Cystic Fibrosis Research News

Title:
Beta sitosterol ameliorates inflammation and *Pseudomonas aeruginosa* lung infection in a mouse model

Lay Title:
A step forward in the development of a safe anti-inflammatory molecule for the chronic respiratory disease of people with CF

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What was your research question?

Beta-sitosterol (BSS) is a plant sterol with chemical structures similar to that of cholesterol present in a wide variety of vegetables with beneficial effects in many different human diseases. BSS is used in traditional medicine to treat respiratory inflammatory diseases. In terms of safety, BSS is recommended as a drug in daily oral use in people with high cholesterol and no adverse effects are seen. We found that BSS reduces the inflammatory response in cystic fibrosis (CF) lung cells. Our question was whether BSS has an anti-inflammatory effect in a living animal model of respiratory infection.

Why is this important?

The introduction of powerful modulators of the defective CFTR protein (CFTR modulators) has a positive impact on improving outcomes in people with CF (pwCF). Unfortunately, due to

long-lasting inflammation and infection, decline of lung function in pwCF still occurs. This fact supports the rationale of combining anti-inflammatory drugs together with CFTR modulators in pwCF.—Further investigation into the effectiveness and safety of BSS on CF lung inflammation is therefore needed.

What did you do?

In this study, BSS was given daily by oral gavage (a tube from the mouth into the stomach) in mice lung infection replicating that of pwCF. This method is which widely used in animal studies to test new anti-inflammatory and anti-bacterial molecules. At the end of the study period, we evaluated the effectiveness of BSS by looking at the markers of inflammation (the number of neutrophils (type of white blood cell), the cytokines (soluble molecules with important role in inflammation) ~~a~~nd the status of the bacterial infection (the number of bacterial colonies) both in the lung fluid and lung tissue.

What did you find?

P. aeruginosa (a type of bacteria) infected mice treated with BSS showed a strong reduction of neutrophils both in the lung fluid and lung tissue when compared with control mice, which means that a large anti-inflammatory effect occurred. Consistently with this finding, those cytokines recruiting neutrophils from the blood into the lung were markedly reduced. Also relevant to note is that the number of bacterial colonies in the lungs of the mice treated with BSS were markedly reduced, indicating that the anti-inflammatory effect of BSS is not harmful for the immune defences, which maintain their full capacity of clearing the bacterial infection.

What does this mean and reasons for caution?

Our findings show that BSS intervenes by reducing the number of neutrophils, a hallmark of CF lung inflammation which contributes to progressive damage of the airways. BSS displays anti-inflammatory activity without damaging the immune defences needed for clearing infections. Considering that BSS is used daily by many persons with high cholesterol with no evidence of side effects (except very rare cases of intestinal discomfort), our findings show a promising step towards anti-inflammatory agents specifically for pwCF. However, positive findings seen in mice lungs as well as safety in pwCF should be further investigated before introducing BBS into clinical use.

What's next?

Assessing how effective BSS is in pwCF is important. The availability of CF animal models spontaneously developing bacterial infection and inflammation like in the lungs of pwCF is

very limited. Thus, moving directly to pilot clinical studies in pwCF will be the next necessary step.

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