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BRN Rev. 2023;9(1):54-64

BRN Reviews

REVIEW

Macrolides: Indications and Contraindications

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ABSTRACT

Recently, there has been a growing interest in the use of chronic macrolides for the prophylaxis of recurrent exacerbations in severe chronic obstructive pulmonary disease (COPD) patients. Macrolides are antibiotics that add important immunomodulatory properties to their antimicrobial effect, making them especially useful for controlling pulmonary and systemic inflammation associated with recurrent exacerbations. The macrolide with the widest evidence is azithromycin; when used as prophylactic treatment, its long half-life allows intermittent dosing of 250-500 mg/day 3 times a week. Long-term azithromycin has been shown to be highly effective in reducing moderate-severe exacerbations of COPD and has been included in recent updates of clinical guidelines. It should be noted that its use is not without potential adverse effects; the increased risk of development of microbial resistance is a matter of particular concern and should be reserved for units specialized in the management of severe COPD where clinical and microbiological monitoring of treatment is ensured.

Keywords: Chronic obstructive pulmonary disease. Exacerbations. Macrolides.

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Received in original form: 05-04-2022
Accepted in final form: 09-11-2022
DOI: 10.23866/BRNRev:2022-M0077
www.brnreviews.com

INTRODUCTION

Chronic macrolides in chronic obstructive pulmonary disease (COPD): Why?

It is known that the risk of COPD is conditioned by the presence of acute exacerbations (AECOPD), which increase in frequency and severity as the disease progresses and are associated with high morbidity and mortality[1-3]. Around 35-40% of COPD patients have an exacerbator phenotype and, in some cases, despite receiving maximum inhaled therapy, they will not achieve good control[4]. Inhaled corticosteroids (ICSs) are the mainstay of anti-inflammatory treatment, reducing AECOPD in a subset of patients with eosinophil-dominant inflammation[5]. However, the use of ICS in neutrophil-dominant disease may exacerbate COPD by delaying neutrophil apoptosis and promoting the overgrowth of pathogenic bacteria[6]. At present, there is no effective neutrophil-targeted anti-inflammatory therapy. This situation has triggered interest in the use of chronic antibiotics for the prevention of AECOPD. Most studies have focused on the use of chronic macrolides, since these antibiotics add valuable immunomodulatory properties to their antimicrobial effect[7]. The use of chronic macrolides in COPD is the result of previous experience acquired in other chronic inflammatory diseases of the respiratory tract such as diffuse panbronchiolitis and bronchiectasis (BQ), especially in association with cystic fibrosis (CF)[8]. Repeated exacerbations in these diseases are associated with increased pulmonary and systemic inflammation, greater structural lung damage contributing to the formation of BQ, which may be present in up to 50% of severe COPD patients[9,10], further disease progression and a greater risk of chronic bronchial infection (CBI). Two of the chronic treatments that have proven useful in breaking this cycle of infection-inflammation, classically known as the "vicious circle hypothesis," have been chronic macrolides and nebulized antibiotics[11].

INDICATIONS

Antimicrobial and immunomodulatory properties of macrolides

Macrolides are a closely related group of antibiotics which characteristically contain a macrocyclic lactone ring and are classified as 14, 15, or 16 membered based on the number of carbon atoms within this structure. Erythromycin is the prototype; the others are semi-synthetic derivatives. Erythromycin, clarithromycin, and roxithromycin belong to the macrolide group with a 14-membered ring, and azithromycin, which belongs to the azalide group, has a 15-membered ring[12]. Neomacrolides (clarithromycin, roxithromycin, and azithromycin) have better bioavailability, oral absorption, and tissue penetration than erythromycin, which means that they can accumulate in alveolar macrophages[13]. Due to its longer half-life, azithromycin can be administered as a single daily or intermittent dose.

The antibiotic effect of macrolides is the result of their binding to the 50S bacteria ribosome subunit, thus reducing protein synthesis and preventing replication. They mainly exert a bacteriostatic effect, together with an indirect antimicrobial effect, through the stimulation of bacterial phagocytosis by alveolar macrophages. Their antibiotic spectrum includes

atypical bacteria such as *Chlamydia pneumoniae, Mycoplasma pneumoniae*, and *Legionella pneumophila*. Despite increasing resistance, they are also effective against Gram-positive microorganisms such as *Streptococcus pneumoniae*, and neomacrolides (clarithromycin and azithromycin) extend their spectrum to Gram-negative bacilli, including sensitive strains of *Haemophilus influenzae* and *Moraxella catarrhalis*, which make up the main group of potential pathogenic microorganisms for AECOPD. Although macrolides do not have a direct antimicrobial effect against *Pseudomonas aeruginosa* infection, they nonetheless play an important role in CBI by this microorganism. Macrolides inhibit the intercellular communication of *P. aeruginosa*, known as "quorum sensing," reducing its virulence and the process of biofilm formation by mucoid strains, thus enhancing the effect of nebulized antibiotics when they are used synergistically with macrolides[14]. Finally, based on the observation that macrolides also reduce the number of common colds in patients with COPD, it has been shown that they also have an antiviral effect, stimulating the pattern of response to interferons (and genes stimulated by them) and enhancing the antiviral response[15].

Macrolides also add various immunomodulatory properties to their antibiotic effect that can be summarized as follows: stimulation of apoptotic cell phagocytosis; reinforcement of innate immunity through its interaction with bronchial epithelial cells favoring their function as barriers and the ciliary function; reduction of the deleterious effect of neutrophilic elastase; reduction of the pro-inflammatory cytokines produced by the respiratory epithelium; and the formation of mucin gels by goblet cells and mucus hyperproduction[16]. Recent studies in patients with neutrophilic COPD have shown that 3 months' treatment with azithromycin at a dose of 250 mg/day is sufficient to induce downregulation in the expression of various genes related to antigen presentation, T-lymphocyte response, and in various inflammatory pathways of the respiratory tract, which suggests that macrolides have a certain capacity to modulate adaptive immunity[17].

Prevention of COPD exacerbations

Recently, there has been a growing interest in the use of long-term chronic macrolides as prophylactic treatment for AEPOCD[7]. Table 1 shows the main published studies, with a placebo-controlled design and of at least 6 months' duration[17-21]. It should be noted that the different studies do not agree on when chronic macrolide treatment should be started (i.e., at what degree of COPD severity and/or number of previous AECOPDs) or on the macrolide of choice, its dosing regimen, and its long-term safety and efficacy when used beyond the 1st year of treatment.

In 2011, Albert et al.[18] published the effect of chronic macrolide administration on the frequency and severity of COPD exacerbations (MACRO) study, the first large trial with long-term macrolides randomizing 1142 COPD patients (forced expiratory volume in one second [FEV_1] <80%) to receive azithromycin 250 mg/day versus placebo for 12 months. Inclusion criteria were at least one severe AECOPD or a moderate event treated with oral steroids in the previous year and/or treated with chronic home oxygen therapy. Despite including a group of patients with a non-exacerbator phenotype, in the intervention group,

Table 1. Long-term placebo-controlled trials of more than 6 months of duration evaluating the effect of chronic macrolides for the prevention of AECOPD

Study	Year	n	FEV_1% macrolide/control	Macrolide	Duration (months)	Main objective and reduction of AECOPD*
Uzun et al.[20]	2014	92	44.2/45.0	Azithromycin 500 mg three tablets/week; placebo	**12**	Ratio of AECOPD* ***Azithromycin HR 0.58** 95% CI 0.42-0.79; p < 0.001
Albert et al.[18]	2011	1117	39/40	Azithromycin 250 mg one tablet/day; placebo	**12**	Time to first AECOPD ***Azithromycin HR 0.73** 95% CI 0.63-0.84; p < 0.001
He et al.[21]	2010	36	44.3/42.1	Erythromycin 125 mg three tablets/day; placebo	**6**	Neutrophils in sputum; ratio of AECOPD *Erythromycin **RR: 0,55** 95% CI 0.31-0.98; p = 0,042
Blasi et al.[22]	2010	22	–	Azithromycin 500 mg three tablets/week; standard treatment	**6**	Number of EACOPD and hospitalizations *Azithromycin RR 0.24 95% CI 0.05-0.843 p < 0.001
Seemungal et al.[23]	2008	109	49.3/50.6	Erythromycin 250 mg 2 tablets/day; placebo	**12**	AECOPD and airway inflammation *Erythromycin RR: 0.65 95% CI 0.49-0.98; p = 0.03

AECOPD: acute exacerbation of chronic obstructive pulmonary disease, CI: confidence interval, FEV_1: forced expiratory volume in one second, HR: hazard ratio, RR: rate ratio.

azithromycin reduced the risk of AECOPD by 27% (hazard ratio [HR] 0.73: confidence interval [CI] 95%, 0.63-0.84; p < 0.001)[18]. However, this study reported an increased risk of developing macrolide resistance in colonizing microorganisms, as well as other adverse effects such as hearing loss due to ototoxicity after long-term use. Subsequent sub-analyses of this study have shown that azithromycin is mainly effective in ex-smokers and has no clear preventive effect in the group of active smokers[18]. One possible explanation for these results might be the stimulatory effect of tobacco on goblet cells, together with an upregulation in the expression of MUC5AC that would lead to increased mucus hypersecretion, counteracting to a certain extent the effect of azithromycin. In parallel to the MACRO study, our group published a study in a highly selected cohort of 20 severe COPD patients who are high exacerbators (mean FEV_1 32%), with ≥ 4 AECOPD in the previous year and/or CBI by *P. aeruginosa*, treated with long-term azithromycin at a dose of 500 mg 3 times a week for 12 months. In this study, compared to the previous year, long-term azithromycin achieved a 70% reduction in the number of moderate-to-severe AECOPD in patients with exacerbations by common potential pathogenic microorganisms, and a 40% reduction in exacerbations in patients with CBI by *P. aeruginosa*, demonstrating a beneficial effect in this subgroup of patients with greater morbidity[19]. In 2014, Uzun et al.[20] published the macrolide maintenance therapy in COPD (COLUMBUS) study, a randomized placebo-controlled trial in 92 patients with severe COPD and also high exacerbator phenotype (mean FEV_1 45%)

with ≥3 AECOPD in the previous year. This group of patients, treated with azithromycin at a dose of 500 mg 3 times a week, had a 42% reduction in the risk of AECOPD (HR 0.58, 95% CI 0.42-0.79; p = 0.001). It should be noted that in the group of patients treated with azithromycin, up to 43% were active smokers[20]. In that study, the number of sputum cultures performed was limited, so no conclusions can be drawn regarding the impact of azithromycin on microbial resistance. More recently, Vermeersch et al.[24] presented the results of the azithromycin during acute COPD exacerbations requiring hospitalization trial, a placebo-controlled trial in 301 COPD patients randomized to receive 3 days of azithromycin at a dose of 500 mgr 48 h after hospital admission, followed by 250 mgr/48 h for a period of 3 months, with subsequent follow-up for another 3 months after stopping treatment with azithromycin. Time-to-first-event analyses evaluated the treatment failure rate within 3 months as a novel primary endpoint, defined as the composite of treatment intensification with systemic corticosteroids and/or antibiotics, a step-up in hospital care or readmission for respiratory reasons, or all-cause mortality. The treatment failure rate within 3 months was 49% in the azithromycin group and 60% in the placebo group (HR, 0.73; 95% CI, 0.53-1.01; p = 0.0526). Treatment intensification, step-up in hospital care, and mortality rates within 3 months were 47% versus 60% (p = 0.0272), 13% versus 28% (p = 0.0024), and 2% versus 4% (p = 0.5075) in the azithromycin and placebo groups, respectively. Clinical benefits were lost 6 months after withdrawal. Although the results were formally negative, the data suggest that a low-dose azithromycin intervention initiated at the onset of a severe AECOPD requiring hospitalization reduces the recurrence of exacerbations, especially those leading to hospital admission and transfer to intensive care in patients at risk. To maintain the clinical benefits, however, prolonged treatment appears to be needed. The proposed intervention could help to address the highest risk period for readmission and provide a new treatment strategy for a severe infectious AECOPD requiring hospitalization[24].

These results are consistent with those obtained by meta-analyses, which conclude that chronic macrolide treatments are useful when used for prolonged periods of time (at least 6-12 months) and when they include azithromycin or erythromycin in their regimens[25].

Positioning in clinical guidelines

In accordance with the evidence published on the use of chronic macrolides for the prevention of AECOPD, the Spanish COPD Guideline (GesEPOC) in 2012 was the first to propose their use in patients with moderate-to-severe COPD with an exacerbator phenotype and at least three AECOPDs in the previous year despite receiving adequate treatment with triple inhaled therapy[26]. Later, in 2017, the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) also incorporated its use in the COPD patient profile[27]. It should be noted that both guidelines highlight the need to reevaluate the indication of ICS, especially in patients with no clinical response, plasma eosinophil counts <100 cells, and/or a history of pneumonia, and to consider their withdrawal. GOLD also restricts the use of chronic macrolides to

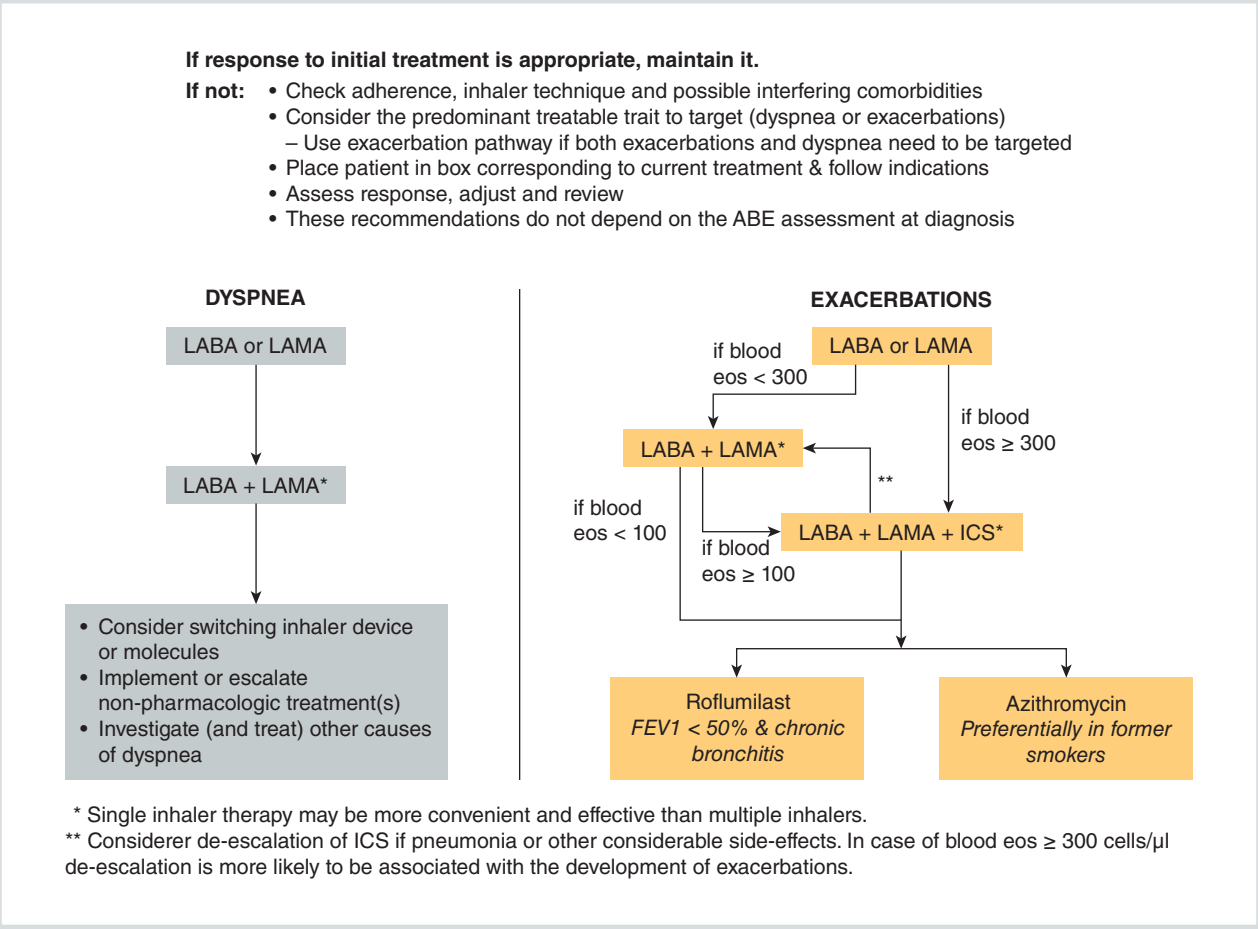

Figure 1. Follow-up pharmacological treatment for stable COPD depending on dyspnea or acute exacerbations according to GOLD guidelines[25]. FEV_1: Forced expiratory volume in one second; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonist.

ex-smokers or light smokers, given their lower efficacy in active smokers[25]. Figure 1 shows the policy on chronic macrolide use as set out in the GOLD guidelines.

CONTRAINDICATIONS

Adverse events and therapeutic monitoring

Treatment with chronic macrolides added to inhale therapy is increasingly prevalent and should be reserved for specific units with experience in the management and control of severe COPD, such as respiratory day hospitals, to monitor its potential adverse events[28-30]. A recent multicenter study that evaluated the efficacy of respiratory day hospitals showed that up to 25-30% of patients treated at these units for AECOPD received prophylactic treatment with weekly cyclic azithromycin[31]. All patients who start treatment with chronic macrolides should be monitored for potential adverse events and long-term complications detailed here:

Cardiovascular system

Macrolides are associated with prolongation of the Q-T interval in the electrocardiogram (ECG) and therefore with a potential risk of tachyarrhythmias such as "*Torsade de pointes*"[32]. Therefore, it is mandatory to perform an ECG before starting treatment to confirm that the patient has a corrected Q-T (QTc) <450 ms. This ECG should be repeated after the start of the macrolide use or after the addition of any other drug that could also potentially prolong the QTc. In patients with QTc prolongation > 450 ms, treatment should be discontinued. Chronic macrolides should be used with caution in patients with cardiac comorbidity, as well as polymedicated patients. It should be borne in mind that quinolones, especially moxifloxacin and levofloxacin, are antibiotics that can also potentially prolong QTc; therefore, when they are used in a patient with AECOPD who is already receiving chronic macrolides, they should be suspended during the cycle with the quinolone antibiotic.

Hearing system

Macrolides are potentially ototoxic, and their chronic use can lead to bilateral sensorineural hearing loss that generally affects low frequencies such as speech[33]. This complication is dose dependent and usually reversible with withdrawal of the drug. The presence of renal insufficiency may increase the risk of ototoxicity; therefore, in patients with reduced creatinine clearance, macrolides should be used at lower doses. In risk groups such as the elderly in whom presbycusis is frequent, an audiometry before the start of treatment is especially recommended, as well as an anamnesis directed at hearing loss in successive control visits.

Digestive system

Among the most frequent causes of early withdrawal of chronic macrolides are digestive disorders, mainly diarrhea, and less frequently nausea and/or abdominal pain. These side effects are caused by the ability of macrolides to stimulate intestinal motility receptors[34]. They are much more common with erythromycin than with neomacrolides and are dose dependent and may, therefore, improve with dose reduction.

Hepatobiliary system

Transient cholestasis is the most common analytical abnormality. Liver function abnormalities are usually mild or moderate, and severe hepatotoxicity is very infrequent, especially if we use azithromycin[35].

Pharmacological interactions

Macrolides produce an inhibition of cytochrome CYP(P450)3A, less significant with azithromycin than with clarithromycin and erythromycin, which can induce toxic concentrations of statins, calcium channel blockers, amiodarone, and colchicine through the inhibition of CYP3A4. Through inhibition of P-glycoprotein, azithromycin, and other neomacrolides can increase plasma concentrations of various substrates such as digoxin, everolimus, sirolimus, tacrolimus, and posaconazole. Macrolides can also interact with warfarin levels[36].

Microbiological control

Treatment with chronic macrolides is associated with a higher risk of the development of resistance to macrolides in macrolide sensitive colonizing germs. Given that macrolides are among the first-line treatments for atypical mycobacterial infections, a mycobacteriological sputum culture should always be performed before starting treatment to rule out mycobacterial infection. This practice avoids covert monotherapy, with the potential risk of missing a first-line drug for the treatment of these microorganisms.

Table 2 specifies the controls that should be performed in all patients with COPD who are started on chronic macrolides.

Table 2. Starting and follow-up controls in COPD patients treated with chronic macrolides

Adverse event	Monitoring	Recommendation
Allergy	Before starting	Rule out macrolide allergy (or intolerance)
Pharmacological interactions	Anytime	Check associated treatments
Hepatotoxicity	Before starting At 6-12 weeks Annually	Analysis of liver function Monitoring liver function. Stop treatment if AST/ALT increases x3 the upper limit of normal values
Cardiotoxicity	Before starting At 6-12 weeks Anytime	ECG with initial measurement of QTc (QTc < 450 mseg) Monitoring QTc (QTc < 450 mseg). Repeat ECG if a new drug that potentially prolongs QTc is added to chronic therapy
Ototoxicity	Before starting	Control audiometry in patients at risk (elderly)
Mycobacterial infection	Before starting	Sputum culture to rule out mycobacterial infection

COPD: chronic obstructive pulmonary disease, ECG: electrocardiogram.

Long-term safety and efficacy

Once the efficacy of chronic macrolides for the prevention of AECOPD has been demonstrated in controlled studies lasting 6-12 months, it remains to be defined whether this efficacy, as well as the clinical safety, is maintained when these agents are used for a longer period of time. On this point the clinical guidelines do not take a clear position; they recommend re-evaluating the risk-benefit of its continuation on an annual and individualized basis in each patient[26,27]. In a study of a cohort of 109 patients with COPD GOLD D treated with cyclic azithromycin (≥4 AECOPD/previous year) at a dose of 500 mg 3 times a week, our group recently published data on clinical efficacy, microbiology, and safety in 39 patients who had received long-term treatment during a follow-up period lasting 2-3 years. Chronic azithromycin demonstrated sustained efficacy over time with mean reductions in AECOPD (with respect to the previous year) of 56%, 70%, and 40% at 12, 24, and 36 months of treatment, respectively, and hospitalization rates of 62%, 75%, and 39% at these same time points. In patients considered responders (≤ 1 moderate AECOPD during at least 12 months of treatment with azithromycin) who underwent an azithromycin withdrawal trial, it had to be reintroduced within a few months in 60% of cases due to recurrence of AECOPD[37]. These data are in agreement with the previous studies that show how the efficacy of the treatment is lost with its withdrawal[24,25]. At the microbiological level, AECOPDs due to common germs were reduced by 12% at 12 months and by 17% at

24 months. The isolation of common germs was reduced by 70% during treatment, due to the antimicrobial effect of the macrolide; however, resistance to these agents increased from 1% of strains at baseline to 50% of those isolated during follow-up with chronic azithromycin. AECOPDs with isolation of *P. aeruginosa* increased by 7% and 13% at 12 and 24 months of follow-up[37]. The previous studies that have evaluated the impact on the bronchial microbiome after 12 months of treatment with erythromycin at a dose of 250 mgr/day in patients with non-CF BQ have already reported significant changes in the microbiota of non-colonized patients by *P. aeruginosa*, with a reduction in the relative abundance of *H. influenzae* and an increase in macrolide-resistant germs, including *P. aeruginosa*, similar to the results observed in the COPD patients included in our study[38]. These data highlight the importance of close microbiological monitoring of COPD patients who are candidates for treatment with chronic macrolides. Finally, as far as safety is concerned, in patients treated for more than 2 years with azithromycin, treatment only had to be suspended in 5% of cases due to the appearance of hearing loss. In patients treated for < 2 years, treatment was withdrawn in 7% due to digestive causes, in 5% due to hearing loss, and in 3% due to analytical alterations in liver biology.

MACROLIDE OF CHOICE AND DOSAGE

The long-term chronic macrolide regimens that have shown efficacy for preventing AECOPD have been erythromycin 250 mg/12 h for 1 year[23], azithromycin 250 mg/day for 1 year[18], azithromycin 500 mg/day 3 days a week for 1 year[19,20], with a single study demonstrating the efficacy of this last regimen beyond the 1st year of treatment and up to 3 years of follow-up[37]. The results of the different studies have coincided in showing a significant reduction in AECOPD. However, the populations studied and the macrolide regimens were different, so it is difficult to make a firm recommendation. The indication of long-term treatment with macrolides should be reserved for high-risk patients with at least three exacerbations during the previous year despite following adequate inhaled treatment[19,20,37]. In our opinion, azithromycin should be considered the macrolide of choice, since its longer half-life allows dosing on alternate days and because it has a better antimicrobial spectrum, better digestive tolerance and a lower risk of drug interactions than erythromycin. By analogy to the therapeutic regimens used in patients with similar characteristics affected by BQ[36], the recommended dose would be azithromycin 500 mg/day/3 days a week (Monday, Wednesday, and Friday) for a period of at least 6 months to a year. In patients with low weight (< 50 Kg), digestive intolerance with this dose or comorbidity due to associated renal failure, the dose should be reduced to 250 mg/day/3 days per week. Hardly any comparative studies have been carried out between azithromycin doses of 500 and 250 mg in terms of clinical efficacy, or the risk of developing microbial resistance or side effects. Our group has recently compared the clinical efficacy of the two doses for chronic treatment (1 year) of patients with severe COPD and repeated exacerbations. One group of patients (n = 37) was prospectively recruited as a multicenter cohort and received

treatment with azithromycin 250 mg/day/ 3 days a week (Monday, Wednesday, and Friday), while the other group (n = 21) was a historical single-center cohort treated with azithromycin 500 mg/day/3 days a week (Monday, Wednesday, and Friday). No differences were observed between groups in terms of AECOPD (moderate and severe) between the year before and the year after starting treatment (66 vs. 60%, p = 0.55) nor in terms of hospital admissions (61% vs. 45%, p = 0.07)[39]. Therefore, in patients who present non-serious adverse events with high-dose chronic azithromycin therapy, the dose can be decreased without reducing clinical efficacy. In the elderly, low weight (< 50 Kg), or highly comorbid patients, it may also be possible to start treatment with azithromycin at the lower dose without losing clinical efficacy.

In patients who respond well (i.e., absence or significant reduction of AECOPD), treatment can be maintained for more than a year, and a withdrawal trial can be considered in the summer periods (June–September) with or without subsequent reintroduction, depending on the tolerance of withdrawal and individualized risk assessment for each patient. If treatment is maintained for more than a year, it is also possible to continue it at a lower dose (from 500 to 250 mg/day/3 days per week). It is important to note that chronic treatment carries an associated risk of development of resistance to macrolides as well as the appearance of potential adverse effects, so its use should be reserved for reference centers that are able to carry out adequate clinical, auditory, hepatic, biochemical, and microbiological follow-up, with an identification of microorganisms in sputum and study of sensitivity to antibiotics.

CONCLUSIONS

The use of chronic macrolides in severe COPD has been shown to be an effective therapeutic alternative for the prevention of AECOPD. It should be reserved for patients who, despite maximum inhaled treatment, persist with at least three moderate-severe AECOPDs in the previous year. Azithromycin is the macrolide of choice, due to its better dosing profile (3 times a week) as well as its lower risk of drug interactions.

FUNDING

None.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the manuscript.

DISCLOSURES

Nothing to disclose.

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