Low-dose Infigratinib, an Oral Selective Fibroblast Growth Factor Receptor Tyrosine Kinase Inhibitor, Demonstrates Activity in a Preclinical Model of Hypochondroplasia

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Background: Fibroblast growth factor receptor 3 (FGFR3) gain-of-function mutations play a crucial role in achondroplasia (ACH), thanatophoric dysplasia (TD), and hypochondroplasia (HCH). HCH is a less severe form of dwarfism than ACH, but similarly is caused by gain-of-function mutations in the FGFR3 gene. HCH is characterized by a
disproportionate short stature and a growth deficit affecting both endochondral and intramembranous ossification. While multiple therapeutic strategies are being tested for ACH, currently there are no approved therapeutic options for individuals with HCH. We tested the hypothesis that the oral, selective FGFR tyrosine kinase inhibitor (TKI) in-figratinib (BGJ398) could improve the HCH phenotype and improve endochondral and intramembranous ossification in a preclinical mouse model of HCH Fgfr3N534K/+.

Methods: The first Hch mouse model studied expresses the most frequent human mutation p.Asn540Lys (Fgfr3Asn534Lys/+), and exhibits a mild dwarfism and most of the hallmarks of the human pathology. Fgfr3N534K/+ mice received subcutaneous injections of in-figratinib or vehicle control every 3 days (1 mg/kg) or daily (1 mg/kg) for 15 days (post-natal day [PND] 4–19) or 21 days (PND 3–24), respectively.

Results: Fgfr3N534K/+ mice treated with 1 mg/kg in-figratinib every 3 days did not show obvious and significant modification of the dwarf phenotype. In contrast, Fgfr3N534K/+ mice treated with 1 mg/kg in-figratinib daily for a total of 21 days showed a statistically significant increase in appendicular and axial skeletal measures. Length of the long bones was statistically significantly increased in Fgfr3N534K/+ mice compared with Fgfr3+/+ mice (tibia +3.18%, femur +3.16%, humerus +3.04%, ulna +2.94%, radius +3.01%). Treatment also modified the skull shape (skull width, skull height, nasal bone length and naso-occipital length), the length of the mandible and skull base, as demonstrated by measurement of the foramen magnum (foramen magnum length +3.72%). In-figratinib treatment modified the cartilage growth plate organization, in particular the hypertrophic chondrocyte area. Finally, the high activation of the MAP kinase pathway due to the HCH missense FGFR3 mutation was reduced by treatment, as revealed by the immunolabelling of phosphorylated Erk1/2 proteins.

Conclusions: Treatment with daily 1 mg/kg in-figratinib improved the length and weight of Fgfr3N534K/+ mice and significantly modified the skull and the axial and appendicular skeleton. We demonstrated in Fgfr3N534K/+ mice that in-figratinib is able to counteract the constitutive activation of FGFR3 due to the heterozygous N540K mutation localized in the tyrosine kinase 1 domain of the protein. These results provide a rationale for targeting FGFR3 with a specific TKI for the treatment of children with HCH.

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