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Pentosan Polysulfate Sodium: A Potential Treatment to Improve Bone and Joint Manifestations of Mucopolysaccharidosis I

Authors : Drago Bratkovic, Curtis Gravance, David Ketteridge, Ravi Krishnan, Michael Imperiale

Abstract : The mucopolysaccharidoses (MPSs) are a group of lysosomal storage diseases that have a common defect in the catabolism of glycosaminoglycans (GAGs). MPS I is the most common of the MPS diseases. Manifestations of MPS I include coarsening of facial features, corneal clouding, developmental delay, short stature, skeletal manifestations, hearing loss, cardiac valve disease, hepatosplenomegaly, and umbilical and inguinal hernias. Treatments for MPS I restore or activate the missing or deficient enzyme in the case of enzyme replacement therapy (ERT) and haematopoietic stem cell transplantation (HSCT). Pentosan polysulfate sodium (PPS) is a potential treatment to improve bone and joint manifestations of MPS I. The mechanisms of action of PPS that are relevant to the treatment of MPS I are the ability to: (i) Reduce systemic and accumulated GAG, (ii) Reduce inflammatory effects via the inhibition of NF-kB, resulting in the reduction in pro-inflammatory mediators. (iii) Reduce the expression of the pain mediator nerve growth factor in osteocytes from degenerating joints. (iv) Inhibit the cartilage degrading enzymes related to joint dysfunction in MPS I. PPS is being evaluated as an adjunctive therapy to ERT and/or HSCT in an open-label, single-centre, phase 2 study. Patients are ≥ 5 years of age with a diagnosis of MPS I and previously received HSCT and/or ERT. Three white, female, patients with MPS I-Hurler, ages 14, 15, and 19 years, and one, white male patient aged 15 years are enrolled. All were diagnosed at ≤2 years of age. All patients received HSCT ≤ 6 months after diagnosis. Two of the patients were treated with ERT prior to HSCT, and 1 patient received ERT commencing 3 months prior to HSCT. Two patients received 0.75mg/kg and 2 patients received 1.5mg/kg of PPS. PPS was well tolerated at doses of 0.75 and 1.5 mg/kg to 47 weeks of continuous dosing. Of the 19 adverse events (AEs), 2 were related to PPS. One AE was moderate (pre-syncope) and 1 was mild (injection site bruising), experienced in the same patient. All AEs were reported as mild or moderate. There have been no SAEs. One subject experienced a COVID-19 infection and PPS was interrupted. The MPS I signature GAG fragments, sulfated disaccharide and UA-HNAc S, tended to decrease in 3 patients from baseline through Week 25. Week 25 GAG data are pending for the 4th patient. Overall, most biomarkers (inflammatory, cartilage degeneration, and bone turnover) evaluated in the 3 patients with 25-week assessments have indicated either no change or a reduction in levels compared to baseline. In 3 patients, there was a trend toward improvement in the 2MWT from baseline to Week 48 with > 100% increase in 1 patient (01-201). In the 3 patients that had Week 48 assessments, patients and proxies reported improvement in PGIC, including “worthwhile difference” (n=1), or “made all the difference” (n=2).

Keywords : MPS I, pentosan polysulfate sodium, clinical study, 2MWT, QoL
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