European Cystic Fibrosis Society

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Cystic Fibrosis Research News

Title:

Safety and pharmacokinetics of Roscovitine (Seliciclib) in cystic fibrosis patients chronically infected with *Pseudomonas aeruginosa*, a randomized, placebo-controlled study

Lay Title:

Results of a clinical evaluation of the safety and efficacy of the therapeutic drug candidate Roscovitine in people with cystic fibrosis.

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What was your research question?

In this study, we wanted to evaluate the safety of a well characterized drug, Roscovitine, in CF patients infected by Pseudomonas aeruginosa, as well as the drug's global therapeutic efficacy.

Why is this important?

Roscovitine is a synthetic product discovered in the late nineties as a molecule inhibiting a key protein regulator of cell division initially purified from starfish eggs. Its name derives from Roscoff, the name of a small village in Brittany, France, which hosts the CNRS laboratory where it was initially discovered and characterized. As roscovitine inhibits cell proliferation it was developed as a potential anticancer drug candidate and tested in various cancers (breast, lung, nasopharyngeal) in more than 500 patients.

In 2014, roscovitine was reported to be correct the intracellular trafficking of the mutated F508del-CFTR and to reduce its intracellular degradation. Consequently, more CFTR activity was observed. One year later, University of Chicago researchers showed that the bactericidal activity of alveolar macrophages (the cells patrolling our lungs to capture and digest bacteria – these cells show reduced activity in people with CF, resulting in increased proliferation of bacteria) was enhanced by roscovitine. Furthermore, roscovitine showed encouraging anti-

inflammatory and bactericidal activity in a mouse model of CF infected with *Pseudomonas aeruginosa*. These findings, in addition to the general anti-inflammatory and analgesic properties of roscovitine, and the fact that roscovitine had already been administrated to more than 500 patients in another context, encouraged us to evaluate this 'old' molecule in people with CF.

What did you do?

In the clinical trial ROSCO-CF, we evaluated the safety and the effects of Roscovitine compared to a placebo in patients with CF chronically infected by *Pseudomonas aeruginosa*. 34 volunteers were enrolled in 13 hospitals in France. They received orally either a placebo or Roscovitine at 200 or 400 or 800 mg daily for 4 days/week/4 weeks. All clinical manifestations and biological variations were recorded as well as spirometry, bacteriological and inflammation data.

What did you find?

In these subjects with polypharmacy, Roscovitine was relatively safe and well-tolerated, especially at the 200 and 400 mg doses. Eight serious adverse events were observed among 5 patients leading to roscovitine withdrawal: 1/8 (12.5%) in the 200 mg group, 1/8 (12.5%) in the 400 mg group and 3/7 (42.8%) in the 800 mg group. Unfortunately, no evidence for significant efficacy, at the levels of inflammation, infection, spirometry, sweat chloride, pain and quality-of-life, was detected in roscovitine-treated groups versus the placebo-treated group.

What does this mean and reasons for caution?

There are several explanations for the absence of evidence for efficacy of Roscovitine: lack of intrinsic efficacy (possibly due to the fact that roscovitine was not initially chemically and biologically developed for CF and may thus not have been optimal for this indication), high pharmacokinetics variability among patients, too short duration of treatment, and/or inappropriate dosing protocol (dose, timing, frequency, etc…).

What's next?

Nevertheless, we have decided to pursue the project by optimizing a new, Roscovitine-inspired, drug candidate by classical medicinal chemistry guided by a CF-relevant cellular test. In addition, as not all patients with CF are improved by the new CFTR modulators (Elexacaftor, Tezacaftor, Ivacaftor), our new product will be evaluated not as an individual agent but in association with these marketed therapeutics.

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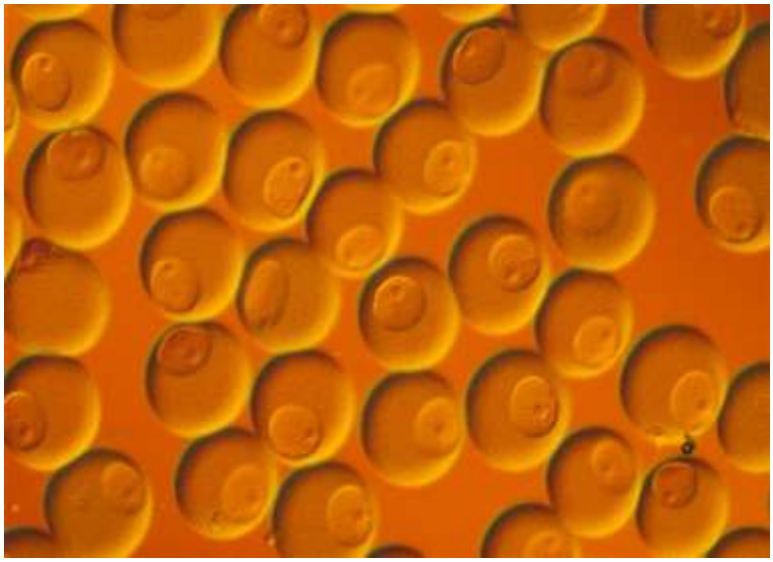

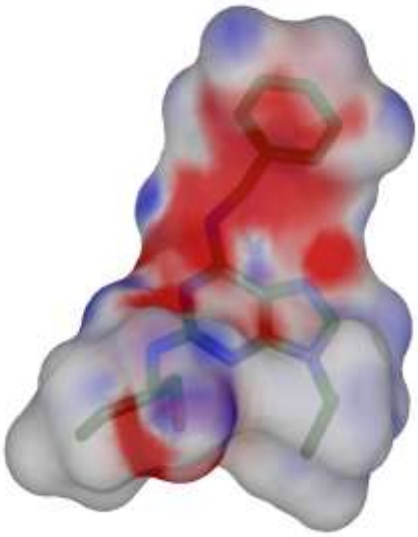

Research carried out in the '80-'90's on starfish eggs (left) led to the discovery of a key regulator of cell division and later to its inhibitor, Roscovitine (right), which was developed as an anticancer drug candidate.
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