Slovenian Medical Journal

Role of macrolide antibiotics in the treatment of chronic pulmonary diseases

Vloga makrolidnih antibiotikov pri zdravljenju kroničnih pljučnih bolezni

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Key words:
macrolide antibiotics; CoPD; asthma; cystic fibrosis; bronchiectasis; exacerbations

Ključne besede:
makrolidni antibiotiki; KOPB; astma; cistična fibroza; bronhiektazije; poslabšanja

Received: 15. 5. 2019
Accepted: 5. 8. 2019

Abstract

Chronic lung diseases are among the leading causes of morbidity and mortality. Despite adequate therapy, some patients fail to fully respond to treatment. Macrolide antibiotics are becoming one of the standard treating options in chronic pulmonary diseases, owing to their anti-inflammatory and antibiotic effects. Firstly, they minimise the adherence and mobility of the bacteria and affect biofilm formation. Secondly, they influence the expression of tight junction proteins and change the mucus composition. They increase antimicrobial susceptibility of bacteria when used in combination with other antibiotics. Beneficial effects on the quality of life and on the number of acute exacerbations in airways diseases have been described. Nonetheless, adverse effects have to be considered. Most importantly, appropriate selection of patients is necessary because long-term use of macrolide antibiotics promotes bacterial resistance in general population.

Izvleček

Kronične bolezni pljuč so eden vodilnih vzrokov obolevnosti in umrljivosti. Pri delu bolnikov kljub priporočeni terapiji ne dosežemo vselej zadovoljivega odgovora. Makrolidni antibiotiki so zaradi protivnetnih in antibiotičnih sposobnosti dobili svoje mesto pri dolgotrajnemu zdravljenju številnih kroničnih boleznih pljuč. Makrolidni antibiotiki zmanjšujejo nastanek biofilma, zmanjšujejo adherenco in mobilnost bakterij, vplivajo na izražanje tesnih stikov, spremenijo sestavo izmečka (mukusa) in povečajo občutljivost bakterij za druge antibiotike. Številne klinične raziskave so predvsem pri boleznih dihalnih poti pokazale pozitivne učinke za kakovost življenja in zmanjšale število poslabšanj. Pri uporabi moramo biti pazljivi na stranske učinke, predvsem pa kritični pri izbiri bolnikov za takšno zdravljenje, saj dolgotrajno jemanje makrolidnih antibiotikov vpliva na bakterijsko odpornost v širši populaciji.

Cite as/Citirajte kot: Badovinac M, Nadrah K, Harlander M. Role of macrolide antibiotics in the treatment of chronic pulmonary diseases. Zdrav Vestn. 2020;89(7–8)446–57.

DOI: https://doi.org/10.6016/ZdravVestn.2955

1 Introduction

Chronic lung diseases are among the leading causes of morbidity and mortality. With current predictions, we are expecting further growth in the numbers of these patients. The clinical picture is most characterised by shortness of breath and acute exacerbations. Despite adequate therapy, some patients fail to fully respond to the treatment. An additional option for the treatment of such patients is to prescribe a long-term macrolide antibiotic treatment. Indications for such therapy are growing increasingly broader and have begun to also include frequent diseases, such as chronic obstructive pulmonary disease (COPD) (1) and asthma (2). They can be potentially useful also for interstitial lung disease therapy (3). Because macrolide antibiotics are one of the basic groups of antibiotics for out-patient therapy of pulmonary infections, this raises the dilemma of the justification of using macrolide antibiotics for this purpose.

This article aims to present to the broader medical public the evidence for long-term use of macrolide antibiotics for lung disease therapy, and related risks.

2 Macrolides

Macrolides are a broad group of compounds of natural origin. They have a characteristic lactone ring to which several deoxy sugars are attached. They have an antibacterial, antifungal or immunomodulatory effect (4). Antibiotic characteristics are most recognisable traits of the macrolides. They form a reversible bind to the ribosomal subunit 50S, and have a bacteriostatic effect by inhibiting bacterial protein synthesis. Their secondary antibacterial characteristics are most well researched for the bacterium *Pseudomonas aeruginosa*. It has been established that they inhibit biofilm by reducing interbacterial communication, and by affecting the genes that contribute to the onset and ripening of biofilm. This weakens the adherence of the bacteria. They can also reduce the bacteria's mobility and the excretion of bacterial toxins (4,5).

Some macrolide antibiotics also have anti-inflammatory characteristics, affecting the immune system. The anti-inflammatory effect is measurable in concentration below their minimum inhibition concentration (MIC) for bacteria (6). They have the biggest effect on neutrophils, inhibiting the response to cytokines (IL-8 and TNF-α), and encouraging their apoptosis. They concurrently stimulate neutrophil degranulation, which should improve their antibacterial action (4). Even though *in vitro* studies have clearly shown anti-neutrophil action of macrolide antibiotics, clinical studies have yet to confirm this. In COPD patients, for whom azithromycin has reduced the number of exacerbations, there was no statistically significant reduction in the concentration of neutrophils in the sputum (7). Further, they also reduce the generation of pro-inflammatory and increase the generation of anti-inflammatory cytokines. In alveolar macrophages, they encourage phagocytosis. They also affect the lymphocyte population; however, the mechanism of this action is not yet fully explained (4).

In *in vitro* studies it has been discovered that macrolide antibiotics affect the expression of close contacts in the bronchial epithelium (8). Through this direct effect on the mucosa cells in airways they reduce the generation, viscosity and secretion of mucous (9). It has been established *in vitro* that clarithromycin increases the effectiveness of amikacin against the bacteria *Pseudomonas aeruginosa*. This is apparently the result of clarithromycin's effect on the biofilm (5).

Macrolide antibiotics are also potentially beneficial in disease exacerbations caused by viruses, because they reduce the generation of cytokines in a viral infection. *In vitro* research has proven that using erythromycin reduces the generation of anti-inflammatory cytokines when infected with the human rhinovirus (10),

which is one of the most frequent agents of exacerbation for COPD and asthma (11,12).

Most information on the action and clinical effectiveness is available on azithromycin. It is classified among azalides. In 1980, a group of researchers at the Zagreb-based Pliva synthesised it by including two nitrogen atoms in a macrocyclic ring of erythromycin (13). The change in the structure increases the lipophilicity and basicity, resulting in a better accumulation in different cells and good tissue absorption (14). Especially in macrophages, it achieves a quick and extended cellular accumulation, while – unlike other macrolide antibiotics – not inhibiting the cytochrome P450 3A4. For this reason, it is metabolically more neutral, with fewer side effects than other macrolides (15).

3 Using macrolides in clinical practice

3.1 Diffuse panbronchiolitis

Diffuse panbronchiolitis is an idiopathic disease with recurring chronic brochities and sinusitis. As it mainly affects the Asian population, it is not well known in Slovenia. The disease had a poor prognosis. Until recently, the 10-year survival rate was only at approximately 20%, as no therapeutic approach managed to bring down the mortality rate (16). The use of macrolides (erythromycin) improved pulmonary function, reduced symptoms, and increased 10-year survival rate to 90%. The successful use of macrolide antibiotics in the diffuse panbronchiolitis in the 1970s was the beginning of their use due to anti-inflammatory characteristics (17).

3.2 Cystic fibrosis

Cystic fibrosis (CF) is a genetic disorder with damage of the two genes for the ion channel, which carries chloride ions through the epithelial cellular membrane. This results in thick secretion. It affects lungs the most, as the thick mucus plugs the airways (18), creating the conditions for recurring and chronic infections with numerous bacteria and fungi. Consequently, epithelial cells generate more IL-8, which is a chemotaxin to neutrophils. A neutrophilic inflammation process in the airways is characteristic for CF patients. Among the most important pathogens is the bacterium *Pseudomonas aeruginosa*. It changes the constitution of the epithelium with proteases. The presence of the *Pseudomonas aeruginosa* bacteria weakens the intercellular close contact, increases viscosity and weakens the ciliary function. The final result of the mucous plugs and infections is the onset of bronchiectases and lung failure (4,19).

Clinical studies have proven that children and adult patients with CF, mostly colonised with the *Pseudomonas aeruginosa* bacteria, who were treated with azithromycin, had an improved pulmonary function (in two studies from 3.6–6%), lower inflammation indicators, improved quality of life (assessed using the CRQ questionnaire), fewer exacerbations (35–63%), and less of a need for intravenous antibiotic therapy (20-23). In the latest study on children (OPTIMIZE) who were colonised with the *Pseudomonas aeruginosa* bacteria, the number of exacerbations decreased by 44%, along with an increase in body mass (23). For children who were not colonised with the *Pseudomonas aeruginosa* bacteria, azithromycin therapy did not improve their pulmonary function, even though they also had a reduction in the number of exacerbations by 50%. They also had an increase in body mass (24).

Since 2007, long-term therapy of CF patients with azithromycin has been included in various guidelines. The current guidelines prepared by the Foundation for Cystic Fibrosis recommend long-term azithromycin therapy for improving pulmonary function and reducing the number of exacerbations for all patients above 6 years who have a chronic infection with

Pseudomonas aeruginosa in their airways (25). For patients older than 6 years and with no colonisation with the *Pseudomonas aeruginosa* bacteria, they recommend a consideration of such therapy. In all patients, colonisation with nontuberculous mycobacteria (NTM) should be excluded before beginning azithromycin therapy, and the presence of NTM should be monitored at regular 6–12-month intervals. The guidelines do not detail the azithromycin dosage. The studies, on which the guidelines are based, used 250 mg 3-times per week on patients with a body mass below 40 kg, and 500 mg 3-times per week on patients with a body mass above 40 kg.

3.3 Bronchiectasis

Bronchiectasis is a chronic pulmonary disease, related to abnormal and irreparable enlargements and transformations of airways. The disease is characterised by chronic productive cough and increases of inflammation (exacerbations). The cause of bronchiectasis is most often (40–45%) unknown, i.e., idiopathic. The most frequent identified aetiology is post-infectious (20-30%). Bronchiectasis can also be accompanied by NMT colonisation. Aetiological connections of bronchiectasis with the presence of NTM have not been conclusively determined (26,27). The presence of mycobacteria means a contraindication for introducing long-term monotherapy with macrolide antibiotics (they can, however, be used in combination with other antibiotics).

Considering all the evidence gathered so far on long-term macrolide antibiotics therapy, the patients with bronchiectasis have a significant reduction in exacerbations. In the randomised and placebo-controlled BAT study, it was established that a 12-month azithromycin therapy increased the time until the first exacerbation, and reduced the risk for exacerbation by 33.5% (28). In a similar 6-month study (EMBRACE, azithromycin 500 mg, 3-times per week), azithromycin reduced the number of exacerbations by 62% (29). In the BAT study, the patients who received azithromycin noted a significant improvement in the quality of life (assessed with a SGRQ questionnaire), while in the EMBRACE study, the improvement in quality of life was not statistically significant. In the BAT study, the pulmonary function had improved; however, the improvement was not statistically significant (26). In the randomised study which compared erythromycin with placebo, it was discovered that erythromycin reduces the number of exacerbation by 43% and improves pulmonary function, while there was no noted improvement in the quality of life (30).

In its guidelines for treating adults with bronchiectasis, the European Respiratory Society (ERS) recommends long-term therapy with macrolide antibiotics (azithromycin or erythromycin) for patients with three or more exacerbations per year (31). For patients who do not have a chronic colonisation with the *Pseudomonas aeruginosa* bacteria, macrolide antibiotics are the therapy of first choice. For patients with a colonisation with the *Pseudomonas aeruginosa* bacteria, the guidelines recommend the use of a macrolide antibiotics for those where therapy with inhaled antibiotics is not feasible, or for those who still have frequent exacerbations in spite of these drugs. The guidelines do not define the recommended dosage or the duration of therapy. Studies most often used azithromycin 500 mg, 3-times per week.

3.4 Chronic obstructive pulmonary disease

COPD is characterised by an irreversible obstruction of airways in exhalation. The clinical picture is most characterised by shortness of breath and acute exacerbations. The basic COPD therapy includes long-acting bronchodilators, and with frequent exacerbations also inhaled corticosteroids (ICS). Inhaled therapy can achieve a significant reduction in the number of exacerbations. However, in a part of pa-

tients, even triple inhalation therapy does not provide a sufficient response. COPD exacerbations cause a faster decline in the pulmonary function, reduce the quality of life and are a risk factor for mortality (1). The airways of COPD patients have a dominating macrophage–neutrophil inflammation, which has a poor response to ICS therapy (32,33). Macrolide antibiotics have been established as an additional option, under assumption that they reduce the intensity of neutrophil inflammation.

The effectiveness of macrolide antibiotics for preventing COPD exacerbation has been researched in 11 studies that included more than 2,500 patients (34). The biggest among them included 1,142 COPD patients who had an exacerbation in the year before the study, or were prescribed permanent oxygen therapy at home (35). Azithromycin therapy (along with other therapies) extended the duration until the first exacerbation and reduced the number of exacerbations by 19%. The analysis of subgroups from this study has shown the effectiveness of azithromycin in all subgroups, except for active smokers. Patients who received azithromycin had their quality of life measured (assessed with a SGRQ questionnaire), with the results showing a statistically insignificant improvement. Other studies yielded similar results (34), with the effect of azithromycin on the number of COPD exacerbations the highest on patients with the highest number of exacerbations in the past years. In the COLUMBUS study, which included COPD patients who had 3 or more exacerbations in the past year, azithromycin therapy reduced the number of exacerbations by 40% (1.94 exacerbations per patient/year in the group with azithromycin, compared to 3.22 exacerbations per patient/year in the placebo group) (36). All these studies researched the effectiveness of azithromycin for 6–12 months, putting forward the question of the longevity of the effect. The two recently published retrospective studies show that the effect is also present after 24 or 36 months (37,38).

COPD therapy guidelines prepared by the Global initiative for chronic obstructive lung disease, recommend prescribing azithromycin (in a 500-mg dose 3-times per week or 250 mg every day) to patients who still have frequent exacerbations in spite of triple inhaled therapy (and appropriate nonpharmacological measures) (1). Azithromycin is not recommended for patients who still smoke. The guidelines do not define the duration of the therapy.

3.5 Asthma

Asthma is also characterised by a chronic inflammation of the airways. Asthma is a heterogeneous disease (39). It is most often characterised by atopy and eosinophilic airway inflammation. The latter responds well to ICS and which is therefore the basis for treating asthma. We also know forms of the disease not marked by eosinophilic inflammation (non-eosinophilic asthma). These are, however, much less responsive to glucocorticoid treatment (40). This has also brought about the assumptions that the inflammation in these patients could be treated with macrolide antibiotics.

In the randomised and placebo-controlled study (AZISAST) of patients with a heavy asthma who suffered frequent exacerbations, using 250 mg azithromycin 3-times per week did on the whole not reduce the number of exacerbations in 6 months. A significant reduction in the number of exacerbation did come in the group of patients with non-eosinophilic asthma (defined as less than 200 eosinophils/μL in the blood) (41). A similar study with more patients was completed in 2017 (AMAZES) (2). In this study, azithromycin treatment significantly reduced the total number of exacerbations compared to placebo (1.07 versus 1.86 exacerbations per patient/year). It also led to a reduction of severe exacerbations that authors defined as exacerbation requiring therapy with systemic glucocorticoids or hospitalisation (1.07 versus 0.61 exacer-

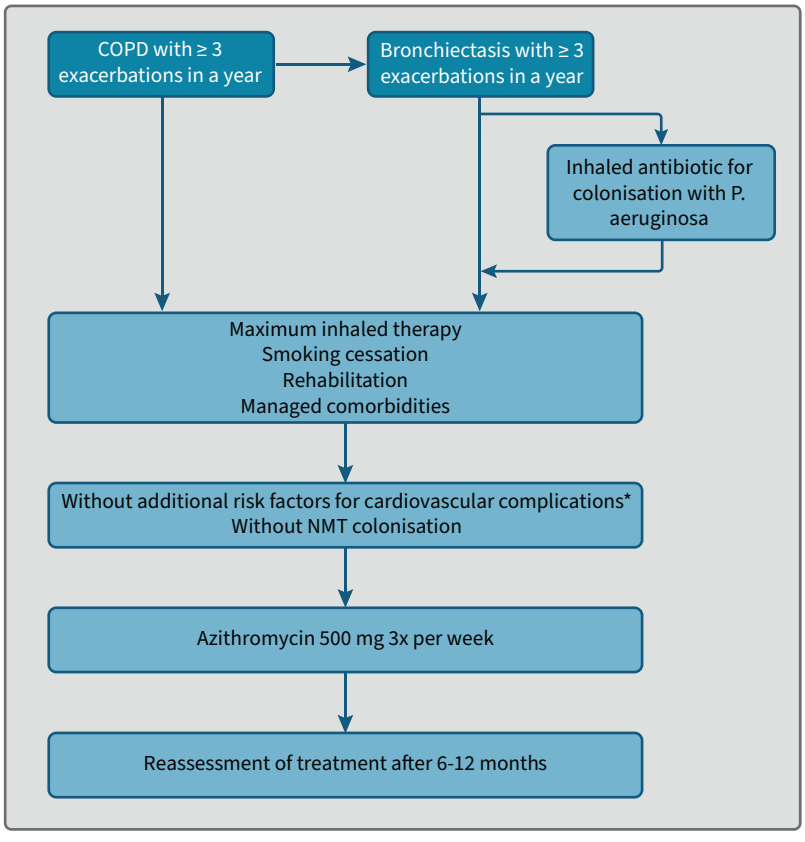

Figure 1: Proposed algorithm of using azithromycin on a patient with COPD and/or bronchiectasis.

* QTc > 450 ms, concurrent therapy with drugs to extend the QT period, significant comorbidity of the heart (heart failure, coronary disease), resting heart rate > 100/min.

**NTM nontuberculous mycobacteria. Taking a sample from the phlegm is recommended before beginning therapy.

bation per patient/year). Somewhat surprisingly, the same effect was noted across all subgroups, regardless of the presence of eosinophilic inflammation or bacterial colonisation. The patients who received azithromycin also had a clinically insignificant improvement in the quality of life (assessed with the ACQ6 questionnaire).

The guidelines for treating asthma currently do not include using macrolide antibiotics (42). Because of fairly limited data, it is not yet possible to define which asthma patients are most suitable for azithromycin therapy. Perhaps it will be patients with non-eosinophilic asthma, for whom there are the fewest alternative therapy options at the moment (43).

3.6 Chronic lung allograft dysfunction after lung transplantation

Chronic lung allograft dysfunction (CLAD) consists of restrictive and obstructive failure types (44). The obstructive type is also named the bronchiolitis obliterans syndrome (BOS), characterised by an inflammation, scarring, and finally a complete closure of small airways (bronchioles). BOS responds poorly to immunosuppressive therapy and is one of the main reasons for lung allograft dysfunction. It has been proven that in some patients, azithromycin can improve the pulmonary function and stops the advancement of the failure (45). In responsive patients bronchoalveolar lavage shows a higher percentage of neutrophils and an increased level of neutrophil inflammation related cytokines, such as IL-8 (46). In the study, conducted patients after lung transplantation, azithromycin treatment (250 mg, 3-times per week for 2 years) has significantly reduced the incidence of the onset of BOS compared to placebo (12% *vs.* 44% patient). Because of the clear effect of azithromycin on the subgroup of patients with BOS, this syndrome is now divided into the classic type and the neutrophilic reversible allograft dysfunction (NRAD) (44).

4 Side effects of macrolide antibiotics therapy

Using macrolide antibiotics can have a toxic effect on various organ systems. The most frequent side effects of macrolide antibiotics are on the digestive tract. Diarrhoea has occurred with 72/1,000 patients, and stomach pain with 62/1,000 (47). Cardiotoxicity has been a greater cause for concern. By inhibiting the calcium canal on myocytes, all macrolide antibiotics extend the QT period and consequently the risk for ventricular arrhyth-

mia. Through cytochrome P450, they affect the metabolism of other prescribed antiarrhythmics. Azithromycin has the lowest effect on cardiotoxicity (15). In a major observatory study, the five-day application of azithromycin was associated with an increased risk of mortality from cardiovascular causes. Risk of mortality was estimated at approximately 1:20,000 (48). Most patients had additional risk factors for cardiovascular events or were receiving additional proarrhythmogenic drugs for regulating heart rate. It should be mentioned that a similar effect has not been detected in a year-long study on the effects of azithromycin on coronary events in patients with a stable angina pectoris nor in other randomised studies conducted so far (49). The effect on the cardiovascular system was also not confirmed by Cochran's systematic analysis, which included studies with a total of 252,886 participants (47). Long-term use of macrolide antibiotics can be ototoxic; however, most likely the effect is reversible. The frequency and the seriousness of this side effect are not known (15). The probability of these side effects apparently increases with the duration of therapy. The study on children with CF (the OPTIMIZE study) did not note an increased number of side effects after more than 12 months of taking the drug (23).

5 Long-term macrolide antibiotic therapy and bacterial resistance

With long-term use of azithromycin a significant risk of generation of macrolide antibiotics-resistant bacteria is expected. All randomised studies that researched the effects of long-term macrolide therapies have found a significant increase in bacterial resistance to macrolide antibiotics. The biggest study with COPD patients found that patients who received azithromycin had 81% of resistant bacteria, compared to 41% for patients who received placebo (35). The results for patients with bronchiectasis in the BAT study were similar – at the end of the study, the group receiving azithromycin had 88% resistant bacteria, while the placebo group had 26% resistant bacteria. An increase in resistance was also confirmed in the AMAZES study in asthma patients, where they noted an increased expression of genes for macrolide antibiotics and tetracyclines resistance (50). The effect of chronic prescriptions of macrolide antibiotics on bacterial resistance in the broader community will generally depend on how strict the measures for selecting (and thereby the number of) patients with appropriate indication are.

A link between increased use of macrolide antibiotics, especially azithromycin, and the development of group A streptococcus and *Streptococcus pneumoniae* resistant to macrolide antibiotics has been proven several times (51,52). In Japan in the 1970s, a reduction of use (from 22% to 8% of all antibiotics) managed to bring down the resistance of the *Streptococcus pyogenes* bacteria from 62% to 2% (52). We also have a similar case in Slovenia. For children the resistance of the *Streptococcus pneumoniae* bacteria to macrolides has been increasing persistently, namely from 17.9% in 2005 to 44.3% in 2011. By raising awareness among the physicians, the use of macrolide antibiotics in 2016 declined by more than 60% compared to 1999 (53), and this in turn also brought down the resistance of the *Streptococcus pneumoniae* bacteria, which stood at 29.8% in 2015 (54). In the general population, resistance declined from 21% in 2011 to 17.6% in 2017 (55,56). A retrospective study on children also proved that resistance develops during therapy. One week after beginning the therapy, they noted a high share of macrolide antibiotics-resistant mouth flora (90%), which then gradually declined. This was not the case for azithromycin, where the high share of resistance persisted for up to six weeks (85%) (57). This condition is most likely related to the longer half-life and the lon-

ger presence (compared to other macrolides) of low azithromycin concentrations in tissues that promote the development of resistance (52,57). Similarly, the increase in the resistance of the *Staphylococcus aureus* bacteria was established in a study in CF patients. With long-term (several year) azithromycin therapy, the share of the resistant *Staphylococcus aureus* bacteria increased from 10% to 100% (83% after the first year of therapy) (58). Authors of the study were then interested whether the resistant strands were transferred into the home environment. They discovered that the share of such transfers is very low (1 in 65 patients) (59). In Slovenia, we have not detected an increase in the resistance of the *Staphylococcus aureus* bacteria to macrolide antibiotics in spite of increased use (12% in 2011, and 11.2% in 2017) (55,56). Increased resistance with increased use of macrolide antibiotics was also noted for the *Helicobacter Pylori* bacteria. The effectiveness of treating the infection declines with the resistance to macrolides. When the resistance exceeds 15%, it is no longer recommended to be included in the therapy scheme (60). In Slovenia, in years 2008 and 2009, we noted 20% resistant strands (60); however, according to the latest data, this percentage has almost halved to 10.5% (61). This decrease can be attributed to the rationalisation of the use of macrolide antibiotics.

Macrolide antibiotics (clarithromycin and azithromycin) are used in combinations for treating NTM infections. Long-term use of macrolide antibiotics in monotherapy could cause the onset of NTM resistance, making therapy significantly more difficult. It could even obscure the clinical picture and decrease the ability to obtain an adequate sputum sample for microbiological examination, and delay the diagnosis (62,63). The connection between resistance and monotherapy is not completely clear yet. A study on mice has established that resistance to clarithromycin only occurs with high inoculums (10^8 CFU), when resistant clones are generated in the bacterial population. Similarly, resistance occurred with HIV patients who already had a significantly reduced CD4 number (below 25) (64). On the other hand, a smaller retrospective study on patients infected with the *Mycobacterium avium* bacteria, who received erythromycin in monotherapy for 6 months, did not note an increase of resistance to clarithromycin (65). It is unclear whether this effect is only related to erythromycin, or whether it could be generalised to all macrolide antibiotics.

Perhaps the question of causing bacterial resistance will be less important in the future, as macrolides without antibacterial properties that still function anti-inflammatorily have already been identified (9).

6 Which pulmonary patient to select for long-term azithromycin therapy?

Long-term use of azithromycin can be justified for patients with frequent exacerbations, who have not shown a satisfactory decrease in the number of exacerbations despite appropriately prescribed pharmacological therapy and non-pharmacological measures. We also have to take the severity of the exacerbations into account. The effect on the lung function and the quality of life is small, so these are not suitable therapeutic targets.

Before prescribing a macrolide antibiotic, we have to conduct appropriate diagnostic examinations to properly define the disease. All comorbidities that could affect the frequency of exacerbations or increase the risk for complications have to be excluded or treated. The presence of NTM in the respiratory system has to be excluded. Figure 1 shows an example of an algorithm for implementing long-term azithromycin therapy for a patient with COPD or bronchiectasis.

When prescribing long-term azithromycin therapy, we have to be aware of the possibility for increased resistance

to macrolide antibiotics, which increases proportionally with use, also in the broader community (52). This resistance has the biggest impact on patients allergic to β-lactam antibiotics, for example, and children, as certain antibiotics of second or third choice have contraindications (e.g., tetracycline, fluoroquinolones). Long-term prescribing of macrolide antibiotics should be in the domain of experts in departments that have experience with treating the most severe pulmonary patients, the ability to perform appropriate diagnostic procedures and directly monitor the patient. It is also recommended to collect the data on the number and characteristic of patients receiving such therapy. Serious consideration of such therapy is especially merited in COPD, which is a frequent disease (prevalence in the adult population is estimated at around 10%), with nearly a third of these patients experiencing exacerbations (1).

7 Conclusion

The use of macrolide antibiotics, especially azithromycin, has its place in the therapy of patients with numerous chronic lung diseases with severe exacerbations. We have to, however, take into account the potential risks for the patient, as well as for the onset of antibiotic resistance in the broader community.

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