Azithromycin: The Holy Grail to Prevent Exacerbations in Chronic Respiratory Disease?

Erythromycin was introduced to the market in 1952 as the first macrolide antibiotic. Newer macrolides such as clarithromycin or azithromycin with a broader microbial spectrum and fewer adverse effects are now recommended in many indications, especially for the treatment of lower respiratory infections and community-acquired pneumonia. Do these antibiotics represent the new holy grail for preventing exacerbations in chronic obstructive pulmonary disease (COPD)?

Diffuse panbronchiolitis, a disease predominantly occurring in East Asia, was the first disease to be treated with long-term macrolide therapy (1). Although no randomized controlled trials are available for use in this indication, macrolide therapy has become a standard treatment for this disease. In another disease with features of bronchiolitis, bronchiolitis obliterans after lung transplantation, azithromycin showed an ability to slow down the progress of chronic allograft dysfunction (2) and is therefore recommended as first-line therapy. As a result of clinical similarities with panbronchiolitis, azithromycin was studied in patients with cystic fibrosis with chronic *Pseudomonas* infection, and a significant decrease in the exacerbation rate could be demonstrated (3). A recently published study also confirmed this for children aged 6 months and older (4). With the "rediscovery" of bronchiectasis as an independent chronic respiratory disease different from COPD, macrolides moved into this indication. The effect of maintenance therapy on the exacerbation rate had been proven in three randomized controlled trials and was greatest in patients with chronic *Pseudomonas* infection (5). The same was shown in patients with COPD with frequent exacerbation (6, 7). Surprisingly, patients with moderately impaired lung function were found to benefit more than the severely ill ones (8). However, airway microbiology was not investigated systematically, so that the effect of chronic infection remained unclear. Bronchiectasis, typically associated with a moderate lung function decline, could have been misdiagnosed as COPD, which is a possible bias in the COPD studies.

Finally, for asthma bronchiale, in contrast to the other obstructive lung diseases mentioned here, randomized controlled trials failed (9) or succeeded (10) in reducing the exacerbation rate. The AMAZES trial (10), however, had the largest size, used an adequate dosage of azithromycin, and had the longest duration of treatment (48 wk), making the results more convincing than those of other studies. Altogether, the decrease in the number of exacerbations, both in eosinophilic and neutrophilic asthma, was impressive.

The mode of action of macrolides in long-term therapy is a subject of a controversial debate. Antibiotic effects do not seem to play a significant role, especially not against *Pseudomonas*, which is naturally resistant against macrolides. Antiinflammatory effects, especially inhibitory effects on tumor necrosis factor α and IL-8, could be demonstrated, but they were not dramatic and not more pronounced than, for example, the effects of inhaled steroids (11). An increase in gastrointestinal motility followed by a decrease in gastroesophageal reflux is known for macrolides, but it does not seem likely that this explains the huge effects of macrolides on exacerbation alone.

The substudy of the AMAZES trial published in this issue of the *Journal* by Taylor and colleagues (pp. 309–317) (12) investigates a different mechanism of action. A significant reduction in the diversity of the respiratory microbiome directly associated with the reduction of the exacerbation rate could be demonstrated. The decrease in diversity is essentially a result of a reduction of *Haemophilus* spp. in the respiratory microbiome. The downregulation of bacterial gene expression responsible for the formation of biofilms that prevent *Haemophilus* from being attacked by the immune response could be an explanation for this. This mechanism, known as quorum-sensing antagonistic activity, also had been discussed for *Pseudomonas* spp., and is in line with the macrolide effects in cystic fibrosis and bronchiectasis (13).

The study has a number of strengths. It is a prospective randomized controlled study, and the microbiome workup had been performed according to established and worldwide accepted standards. Nevertheless, the study results leave me helpless. The decrease in microbiome diversity has been shown to be detrimental with regard to the long-term prognosis in different diseases. The subgroup analysis of the BLESS study in bronchiectasis showed that the reduction of *Haemophilus* spp. opens a niche that is later filled by *Pseudomonas*, the most important parameter for disease deterioration over the long term (14). The increase of macrolide resistance is not good news. Although *Streptococcus viridans* is predominantly affected, a transmission of resistance genes to other pathogens by plasmid transfer could create a rapid increase in resistances in many pathogens (15).

The work published here shows that the respiratory microbiome and its integrity seem to be important factors to prevent exacerbations of chronic respiratory diseases, including asthma. The respiratory microbiome is directly related to the gastrointestinal microbiome. The potential of several measures, ranging from nutritional supplementation to stool transplantation, to restore a pathologic gastrointestinal microbiome has been recently demonstrated. Whether this has an effect on the airway microbiome remains unclear, but it seems to be very likely. There is no doubt that antibiotics affect both the gastrointestinal and the respiratory microbiome. However, in

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the age of a worldwide increase in antibiotic resistance, it is questionable whether the broad use of antibiotics as maintenance treatment for chronic diseases is a wise decision, as antibiotic resistance is closely correlated to infectious disease–related mortality. King Arthur and the Knights of the Round Table died, and the Holy Grail was lost forever. Even though this is only a Welsh tale, it should be a lesson. ■

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Is More Better? Promising Biological Effects of Double-Dose Alpha 1-Antitrypsin Therapy

The pilot study reported in this issue of the *Journal* by Campos and colleagues (pp. 318–326) tests the hypothesis that a higher concentration of circulating alpha-1 antitrypsin (AAT) than that achieved with the current standard AAT therapy will more effectively decrease the protease and inflammatory burden in AAT-deficient (AATD) patients (1). Enrolling 10 patients with AATD who were treated with a standard weekly intravenous dose of AAT (60 mg/kg/wk), they administered AAT at twice the dose (120 mg/kg/wk) for 4 weeks, followed by return to standard dose for another 5 weeks. This approach follows this group's previous analysis of the safety profile and pharmacokinetics of double-dose AAT over the course of 8 weeks in a crossover design with standard dose administration (2). In the current study, the investigators perform study bronchoscopies to more thoroughly explore the effect of double-dose AAT on airway and airspace parameters of proteolysis and immune responses.

Similar to their previous report, the double-dose administration had few adverse effects, most of which were mild and related to bronchoscopy, prompting the withdrawal of two subjects. Compared with the standard dose, the double-dose AAT administration in the remaining eight subjects led to significant reductions in biochemical markers of protease activation and elastolysis and of immune system activation. The latter effect included diminished levels of IL-17 and TNFα (tumor necrosis

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