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Oral Infigratinib Therapy in Children with Achondroplasia

TO THE EDITOR: In their article on the PROPEL2 trial, Savarirayan and colleagues (Feb. 27 issue)[1] describe the results of a phase 2 dose-finding trial of infigratinib in children with achondroplasia between the ages of 3 and 11 years. This condition is caused by variants in the gene encoding fibroblast growth receptor 3 (*FGFR3*). In an editorial accompanying the article, Hoyer-Kuhn[2] interpreted the results of this trial as a "valuable milestone" in the treatment of achondroplasia, pending the results of the phase 3 PROPEL3 trial (ClinicalTrials.gov number, NCT06164951).

However, infigratinib, a selective tyrosine kinase inhibitor, has effects on FGFRs other than FGFR3. The half-maximal inhibitory concentrations of the drug are 0.9 nmol per liter, 1.4 nmol per liter, 1 nmol per liter, and 60 nmol per liter for FGFR1, FGFR2, FGFR3, and FGFR4, respectively. Adverse reactions that have been reported in patients receiving infigratinib include stomatitis, dry eye, fatigue, alopecia, palmar–plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, diarrhea, decreased appetite, blurred vision, and vomiting.[3] In the trial by Savarirayan et al., the investigators report that the majority of children had adverse events that were either mild (in 54%) or moderate (in 39%) and that no patients discontinued treatment because of an adverse event. However, it seems that infigratinib is not selective enough to treat achondroplasia without the risk of such side effects.

TYRA-300, which was developed by Robert Hudkins[4] as an FGFR3-selective inhibitor, may avoid some of the toxic effects associated with the inhibition of FGFR1, FGFR2, and FGFR4. Another FGFR3-selective drug under development, LY3866288 (LOXO-435), was described in the initial results from the FORAGER-1 trial.[5] Future research should focus on FGFR3-selective inhibitors for the treatment of achondroplasia, treatments that do not have side effects caused by influence on FGFR pathways other than the FGFR3 signaling pathway.

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TO THE EDITOR: Savarirayan et al. report that oral administration of the FGFR inhibitor infigratinib to children with achondroplasia improves longitudinal growth and skeletal proportions. Their study represents an important advance over current vosoritide therapy in terms of efficacy (higher annualized height velocity) and administration (oral vs. daily injections). However, the boundaries of achondroplasia therapy can be pushed even further.

First, perinatal or even fetal therapy with infigratinib should be explored to maximize the effect on long-bone growth and prevent defects that arise during prenatal development, such as the abnormal ossification of the skull base that underlies the neurologic complications of achondroplasia.[1] Second, at least 12 FGFR inhibitors are currently in clinical development for cancer,[2] drugs that may be repurposed for achondroplasia. Irreversible inhibitors such as TAS-120 and FIIN-2 may have a more sustained effect, whereas FGFR3-selective inhibitors such as TYRA-300 and LOXO-435 may have fewer side effects than infigratinib.[3,4] The relocalization of existing FGFR inhibitors could lead to rapid progress in the treatment of achondroplasia in the near future.

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THE AUTHORS REPLY: The adverse reactions associated with infigratinib that Bittmann lists were reported in adult patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma who had received infigratinib at a dose of 125 mg per day.[1] Nail toxic effects, stomatitis, dry eye, alopecia, palmar–plantar erythrodysesthesia syndrome, dysgeusia, constipation, dry mouth, eyelash changes, blurred vision, and dry skin were not observed in the children in our phase 2 trial, in which the daily doses of infigratinib ranged from 0.016 to 0.25 mg per kilogram of body weight. One case of mild hyperphosphatemia was reported among the 72 children enrolled in the trial, and fatigue, arthralgia, constipation, and decreased appetite were reported in less than 10% of the children, with none of these adverse reactions considered to be serious or leading to the discontinuation of infigratinib.

These findings suggest that at the doses we investigated in this population, there was no influence on other FGFRs that would be likely to result in clinically significant effects. The phase 3, randomized, controlled PROPEL3 trial that is evaluating infigratinib at a dose of 0.25 mg per kilogram per day is currently ongoing and will further inform the safety profile of this agent in children with achondroplasia.

Data from clinical trials will be required to assess other FGFR3 inhibitors as to the balance of their harms and benefits for the treatment of children with achondroplasia. The in vitro selectivity data published for FGFR3-selective inhibitors need to be cautiously interpreted, and their selectivity beyond the FGFRs needs to be assessed. For example, these drugs have been shown to be highly potent against fms-related tyrosine kinase 4 (FLT4),[2] which presents a consideration for safety monitoring in future potential clinical trials.

We agree with Rico-Llanos and colleagues that the boundaries of achondroplasia therapy can be pushed further. The clinical development of infigratinib in children with achondroplasia includes the evaluation of its safety and efficacy at younger ages, including in newborns and infants, in whom its potential effects on the development of the base of the skull can be observed. Regarding the therapeutic potential of the other FGFR inhibitors, clinical trial data in children with achondroplasia treated with these potential drugs are required to provide evidence of their safety and efficacy that can support possible theoretical benefit over infigratinib.

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Since publication of the article, the authors report no further potential conflict of interest.

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Levofloxacin for the Prevention of Multidrug-Resistant Tuberculosis

TO THE EDITOR: The articles by Fox et al.[1] and Hesseling et al.[2] and the editorial by Dorman[3] (Dec. 19/26 issue) on the use of levofloxacin for tuberculosis prevention underscore the many difficulties that investigators face when approaching populations at risk. Despite the strengths of the trials, the pill-counting and questionnaire methods that were used to assess adherence are known to have numerous shortcomings.[4] Given the multiple difficulties in conducting these trials, was any effort made to measure blood drug levels in trial participants? Because differences in adherence, absorption, and metabolism may play an important role in trial outcomes, pharmacokinetic data may be useful in assessing the real effectiveness of the proposed approach, particularly if nonadherence in the active-treatment group occurred. Modeling for levofloxacin pharmacokinetics may shed a different light on the outcome of both these trials.

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TO THE EDITOR: I wish to highlight the possible inadequacy of the dose-administration strategy used in the VQUIN MDR trial reported by Fox et al. The trial assessed levofloxacin to prevent multidrug-resistant (MDR) tuberculosis in high-risk contacts and showed fewer cases in the levofloxacin group than in the placebo group, although the difference was not significant. Suboptimal dose administration may have influenced these findings.

The trial used a lower levofloxacin dose (10 to 15 mg per kilogram of body weight daily for adults, with a maximum dose of 750 mg), in contrast with evidence supporting higher doses for MDR tuberculosis. Deshpande et al. found that achieving an area under the curve to a minimum inhibitory concentration (MIC) ratio of more than 160 maximized bacterial killing, which requires doses of up to 25 mg per kilogram per day.[1] Another study showed that the target maximum concentration of more than 8 μg per milliliter was more frequently reached with 1000 mg daily than with 750 mg daily.[2] Recent trials of short-course treatment for MDR tuberculosis