Support for a new therapeutic approach of using a low-dose FGFR tyrosine kinase inhibitor (infigratinib) for achondroplasia

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Introduction

Fibroblast Growth Factor Receptor 3 (FGFR3) plays a crucial role in the process of endochondral ossification as indicated by FGFR3 mutations resulting in severe forms of short stature like diaphyseal, such as achondroplasia (ACH).

ACH is the most common cause of micromelia; however, a subclinical condition also exists in which 1 in 10,000 and 1 in 20,000 live births are abnormal. In 95% of cases, ACH is caused by an arginine-to-glycine substitution at residue 380 (p.Gly380Arg) in the FGFR3 gene, which is an autosomal dominant gain-of-function mutation that demonstrates 100% penetrance and is deceased in 80% of cases.

The ACH phenotypes include rhizomelic (shortening of the limbs with proximal segments affected disproportionately), large head (occipital horn syndrome), hypoplastic, and relatively normal trunk, with excessive lumbar lordosis.7

Even though they are rare, serious complications are associated with ACH, including severe neurocranial malformations, failure to thrive, and impaired locomotor development. These complications are associated with ACH, as various therapeutic strategies have been considered, the most advanced being an analog of C-type Natriuretic Peptide (CNP, vosoritide), which is given as a daily subcutaneous injection and acts by antagonizing the MAP kinase pathway. However, both STAT1 and MAPK signaling is upregulated in the achondroplasia phenotype.

In this study, we evaluated a therapeutic strategy that targets all pathways downstream of FGFR3.

Methods

In-vitro observations

Data from our previous studies were used to confirm the effects of infigratinib on the growth of chondrocytes from ACH mouse models.

In-vivo observations

To confirm the effects of infigratinib on the growth of chondrocytes in vivo, we used a mice model of achondroplasia (ACH). We hypothesized that infigratinib would have greater potency at lower doses than a CNP analog (e.g., vosoritide). We sought to determine if a very low dose of infigratinib would be able to improve defective bone formation in proximal and distal femurs.

In-vivo safety

Chondrocyte proliferation was measured using X-rays and on the hind legs of mice. Animals were placed in a polymethyl methacrylate (PMMA) tube and x-rayed at three time points: at the time of sacrifice or post-treatment.

Results

In-vitro results

We observed that infigratinib inhibited chondrocyte proliferation in a dosedependent manner, with the lowest dose showing a more significant effect. We also observed that infigratinib treatment led to statistically significant inhibition of ERK and JNK phosphorylation at concentrations of 10-6M to 10-10M, indicating a dose-response relationship.

In-vivo results

In the ACH mouse model, treatments were well tolerated, with no apparent toxicity observed in treatment mice or via laboratory measures performed. On the contrary, treatment of mice with infigratinib can affect dysfunctional FGFR3 signaling in an ACH mouse model. Reductions were observed in an dose-dependent manner, based on total dose given over the treatment period.

We hypothesized that a very low dose of the select FGFR3–1 tyrosine kinase inhibitor (TKI) infigratinib (BGJ398) would improve defective bone formation and have greater potency at lower doses than a CNP analog, suggesting that inhibition of multiple key pathways downstream of FGFR3 controlling proliferation and differentiation of the chondrocytes leads to better efficacy compared with MAPK inhibition alone.

We also observed that vosoritide treatment led to statistically significant inhibition of ERK phosphorylation at concentrations of 10-6M to 10-10M, indicating a dose-response relationship.

In addition to the gain of growth, we observed modifications of the growth plate structure, improving the efficacy of infigratinib as a treatment for ACH, with clinical studies planned to begin this year.

Discussion

In-vivo data demonstrate that infigratinib has superior activity over a CNP analog, suggesting that inhibition of multiple key pathways downstream of FGFR3 controlling proliferation and differentiation of the chondrocytes leads to better efficacy compared with MAPK inhibition alone.

In-vivo data demonstrate that low, as well as intermediate, doses of infigratinib promote growth in the ACH mouse model.

Statistical analysis

Differences between experimental groups were assessed using ANOVA with Tukey’s post hoc test at Mann-Whitney U test. The significance threshold was set at p<0.05.

Conclusions

In-vivo findings

The ACH mouse model used in this study, with the gain of growth, the modified growth plate structure, and the improvements observed in bone development, supports the continued development of infigratinib as a treatment for ACH, with clinical studies planned to begin this year.

References


Figures

Figure 1. Overall findings by dose.

Figure 2. X-ray assessments.

Figure 3. Overall findings by dose.

Figure 4. In-vitro findings.

Figure 5. In-vivo findings.

Figure 6. Effects of infigratinib treatment on the interverbal disc.

Figure 7. FGF23 levels in plasma.

Figure 8. Survival data.