotor and placebo in hemoglobin change from baseline (mean difference [MD]: 0.87, 95% confidence interval [CI]: 0.67–1.06) (Figure 1). Voxelotor also reduced markers of hemolysis, MD: -36.79, 95% CI: (-75.05)-1.48 for unconjugated bilirubin that changes from baseline; MD: -19.09, 95% CI: (-44.06)-5.88 for the percentage of reticulocytes that change from baseline and MD: -23.29, 95% CI: (-65.14)-18.55 for LDH that change from baseline) but not reached to statistically significance. The incidence of the minimum number of 1 vaso-occlusive crisis events was 63.6% in the voxelotor group and 60.9% in the placebo group (risk ratio [RR]: 1.27, 95% CI: 0.41–3.92). The incidence of diarrhea was 18.1% in the voxelotor group and 8.7% in the placebo group (RR: 2.21, 95% CI: 0.71-6.85). No difference was found in headache incidence

(RR: 0.65, 95% CI: 0.37-1.13), pain (RR: 1.41, 95% CI: 0.63-3.15), back pain (RR: 0.85, 95% CI: 0.36-2.03), and rash (RR: 1.16, 95% CI: 0.52-2.60) between the voxelotor and placebo groups.

Voxelotor significantly increased hemoglobin levels which of 1 g/dL elevation predicts a reduced risk of stroke, albuminuria, pulmonary hypertension, and mortality[12]. Even the results of hemolysis parameters and the symptoms included in this meta-analysis did not reach a statistical significance, but signals are important if the number of the available studies and the sample size is small. In this case, such signals among the hemoglobin levels of the patients who received voxelotor were elevated with a difference of 0.87 mg/dl. Further multicenter, randomized, placebo-controlled studies are needed and will provide more evidence to see the potential of disease-modifying effects of voxelotor.

Keywords: Voxelotor, sickle cell anemia, HbS polymerization, meta-analysis, hemolytic anemia.

Author contribution statement

L.H.T. and A.S. designed research and performed literature search and statistical analysis, H.P. resolved disagreements in the screening and selection of studies and L.H.T. and A.S. wrote the paper. H.P. and M.A.E. revised the final document.

Conflict-of-interest disclosure

No potential conflict of interest relevant to this study.

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Figure Legends:

Figure 1. (A) Forest plot of mean difference for hemoglobin change from baseline. (B) Summary of risk of bias assessment.