Cystic fibrosis bone disease: is the CFTR corrector C18 an option for therapy?

To the Editor:

Mutations in the gene encoding the chloride ion channel CFTR (cystic fibrosis transmembrane conductance regulator) results in cystic fibrosis (CF), the most common lethal autosomal recessive genetic disease, which causes a number of long-term health problems, such as the bone disease. Osteoporosis and increased vertebral fracture risk associated with CF disease are becoming more important as the life expectancy of patients continues to improve. The aetiology of low bone density is multifactorial, and is most probably a combination of inadequate peak bone mass during puberty and increased bone loss in adults [1]. Body mass index, male sex, advanced pulmonary disease, malnutrition and chronic therapies are established additional risk factors for CF-related bone disease. In multiple studies with a large cohort of adolescent and adult CF patients, the incidence of osteopenia and osteoporosis ranges from 34% to 79% [1, 2]. This further translated to a 100-fold greater risk of vertebral compression, which can decrease lung function, thus accelerating the course of the disease and decreasing the patient’s quality of life.

Emerging data suggest a direct genetic component to the development of CF-related bone disease. F508del is the most common CFTR mutation, with >80% of patients being at least heterozygous [3]. We recently discovered a defective CFTR-mediated chloride channel activity and severe deficit of the release of osteoprotegerin (OPG) in primary osteoblasts (cells that form bone) obtained from a 25-year-old CF male with F508del/G542X mutation in CFTR [4]. Recent evidence from clinical and CF model studies suggests that loss of functional CFTR not only causes osteoblast dysfunction in bones [5, 6] but also in airway cartilage, which may be important for airway development and dysfunction. Reports have shown that CF mice and pigs, but not epithelial sodium channel-overexpressing mice with CF-like lung disease, show abnormalities in tracheal cartilage development with early airflow obstruction [7–10], suggesting a critical role of CFTR dysfunction independent of deficient ion transport/airway surface liquid depletion. From rib explants harvested during lung transplantation in adolescents with CF, we validated the genetic contribution by which F508del mutation in CFTR resulted in a severe, defective osteoblast maturation arising from an increased RANK ligand (RANKL)/OPG mRNA ratio and a drastic reduction in production of the cyclo-oxygenase (COX)-2 metabolite prostaglandin (PG)E2, a key regulator of bone turnover [11]. Another report also showed an elevated RANKL/OPG ratio in the serum of children and adolescents with CF compared with that observed in healthy controls [2].

New treatments that target the F508del mutation through the use of potentiators and correctors of chloride channels are being developed in the care of CF-related lung pathology. Certain small molecules defined as “dual-acting potentiator–correctors” with both activities have been shown to partially rescue the functional expression of F508del-CFTR on the membrane of epithelia in patient-derived airway cultures, providing the rationale for clinical trials of the best compounds, including VX-809 [12, 13]. Recent in vitro studies have shed considerable light on the potential mechanism of action of the structurally related compounds VX-809 and C18 (also known as VRT-534), showing these correctors bind to full-length F508del-CFTR and enhance the channel-active form of the metastable F508del-CFTR protein after its biosynthetic rescue [12]. We therefore tested the effect of the corrector C18 on CFTR channel activity, the expression level of RANKL/OPG mRNA ratio and COX-2/PGE2 expression and production in osteoblasts with the F508del mutation. F508del osteoblasts were obtained from trabecular bone explants prepared from rib fragments harvested during lung transplantation, as previously described [11]. Normal osteoblasts, used as controls, were obtained from fresh trabecular bone explants of healthy young adults who underwent trauma surgery. The bone samples were obtained with informed patient consent after approval by the local research ethics committee.

First, we examined the efficacy of C18 in enhancing F508del-CFTR chloride function in primary osteoblast cell cultures obtained from four different adolescents with CF (three young patients: two 13- and 15-year-old females and a 14-year-old male homozygous for the F508del CFTR mutation, and a 14-year-old male a with the heterozygous F508del/G542X mutation in CFTR). C18 was found to greatly enhance F508del-CFTR channel function in all F508del osteoblast cultures. The extent of functional rescue caused by C18 treatment was ~85% of the mean CFTR function measured in healthy osteoblasts as
reported in figure 1a and b. We found a similar functional rescue in F508del osteoblasts when treated with the small molecule VX-809, a structurally related corrector compound in clinical trials (data not shown).

Second, real-time PCR showed that F508del osteoblasts treated with C18 have a 34% reduction of RANKL/OPG mRNA ratio compared with untreated F508del osteoblasts in which RANKL/OPG ratio was higher as compared with that found in normal osteoblasts (fig. 1c). Interestingly, we also found that treatment with C18 resulted in a significant increase of COX-2 expression and PGE2 production in F508del osteoblasts (fig. 1d and e). Prior reports have shown that COX-2 activity and PGE2 production are required for a full activation of Wnt/β-catenin signalling pathway in osteoblasts that is critically involved in
the regulation of skeletal growth and efficient bone fracture healing. Moreover, osteoblast differentiation and maturation of bone marrow stem cells is deficient in the absence of COX-2, and this can be compensated for by the addition of PGE2 [14].

Clinical trials are underway with the goal of finding new potential treatments that might prevent the development of CF-related bone disease, including antiresorptive agents such as oral bisphosphonates, and anabolic agents such as human recombinant growth hormones and parathyroid hormone [1]. A recent clinical study provides convincing evidence that the oral bisphosphonate alendronate is effective, well tolerated and safe for young patients with CF [15]. However, the use of bisphosphonates in children with CF is controversial because of potential long-term safety concerns including oversuppression of bone formation. The European CF bone mineralisation guidelines recently highlighted controversial issues, such as the use of bisphosphonates and vitamin D supplementation regimens in children and adolescents, indicating the need for other therapeutic trials for treating CF-related skeletal deficits [1]. Thus, there is an urgent need for an efficient and safe antosteopenic treatment to ameliorate osteoblast activity and, thus, favour the bone formation in patients with CF.

Therefore, the discovery of CFTR modulators acting as a “dual” F508del-CFTR correctors and potentiators, such as C18, leading to an increase of COX-2/PGE2 expression and production, and countering an elevated RANKL/OPG ratio in osteoblasts with the F508del mutation, represents a step forward in the development of potential new therapies to treat bone disease in patients with CF bearing the F508del mutation.

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CFTR corrector-potentiators may be new therapies for CF bone disease http://ow.ly/DSgyi

Frédéric Velard1, Martial Delion1, Flora Lemaire1, Olivier Tabary2, Christine Guillaume1, Françoise Le Pimpec Barthès1, Lhoussine Touqui1, Sophie Gangloff1, Isabelle Sermet-Gaudelus1 and Jacky Jacquot1

1EA 4691 «Biomatériaux et Inflammation en site osseux», SFR CAP-Santé (FED 4231), Université Reims Champagne-Ardenne, Reims, France. 2Inserm U938, Hospital St-Antoine, Paris, France. 3Département de Chirurgie Thoracique, Hôpital Européen Georges Pompidou, Paris, France. 4Inserm U874, Unité de Défense Innée et Inflammation, Institut Pasteur, Paris, France. 5Unité de Pneumo-Pédiatrie Allergologie, Hôpital Necker, Inserm U1551, Université Paris Sorbonne, Paris, France.

Correspondence: Jacky Jacquot, EA 4691, BIOS, SFR CAP-Santé (FED 4231), Université Reims Champagne Ardenne, 1, Avenue du Maréchal Juin, 51095, Reims, France. E-mail: jacky.jacquot@inserm.fr

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References


