Low dose, daily or intermittent administration of infigratinib (BGJ398), a selective FGFR inhibitor, as treatment for achondroplasia in a preclinical mouse model

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Introduction

Fibroblast growth factor receptor 3 (FGFR3) plays a crucial role in the process of endochondral ossification as shown by the FGFR3 gain-of-function mutations that result in short stature skeletal dysplasia, such as achondroplasia (ACH).

ACH is the most common cause of rhizomelic dwarfism, an autosomal dominant disorder with an incidence between 1 in 10,000 and 1 in 20,000 live births worldwide.1

In >95% of cases, ACH is caused by an arginine-to-glycine substitution at residue 380 (p.Gly380Arg) in FGFR3; this is a hereditary mutation that demonstrates 100% penetrance and is de novo in 80% of cases.1

The ACH phenotypes include rhizomelia (shortening of the limbs with proximal segments affected disproportionally), large head with frontal bossing, mid-face hypoplasia, and relatively normal trunk, with excessive lumbar lordosis.2 In >95% of cases, ACH is caused by an arginine-to-glycine substitution at residue 380 (p.Gly380Arg) in FGFR3; this is a hereditary mutation that demonstrates 100% penetrance and is de novo in 80% of cases.1

In-vivo observations

In-vivo observations for severity of effect were performed twice a week (hindlimb movement, posture, tail, padded, including assessment for survival). Detailed in-vivo observations were performed at the time of scoring.

Discussion

These data demonstrate that low, as well as intermittent, doses of infigratinib promote growth in this ACH mouse model:

- Low-dose infigratinib treatment of FGFR3Y367C mice over 15 days improved the endochondral ossification processes in an ACH mouse model.

- Skeletal changes were observed in a dose-dependent manner, based on total dose given over the 15-day treatment period.

- No apparent toxicity of infigratinib was observed; on the contrary, treatment of FGFR3Y367C mice with infigratinib improved survival compared with untreated FGFR3Y367C mice.

Conclusion: These results suggest that, at low doses, TKI therapy with infigratinib has the potential to be a valuable and relevant option for children with ACH. These findings support the continued development of infigratinib as a therapeutic option for ACH, with clinical studies planned to begin in 2020.

References