GeNeXpreSS

# Emerging Therapies for Rare Genetic Disorders

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## Burosumab in X–linked hypophosphatemia (Carpenter et al., 2018)

X-linked hypophosphatemia, the most common heritable form of rickets, is caused due to loss-of-function mutations in the *PHEX* gene. It is characterized by increased secretion of fibroblast growth factor 23 (FGF-23) which leads to renal phosphate wasting, hypophosphatemia, rickets and osteomalacia, stunted growth, skeletal deformity, pain and limitation of daily activities. Conventional therapy with oral phosphate salts and vitamin D analogues is associated with poor compliance, incomplete healing of rickets, residual skeletal deformity, persistent short stature, gastrointestinal side effects and risks of hypercalciuria, nephrocalcinosis, and hyperparathyroidism. Burosumab is a recombinant human lgG1 monoclonal antibody that targets FGF-23. The authors have studied the effect of Burosumab in children aged 5-12 years. A total of 52 cases with active rickets and confirmed diagnosis of X-linked hypophosphatemia were taken. The authors concluded that 2 weekly regimen provided a sustained increase in the serum phosphorus level. There was substantial healing of rickets in all children with severe rickets with improvements in multiple related efficacy endpoints. However, effect on adult height is unknown which will take years to evaluate. Also, long term treatment is required for proper assessment of joint related complications and risk of nephrocalcinosis.

## Intraventricular Cerliponase Alfa for CLN2 Disease (Schulz et al., 2018)

Neuronal ceroid lipofuscinosis type 2 is a rare neurodegenerative disorder characterized by seizures and rapid decline in vision, motor, language, and cognitive functions. It is an autosomal recessive condition caused due to deficiency of the lysosomal enzyme Tripeptidyl peptidase 1 (TPP1). Cerliponase alfa is a recombinant form of human TPP1 and can be used as an enzyme-replacement therapy in patients with CLN2. In this study, the authors have evaluated the role of Cerliponase alfa in children with CLN2. A total of 24 children between the ages of 3 to 16 years were enrolled and they received intraventricular infusions of 300 mg every 2 weekly for a total duration of 96 weeks. The authors have concluded that intraventricular infusion of cerliponase alfa is associated with less decline in motor and language function as compared to historical cohorts.

## Prophylaxis for hereditary angioedema (Syed et al., 2018)

Hereditary angioedema is an autosomal dominant condition characterized by recurrent attacks of angioedema. It is caused due to mutation in the *SERPING1* gene encoding C1 inhibitor. There may be reduction in levels of C1INH (C1 esterase Inhibitor) or there may be reduced functional activity leading to uncontrolled activity of plasma kallikrein causing excessive bradykinin production and angioedema. Lanadelumab is a human monoclonal antibody that inhibits plasma kallikrein. This drug has been approved for prophylactic use by US FDA in patients aged more than 12 years. The drug is given subcutaneously and can be self – administered.

## Vestronidase alfa for mucopolysaccharidosis VII (Harmatz et al., 2018)

Mucopolysaccharidosis type VII is a rare genetic disorder caused by deficiency of the lysosomal enzyme $\beta$-glucuronidase. The authors have used

blind start trial design due to the small number of patients. A total of 12 patients were divided into four groups. After 24 weeks of treatment with Vestronidase, there was a significant reduction in urinary glycosaminoglycan excretion. Ten patients had improvement in the overall clinical outcome scores.

## Emicizumab prophylaxis in Hemophilia A patients with or without FVIII inhibitors (Le Quellec et al., 2018)

Emicizumab is a recombinant monoclonal antibody that acts as a bridge between activated Factor IX and Factor X and thereby mimics the function of Factor VIII. In the phase 3 HAVEN1 trial conducted on 109 Hemophilia A patients, once weekly subcutaneous dosage regimen was found to maintain lowest factor levels to at least 10-15 IU/dl. It was also found that Emicizumab prophylaxis significantly reduced the bleeding episodes as compared to conventional episodic treatment with bypassing agents in case of patients with inhibitors against Factor VIII. There is increased risk of thrombotic events especially if the drug is used along with bypassing agents (BPAs) such as activated Prothrombin Complex Concentrates (aPCCs) and recombinant factor VIIa (rVIIa) during the episodes of breakthrough bleeding. There are concerns over use of this drug versus use of immune tolerance induction (ITI) therapy in children with inhibitors, as treatment with Factor VIII is more effective in comparison to BPAs in case of breakthrough bleeds. Also, as there is increased risk of thrombosis associated with BPAs, it has been proposed to start prophylaxis with Emicizumab along with ITI therapy in children with inhibitors.

## References


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