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Cystic Fibrosis Research News

Title:

Bone demineralization is improved by ivacaftor in patients with cystic fibrosis carrying the p.Gly551Asp mutation

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What was your research question?

Emerging data suggest a direct role of CFTR (CF gene) in bone formation. As Ivacaftor (Kalydeco), a drug which can correct the expression and/or function of mutated CFTR, strongly improves respiratory function and nutritional status in people with cystic fibrosis (CF) carrying the G551D mutation, we hypothesized that it could also improve bone mineral defects.

Why is this important?

Low bone mineral density (BMD) is a common problem in adults with CF leading to bone weakness and increased risk of breakage. Currently there is no efficient treatment to reverse this problem in people with CF.

What did you do?

We studied the bone density in the spinal cord of 7 people with CF carrying the G551D mutation (compound heterozygote or homozygote) and treated with Kalydeco. Their age range was between 26 years to 52 years. We checked the bone density of CF patients before and after at least 1 year of treatment with Kalydeco using a form of x-ray called Dual energy X-ray absorptiometry (DXA). We also collected data on any changes in Vitamin D level, nutritional and respiratory status of the patients over the research period. Further, it was made certain that no patients were treated with medications designed to improve bone

mineralization, nor experienced changes in vitamin D supplementation during the testing period.

To gain further insight into whether drugs that correct CFTR directly might improve bone formation, we assessed the effect of another corrector called C18 which specifically acts upon the F508del CFTR mutation (most common) using osteoblasts (bone cells). By looking at the changing expression of genes known to be involved in bone destruction, we were able to evaluate whether compound 18 had any beneficial effects on bone cell health.

What did you find?

Kalydeco treatment improved BMD in 5 out of 7 patients carrying the G551D mutation after an average of 1.7 years of treatment. One patient restored his bone density to normal levels within 12 months. The two patients who did not see an increase in bone density nevertheless remained stable without any further BMD loss.

As expected, treatment with Kalydeco led to significant nutritional and respiratory improvements. However, increase in bone mineralization was not statistically related to changes in respiratory function, weight, antibiotic courses or level of vitamin D in the blood. We also observed a decrease in the level of factors increasing bone destruction, which suggests an improvement in osteoblast function, after incubating the bone samples of the F508Del patients with the C18 corrector.

What does this mean and reasons for caution?

This research suggests that the correction of the CFTR protein improves bone structure and density to a more normal state and represents a step forward in the development of potential new therapies for CF-related bone disease.

Ideally, the best way to demonstrate the positive effects of Kalydeco on bone health would have been to also show normalization of osteoblasts from G551D patients. However, it was not possible to get such samples during the current study.

What's next?

Our future studies will aim to investigate Kalydeco efficacy on bone mineralization on a larger set of CF patients.

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