A literature review of the potency and selectivity of FGFR-selective tyrosine kinase inhibitors, such as infigratinib, in the potential treatment of achondroplasia

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Background

• Large data sets in fibroblast growth factor receptor-1 (FGFR1)-null cells can cause skeletal dysplasia and craniosynostoses.
• Malate in FGFR1 (ex. 520, 2517, 3521, 3357, and 4354) and (ex. 6200, 4520, 1725) are known to cause autosomal recessive conditions including craniosynostosis, short-limb syndrome such as achondroplasia and hypochondroplasia, and thalidomide embryopathy.
• Over the past decade, several FGFR1–3 tyrosine kinase inhibitors (TKIs), such as infigratinib (BGJ398), AZD4547 and ASP5878 have been studied in a variety of preclinical models of FGFR-driven skeletal dysplasia.

Achondroplasia is the most common form of disproportionate short stature driven by an FGFR4 genetic alteration. It is most commonly caused by an autosomal dominant (G380S substitution in FGFR4).

Achondroplasia is the most frequently studied FGFR-driven skeletal dysplasia although, to date, no study has comprehensively reviewed the literature regarding the potential therapeutic usage of FGFR1–3 TKIs in achondroplasia or other FGFR-driven skeletal dysplasias.

Purpose:

• Explore the publicly available literature to evaluate the dose dependency and toxicity profiles of FGFR-selective TKIs in preclinical skeletal dysplasia models.
• Evaluate, based on the comprehensive non-clinical evidence of safety and efficacy of FGFR-selective TKIs, the potential for a therapeutic option in FGFR-driven skeletal dysplasia.

Methods

A systematic literature review was performed to investigate non-clinical data from studies of infigratinib and other FGFR-selective TKIs relevant to FGFR1–3.

Two major types of sources were searched on October 20/32 2019 (all databases were searched for relevant articles from the past 10 years.

• Chemical databases (e.g., NCI-SDR, desktop, CDD, ACD, A2M2) were searched for relevant abstracts from the past 3 years.

Full text was included where possible.

Directly relevant publications were included in 2020:

Over the past decade, several FGFR1–3 tyrosine kinase inhibitors (TKIs), such as infigratinib (BGJ398), AZD4547, and ASP5878 have been studied in preclinical skeletal dysplasia models. Key results for infigratinib show:

• In vitro: 10-fold increase in growth of long bones and foramen magnum at 7 nM and an ‘optimal concentration’ of 5–10 nM (Figure 2).
• In vivo: studies: dose-dependent improvements in femoral length and bone length in E15.5 mice at SC doses of 0.2–2 mg/kg/day (Figure 3).
• A study of ASP5878 found that a minimum dose of 300 μg/kg was necessary to achieve dose-linear bone and bone formation.

Endogenous infigratinib exposure at this dose was below levels associated with minimal adverse effects seen with ARQ587 in juvenile mice.

In relation to other FGFR1–3 TKIs besides infigratinib:

• 11 significant survival advantage for infigratinib-treated ACH mice (Figure 4).
• One study of PD173074/100 mg showed significant rescue of primary cilia overgrowth in fibroblasts (Figure 5).
• One study demonstrated restoration of normal growth plate architecture and 60% growth improvement compared with controls in mice (Figure 6).
• One study showed ADC4547 decreased survival in neonatal wild type mice (20% treated at doses of 10 mg/kg at 10 mg/kg).

Conclusions

• While two studies suggest toxicity with FGFR-selective TKIs, this was produced at doses significantly higher than pharmacologically relevant doses in mice. The treatment of other skeletal dysplasias and in vivo studies in mice models of achondroplasia with low doses of infigratinib did not result in any of these adverse findings.

In vivo studies in an achondroplasia mouse model treated with low doses of infigratinib showed increase in growth of long bones and foramen magnum with a good dose-response relationship. No toxic effects were observed at low doses of infigratinib where efficacy was also seen.

One study demonstrated a survival advantage in mice treated with infigratinib.

Clinical relevance:

Given the totality of evidence, low doses of FGFR inhibitors, in particular infigratinib, appear to be a potentially safe option for further development in children with achondroplasia.

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