Miglustat therapy normalizes bone mass in mouse model of cystic fibrosis

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BACKGROUND

- Brittle bones have been reported in children, adolescents and adults with cystic fibrosis (CF), independently of sex; this has been termed CF-related bone disease. In CF patients with the F508del mutation in the CFTR gene, vertebral fractures and the subsequent dorsal kyphosis decrease pulmonary function, thus accelerating the course of the disease and decreasing the quality of life in CF patients.

- Male and female mice with the homozygous F508del mutation in CFTR develop a severe osteopenic phenotype early on (Le Henaff C. et al, 2012).

- Miglustat (N-butyldeoxynojirimycin), the active ingredient of Zavesca®, was reported to normalize sodium and CFTR dependent chloride transport in primary human F508del CFTR airway cells and in nasal mucosa in F508del CF mice.

- Administration of 120mg/kg/day miglustat (Zavesca®, Actelion Pharmaceuticals) was realized once a day for 28 days by oral gavage to male mice aged of 6 weeks. Control groups received the same volume of vehicle, i.e. PBS solution. Values represent the mean +/- SEM of n = 5-8 mice per group.

- To evaluate changes in bone phenotype, we have analyzed:
  - the body weight of mice
  - the trabecular network of lumbar spine by micro Computer Tomography (µCT, SkyScan)
  - the histomorphometric parameters on sagittal sections (Bonolab, histolab, SkyScan)
  - the dynamic parameters of bone formation (double labelling: calcein/tetracyclin).

OBJECTIVE

- To evaluate the efficacy of oral miglustat treatment on parameters of the bone microarchitecture, histomorphometry and bone formation rate in F508del mice.

RESULTS

- Miglustat increases the body weight of F508del mice.

- Miglustat induces an increase in mineral apposition rate in F508del mice.

- Miglustat induces an increase in 17β estradiol level in F508del mice.

CONCLUSION

Oral administration of miglustat normalizes bone mass by increasing bone formation in F508del mice. This study strongly supports miglustat therapy in patients with CF-related bone disease.