The role of macrolide antibiotics in chronic rhinosinusitis

BY ANDERS CERVIN

The use of long-term antibiotics in the treatment of chronic rhinosinusitis is a contentious issue, not only because of the increasing problem with antibiotic resistance but also because of the potential cardiac risks, including sudden death. In this article, **Anders Cervin** reviews the available evidence for macrolide antibiotics.

Macrolide antibiotics such as erythromycin, clarithromycin, roxithromycin and azithromycin have been used for over three decades to treat inflammatory disorders of the airways [1]. In spite of this, their role in the upper airways is not undisputed, largely due to lack of adequately sized randomised studies and the lack of a proper characterisation (phenotyping) of patients included.

The lower airway

In the lower airways however, macrolide antibiotics have a widespread role as maintenance treatment in chronic lung disorders exhibiting a neutrophilic pathway, such as cystic fibrosis, exacerbation-prone chronic obstructive pulmonary disease, severe asthma and bronchiectasis [2, 3]. In contrast to macrolide treatment of chronic rhinosinusitis (CRS) where the evidence is still conflicting and studies are usually of lower impact, the respiratory physicians have pulled off large studies confirming the role of macrolides.

A short history of macrolides

Having said this, there is increasing evidence for the potential benefit of macrolides in the treatment of CRS. In this overview I will focus on trials including a control group. But first a short history of the use of macrolides in CRS. After Kudoh's report in 1984 on the efficacy of erythromycin in patients with panbronchiolitis, who all had CRS by the way, macrolide treatment of CRS was picked up by Japanese ENT surgeons and reported in early 1990 [4]. The dissemination from Japan to Europe was slow and the first report on Caucasian patients was by yours truly in 2002 [5].

Randomised studies do exist – but often lack a proper description of the patients.

The first randomised controlled trial was the result of myself spending a research year in Australia and in collaboration with Dr Ben Wallwork and others we published in 2006 [6]. The strength of the study was that we included only CRS patients (n = 64) without polyps (CRSsNP) and we measured serum IgE. We had understood from reading the Japanese studies that patients were less likely to respond if they had pronounced eosinophilia, as in CRS with polyps (CRSwNP). We could also show that our patients with elevated IgE were less likely to respond. There was another wait of five years before the next randomised study. It was a European collaboration and it did not show any effect of azithromycin in CRS patients (n = 60) [7]. It has been criticised for not controlling for elevated IgE and its inclusion criteria did not exclude patients with polyps.

Recently there has been an addition of placebo controlled trials. In 2015 a randomised controlled trial from Germany used erythromycin (250 mg od) or placebo as adjunct therapy postoperatively in patients both with and without nasal polyposis (n = 67). Erythromycin did not differ from placebo regarding symptom control, evaluated by a SNOT-20 questionnaire. A subgroup analysis suggested a trend for improvement in the patient group without polyps [8]. One could criticise this study for once again not considering the phenotype of the patients and the choice of a very low dose of erythromycin; other studies use at least 500 mg daily. Another postoperative study used azithromycin 250 daily for three months in addition to fluticasone nasal spray and saline nasal lavage after FESS surgery (n = 66) [9]. Patients were evaluated by SNOT-22. There was a significant difference ($p < 0.05$) in improvement in SNOT-22 scores in favour of the azithromycin group, especially for post-nasal discharge and nasal blockage. However, the effect size was small to moderate. The strength of this study is the proper randomisation and the fact that it is double blinded, however we have the same problem with a lack of defininition of patient characteristics. Another postoperative study divided the patients into three groups. All received mometasone furoate as postoperative maintenance therapy, and in adjunct either clarithromycin 250 mg daily for 12 weeks or 24 weeks, or placebo (n = 66) [10]. Assessment by SNOT-20 scores showed a significant benefit in the azithromycin groups but

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no significant change in VAS for disease severity suggesting that the changes in SNOT scores were small to moderate. This a well presented study, however it loses impact by dividing the patients into three groups.

Does dose and duration matter? Studies without a control group

Another study of interest compared clarithromycin 250 mg with 500 mg (n = 43), and found that the higher dose was significantly more effective for symptom control evaluated with SNOT-20, suggesting a dose-response relationship [11]. Regarding treatment duration, a recent Japanese study compared use of clarithromycin 250 mg daily for three months with six months and showed that at 12 months follow-up, the group treated for longer were significantly better in their nasal symptoms (n = 100) (12). This is in agreement with our own study that suggested that responders at three months treated for an additional nine months had further improvement (n = 17) [5]. Unfortunately, both studies lack a control group.

Risks of macrolides – cardiac death and microbial resistance

The risk-benefit ratio of macrolide treatment has primarily been associated with the risk of microbial resistance in the population, as side-effects usually are mild. However, lately the risk of increased mortality in cardiovascular events has been debated [13, 14]. Although recent reviews indicate that the majority of patients suffering cardiac arrhythmias from macrolides have multiple risk factors and that the risk has been overestimated, the FDA has strengthened the warnings on azithromycin drug labels [15]. It is advisable to take a history of cardiac events before prescribing macrolides. If any uncertainties arise, an ECG is recommended to exclude arrhythmia, especially long QT syndrome. It is also important to rule out any pharmacological interactions. Of special interest are warfarin and statins and drugs that may affect the QT interval. Unfortunately, that list seems to be growing [16].

Should I prescribe macrolides or not?

What to make of all this? Can you prescribe macrolide antibiotics to patients with CRS? I think you can, but only if standard medical therapy has failed. How do you a pick a likely responder to macrolide treatment? Well, the evidence is somewhat conflicting, but as a rule of thumb, patients with pronounced eosinophilic inflammation, for which elevated serum IgE is a reasonable marker, are less likely to respond. At the end of the day, whatever you feel about the evidence for long-term macrolide treatment, they are by far the best investigated antibiotics for the treatment of CRS.

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None declared.