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REVIEW ARTICLE

# Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases

**P. Zarogoulidis · N. Papanas · I. Kioumis · E. Chatzaki · E. Maltezos · K. Zarogoulidis**

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**Abstract**
*Background* Macrolides have long been recognised to exert immunomodulary and anti-inflammatory actions. They are able to suppress the "cytokine storm" of inflammation and to confer an additional clinical benefit through their immunomodulatory properties.
*Methods* A search of electronic journal articles was performed using combinations of the following keywords: macrolides, COPD, asthma, bronchitis, bronchiolitis obliterans, cystic fibrosis, immunomodulation, anti-inflammatory effect, diabetes, side effects and systemic diseases.
*Results* Macrolide effects are time- and dose-dependent, and the mechanisms underlying these effects remain incompletely understood. Both in vitro and in vivo studies have provided ample evidence of their immunomodulary and anti-inflammatory actions. Importantly, this class of antibiotics is efficacious with respect to controlling exacerbations of underlying respiratory problems, such as cystic fibrosis, asthma, bronchiectasis, panbrochiolitis and cryptogenic organising pneumonia. Macrolides have also been reported to reduce airway hyper-responsiveness and improve pulmonary function.
*Conclusion* This review provides an overview on the properties of macrolides (erythromycin, clarithromycin, roxithromycin, azithromycin), their efficacy in various respiratory diseases and their adverse effects.

**Keywords** Antibiotics · Inflammation · Immunomodulation · Macrolides

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## Introduction

Macrolides are a group of antibiotics whose activity is ascribable to the presence of the macrolide ring, a large macrocyclic lactone ring, to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. Lactone rings usually harbour 14, 15 or 16 members. Members of the macrolide group are divided into four categories: (1) Antibiotic macrolides: These may be further divided into the US FDA-approved azithromycin (AZM, unique in that it does not inhibit CYP3A4 and is technically an azalide derived from macrolides), clarithromycin, dirithromy-

cin, erythromycin, roxithromycin, telithromycin), and the not US FDA-approved [carbomycin A, josamycin, kitamycin, midecamycin/midecamycin acetate, oleandomycin, solithromycin, spiramycin (approved in Europe and other countries), troleandomycin (used in Italy and Turkey), tylosin/tylocine (used in animals)]. (2) Ketolides: Ketolides are a new class of antibiotics that are structurally similar to macrolides. They are used to treat respiratory tract infections caused by macrolide-resistant bacteria. Ketolides are especially effective as they generally have two ribosomal binding sites, while the newer fluoroketolides have three ribosomal interaction sites. Ketolides include telithromycin, cethromycin, solithromycin (the first fluoroketolide), spiramycin (used for toxoplasmosis), ansamycin, oleandomycin, carbomycin, tylomycin. (3) Non-antibiotic macrolides: Tacrolimus, pimecrolimus and sirolimus, which are used as immunosuppressants or immunomodulators, are also macrolides. They have similar activity to cyclosporin. (4) Toxic macrolides: A variety of toxic macrolides produced by bacteria have been isolated and characterised, such as the mycolactones (Fig. 1) [1]. Mycolactone (A–F) is a polyketide-derived macrolide, which is produced and secreted by a group of closely related pathogenic mycobacteria that have been assigned a variety of species names including *M. ulcerans*, *M. liflandii* (an unofficial designation), *M. pseudoshottsii*, and some strains of *M. marinum*. These mycobacteria are collectively referred to as mycolactone-producing mycobacteria (MPM) [2, 3].

Antibiotic macrolides are used to treat infections caused by Gram-positive bacteria, *Streptococcus pneumoniae* and *Haemophilus influenzae* infections, such as respiratory tract and soft-tissue infections. The antimicrobial spectrum of macrolides is wider than that of penicillin. Of note, macrolides usually do not cause allergic reactions, unlike penicillin and other beta-lactam agents. Therefore, macrolides are commonly used in patients with allergy to penicillin. Beta-haemolytic streptococci, pneumococci, staphylococci and enterococci are usually susceptible to macrolides. Unlike penicillin, macrolides have also been shown to be effective against *Legionella pneumophila*, mycoplasma, mycobacteria, some rickettsias and chlamydia.

Macrolides act by inhibiting bacterial protein biosynthesis. This is accomplished by two main mechanisms. The first involves preventing peptidyl-transferase from adding the peptidyl attached to transfer-RNA to the next amino acid (similarly to chloramphenicol), as well as by inhibiting ribosomal translocation [4]. The second mechanism is premature dissociation of the peptidyl-transfer-RNA from ribosomes [5].

Macrolides act as antibacterials by reversibly binding to the P site on the 50S subunit of bacterial ribosomes. This action is mainly bacteriostatic, but it can also become bactericidal at high concentrations. Macrolides tend to accumulate within leukocytes and are therefore transported into the site of infection. Two properties are inherent in this

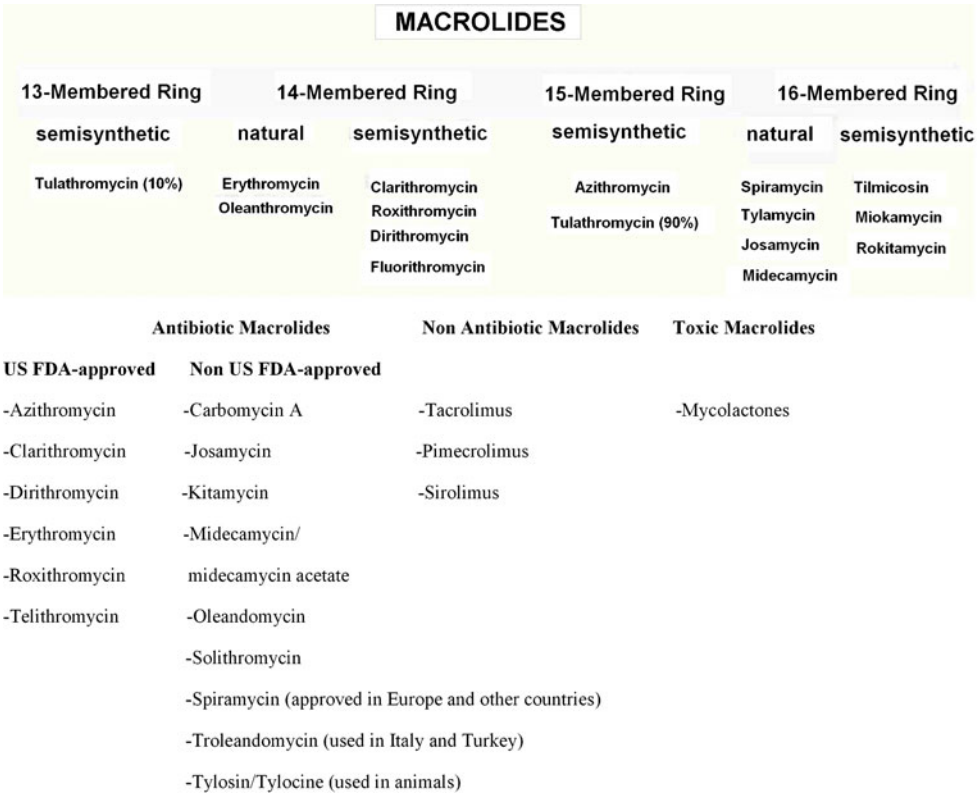


**Fig. 1** Categories of macrolides

group of drugs, the immunomodulatory and the anti-inflammatory actions, ensuring excellent efficacy in a wide spectrum of infections [6–42].

The present review provides an overview of the properties of macrolides (erythromycin, clarithromycin, roxithromycin, azithromycin), their efficacy in a range of respiratory disease, and their adverse effects.

## Search strategy

We performed an electronic article search through PubMed, Google Scholar, Medscape and Scopus databases, using combinations of the following keywords: macrolides, COPD, asthma, bronchitis, bronchiolitis obliterans, cystic fibrosis, immunomodulation, anti-inflammatory effect, diabetes, side effects and systemic diseases. All types of articles (randomised controlled trials, clinical observational cohort studies, review articles, case reports) were included. Selected references from identified articles were searched for further consideration.

## Anti-inflammatory and immunomodulatory properties

A growing body of evidence has established that macrolides may induce anti-inflammatory effects. The latter are time- and dose-dependent, and the underlying mechanisms remain incompletely understood. Macrolides can down-regulate prolonged inflammation, increase mucus clearance, prevent the formation of bacterial biofilm, and enhance or reduce activation of the immune system. Furthermore, macrolides may influence phagocyte activity by modifying

**Table 1** Anti-inflammatory and immunomodulatory properties of macrolides

| Target | Effects |
|---|---|
| Mucus production and rheological properties | Decrease volume/secretion; increase mucociliary clearance, elasticity and ciliary motility |
| Bronchial hyper-responsiveness | Decreased bronchial hyper-responsiveness/endothelin-1; inhibition of bronchial muscle contraction |
| Epithelial damage and bioactive phospholipids | Protection against reactive oxygen species; protection of the respiratory ciliated epithelium |
| Adhesion | |
| Molecules | Reduction of the expression of ICAM-1, sICAM-1, e-selectin, β-2-integrins (CD11b/CD18), VCAM-1, LFA3, Mac-1, beta-2-integrins (CD11b/CD18) |
| Bacterial | Decrease in bacterial adhesion to the epithelium |
| Cytokines/chemokines | Suppression of IL-1b/NTF in monocytes; suppression of IL-1b,IL-4, IL-5, IL-6, IL-8, IFN-γ, PGF1a, PGE2, NTFa, GM-CSF in mast cells; no changes in IL-2 and LTB4; suppression of IL-8, ENA78, MIP-1 in macrophages and leucocytes; inhibition of eotaxin and GM-CSF; decrease in CCL-2 and CX |
| T cells | Dose-dependent inhibition of the production of IL-4, IL-5, IL-10, IL-13 |
| Production of oxidising species | Increase/decrease of NO release via cNOS/iNOS; decrease in NADPH oxidase and nitroso-synthase |
| Polymorphonuclear cells | Inhibition of neutrophil elastase/anions; stabilisation of cell degranulation; accelerated neutrophil apoptosis due to increased cAMP |
| Signal protein | Decrease in VEGF; increase in EGF |
| Enzymes | Reduction in glutathione S-transferase (GST) activity |
| Effects on *Pseudomonas aeruginosa* | Reduction in bacterial adhesion to the epithelium; altered virulence factors: decreased biofilm production and reduced mobility; altered quorum sensing system: reduced transcription of implicated genes (Iasl and rhlR); decreased expression of stress proteins (Gro-ELK) |
| Plasma antibodies | No effects in BPI-Anca |
| Cell junctions | Increased expression of molecules for tight junctions, claudins, occludins, JAM |
| Membrane transporters | Increased expression of MPR1 and MDR1 |
| Intracellular signaling metabolic pathways | Altered protein kinase pathway (MAPK): JNK |
| Nuclear transcription factors and gene regulation pathways | Changes in NF-I-B and AP-1 DNA junctions and promoters for proinflammatory cytokine genes; inhibition of the expression of genes coding for mucoid proteins via ERK |

*DNA* Deoxyribonucleic acid, *AP-1* activator protein-1, *BPI-Anca* antineutrophil cytoplasmic autoantibodies against bacterial permeability-increasing protein, *CD* cluster of differentiation, *ERK* extracellular signal regulated kinase, *GM-CSF* granulocyte-macrophage colony stimulating factor, *ICAM-1* intercellular adhesion molecule-1, *IFN* interferon, *IL* interleukin, *JAM* junction adhesion molecules, *JNK* c-jun N-terminal kinase, *LFA-3* lymphocyte function-associated antigen 3, $LTB_4$ leukotriene B-4, *Mac-1* macrophage adhesion molecule 1, *MAPK* mitogen active protein kinase, *MDR1* multi-drug resistance protein 1, *MPR1* multi-drug resistance associated protein 1, *NADPH* nicotinamide adenine dinucleotide phosphate reduced, *NF-κ-B* nuclear factor-kappa B, $PGE_2$ prostaglandin E-2, $PGF_{1a}$ prostaglandin F-1a, *TNF-a* tumour necrosis factor alpha, *VCAM-1* vascular cell adhesion molecule, *VEGF* vascular endophelial growth factor, *EGF* epidermal growth factor

**Table 2** Macrolide studies evaluating respiratory capacity

| Study | Macrolide | $FEV_1$ | FVC | DLCO | PEF/FEF/VC | Background | Overall | Time | Exacerbations | Dose | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| He Z-Y (2010) | EMC | √ | √ | – | – | COPD | Increase | 6 months | Decrease | 475 mg | [101] |
| Seemungal TA (2008) | EMC | √ | – | – | – | COPD | Increase | 6 months | Decrease | 500 mg | [100] |
| Zervos M (2007) | AZM | √ | | | – | COPD | Increase | 3 day | Decrease | 500 mg | [106] |
| Watz H (2007) | Review | √ | – | – | – | COPD | Increase | 5/7 day | Decrease | Review | [110] |
| Gotfried MH (2004) | CAM | √ | – | – | – | COPD | Increase | 5 day/7 day | Decrease | 1,000 mg | [107] |
| Lode H (2004) | CAM | √ | – | – | – | COPD | Increase | 1 year | Decrease | 500 mg | [122] |
| Piacentini GL (2007) | AZM | √ | – | – | – | Asthma | Increase | 2 months | Decrease | 250–500 mg | [155] |
| Richeldi L (2005) | Review | √ | √ | – | – | Asthma/CF | No difference | 1 month | Decrease | Review | [151] |
| Ferrara G (2005) | Review | √ | √ | – | – | Asthma/CF | Increase/no difference | Review | Decrease | Review | [158] |
| Gryglicka B (2003) | AZM | √ | √ | | – | Asthma | Increase | 1 a week | Decrease | 1,000 mg | [169] |
| Ekici A (2002) | AZM | √ | – | – | – | Asthma | No difference | 2 months | Decrease | 250 mg | [160] |
| Black PN (2001) | RXM | – | – | – | √ | Asthma | Increase | 6 weeks | No difference | 300 mg | [167] |
| Shimizu T (1997) | RXM | √ | – | – | – | Asthma | No difference | 2 months | No difference | 150 mg | [170] |
| Cai Y (2011) | Review AZM | √ | √ | – | – | CF | Increase | Review | Decrease | Review | [195] |
| Saiman L (2010) | AZM | √ | – | – | – | CF | No difference | 3 months | No difference | 250–500 mg | [224] |
| Kabra SK (2010) | AZM | √ | – | – | – | CF | No difference | 6 months | No difference | 250–500 mg | [198] |
| Oliynyk I (2009) | AZM | √ | – | – | – | CF | Increase | 6 months | Decrease | 500 mg | [199] |
| Florescu DF (2009) | AZM | √ | √ | – | – | CF | Increase | Review | Review | Review | [200] |
| Steinkamp G (2008) | AZM | √ | – | – | – | CF | Increase | 2 months | Decrease | 500–1,250 mg | [203] |
| Nguyen D (2007) | AZM | √ | – | – | – | CF | Increase | 6 month | Decrease | 250 mg | [205] |
| Tramper-Stranders GA (2007) | AZM | √ | – | – | – | CF | Increase | 3 years | Decrease | 250–500 mg | [53] |
| Clement A (2006) | AZM | √ | – | – | – | CF | Increase/no difference | 12 months | Decrease | 250–500 mg | [223] |
| Equi AC (2006) | AZM | √ | √ | – | – | CF | Increase/no difference | 2 weeks | Decrease | 500 mg | [194] |
| Hansen CR (2005) | AZM | √ | √ | – | – | CF | Increase | 12 months | Decrease | 250 mg | [202] |
| Saiman L (2005) | Review AZM | √ | – | – | – | CF | Increase | 3 months | Decrease | 250–500 mg | [227] |
| Pukhalsky AL (2004) | CAM | √ | – | – | – | CF | Increase | 12 months | Decrease | 250 mg | [218] |
| Southern KW (2004) | Review AZM | √ | – | – | – | CF | Increase | Review | Decrease | Review | [70] |
| Carr RR (2004) | Review | √ | – | – | – | CF | Increase | 3 weeks to 6 months | Decrease | Review | [213] |
| Saiman L (2004) | Review | √ | – | – | – | CF | Increase | Review | Decrease | Review | [211] |
| Saiman L (2003) | AZM | √ | – | – | – | CF | Increase | 3 months | Decrease | 250–500 mg | [222] |
| Wolter J (2002) | AZM | √ | √ | – | – | CF | Increase | 3 months | Decrease | 250 mg | [220] |
| Anwar GA (2008) | AZM | √ | – | – | – | BR | Increase | 3 months | Decrease | 250 mg | [235] |
| Cymbala AA (2005) | Review AZM | √ | √ | – | √ | BR | Increase | 6 months | Decrease | Review | [237] |
| Davies G (2004) | AZM | √ | √ | √ | – | BR | Stable | 10 months | Decrease | 250 mg | [243] |
| Tsang KW (1999) | EMC | √ | √ | – | – | BR | Increase | 2 months | Decrease | 500 mg | [239] |

**Table 2** (continued)

| Study | Macrolide | $FEV_1$ | FVC | DLCO | PEF/FEF/VC | Background | Overall | Time | Exacerbations | Dose | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Koh (1997) | RXM | √ | – | – | – | BR | Stable | 12 weeks | Stable | 250–500 mg | [244] |
| Jain R (2010) | AZM | √ | – | – | – | DPB | Increase | 5 day | Decrease | 250–500 mg | [256] |
| Vos R (2010) | AZM | √ | – | – | – | DPB | Increase | 5 years | Decrease | 250 mg | [266] |
| Fietta AM (2008) | AZM | √ | – | – | – | DPB | Increase | Review | Decrease | 250 mg | [248] |
| Gottlieb J (2008) | AZM | √ | – | – | – | DPB | Increase | 6 months | Decrease | 250 mg | [249] |
| Porhownik NR (2008) | AZM | √ | – | – | – | DPB | Increase | 12 months | Decrease | 250 mg | [257] |
| Verleden GM (2006) | AZM | √ | – | – | – | DPB | Increase | 6 months | Decrease | 250 mg | [260] |
| Shitrit D (2005) | AZM | √ | – | – | – | DPB | Increase | 10 months | No difference | 750 mg | [250] |
| Yates B (2005) | AZM | √ | – | – | √ | DPB | Increase | 3 months | Decrease | 250 mg | [258] |
| Khalid M (2005) | AZM | √ | √ | – | – | DPB | Increase | 3 months | Decrease | 500 mg | [265] |
| Kadota J (2004) | EMC, RXM, CAM | √ | √ | – | – | DPB | Increase | 7–9 years | Decrease | 600, 150, 250 mg | [251] |
| Verleden GM (2004) | AZM | √ | – | – | – | DPB | Increase | 3 months | Decrease | 250 mg | [230] |
| Kadota J (2003) | CAM | √ | – | – | – | DPB | Increase | 4 years | Decrease | 500 mg | [254] |
| Gerhardt SG (2003) | AZM | √ | – | – | – | DPB | Increase | 3 months | Decrease | 250 mg | [262] |
| Liu Y (1999) | Review | √ | √ | – | – | DPB | Increase | 24 months | Decrease | Review | [255] |
| Lee J (2011) | Macrolide | √ | √ | √ | – | COP | Increase | 15 days | Decrease | – | [292] |
| Ichikawa Y (1993) | EMC | √ | √ | √ | √ | COP | Increase | 4 weeks | Decrease | 600 mg | [284] |

Pulmonary function tests: *$FEV_1$* forced expiratory volume in 1 s, *FVC* forced vital capacity, *DLCO* diffusing capacity of the lung for carbon monoxide, *VC* vital capacity, *PEF* peak expiratory flow, *FEF* forced expiratory flow. Background: *COPD* chronic obstructive pulmonary disease, *CF* cystic fibrosis, *BR* bronchiectasis, *DPB* diffused panbronchiolitis, *COP* cryptogenic organising pneumonia. Macrolides: *EM* erythromycin, *AZM* azithromycin, *RXM* roxithromycin, *CAM* clarithromycin

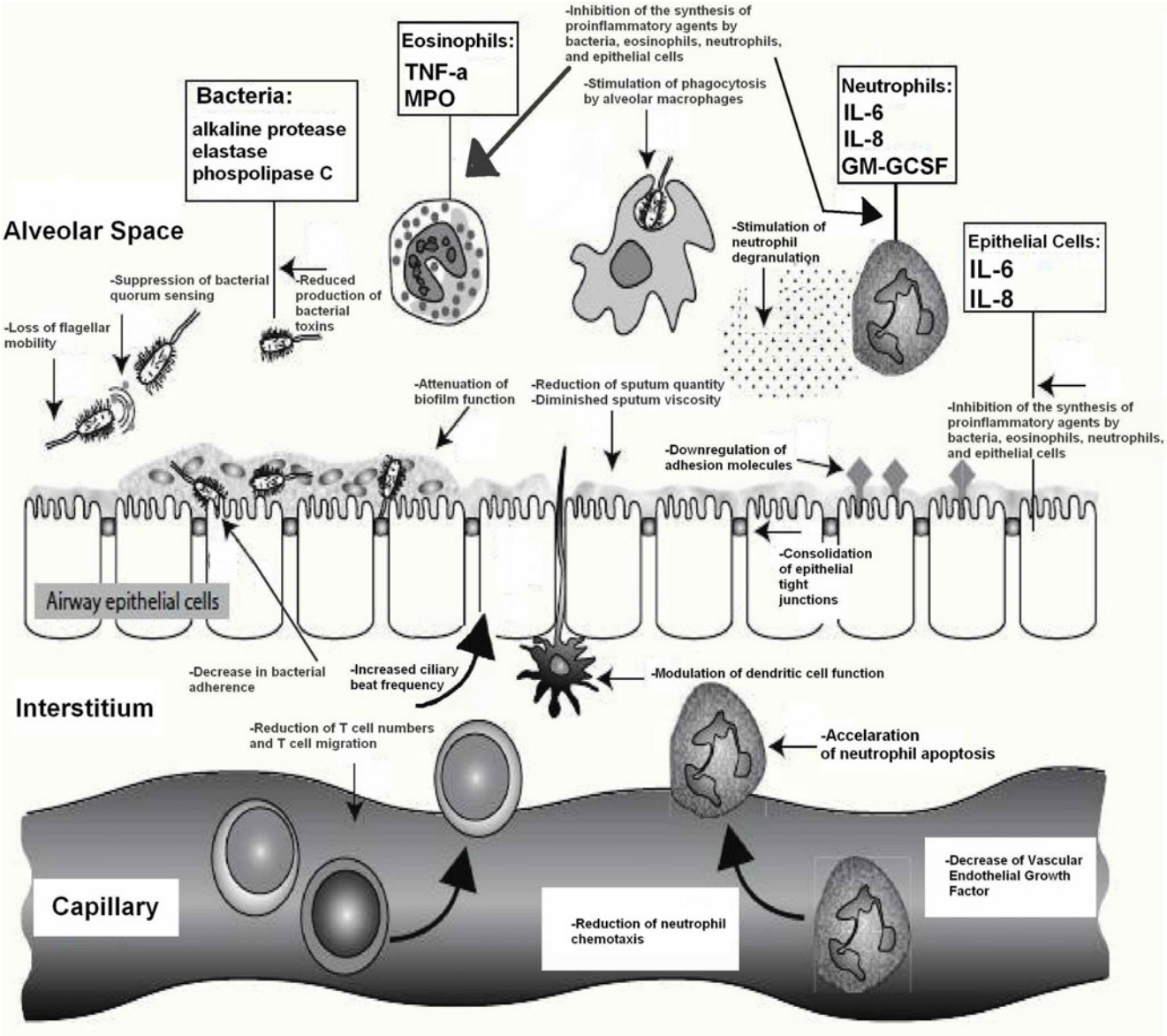


**Fig. 2** Anti-inflammatory and immunomodulatory actions: underlying mechanisms. Figure reproduced and modified from Altenburg, J. et al: Respiration 2011;81:67–74 with permission from S. Karger AG Basel

their miscellaneous functions (chemotaxis, phagocytosis, oxidative burst, bacterial killing and cytokine production) (Tables 1, 2) (Figs. 2, 3).

Macrolides also demonstrate several immunomodulatory activities both in vitro and in vivo: they downregulate inflammation, decrease the production of reactive oxygen species, inhibit neutrophil activation and mobilisation, accelerate neutrophil apoptosis, and block the activation of nuclear transcription factors. Anti-inflammatory and immunomodulatory actions are herein presented together, since they are closely interrelated by common underlying mechanisms (Fig. 3).

Macrolides have been demonstrated to exert a chemotactic and phagocytotic action on in vitro production of inflammatory cytokines/mediators in sulfur mustard (SM)-exposed monocyte THP-1 cells (pro-monocytic leukaemia cell line). First, SM-induced overproduction of pro-inflammatory cytokines and mediators is reduced, suggesting that macrolides might be of value as vesicant respiratory therapeutic adjuncts [43]. In other studies, clarithromycin and azithromycin treatment decreased interleukin (IL)-8, IL-4, IL-5, IL-13, chemokine (C-X-C motif) ligand 2 (CXCL2), chemokine ligand 2 (CCL2), chemokine ligand 3 (CCL3) and chemokine ligand 4 (CCL4) in bronchoalveolar lavage. At the same time, they markedly reduced inflammatory cell accumulation in bronchoalveolar lavage and in the lungs, as revealed by histopathological examination. Furthermore, clarithromycin-induced reduction in inflammation was accompanied by normalisation of airway hyper-responsiveness [44–49].

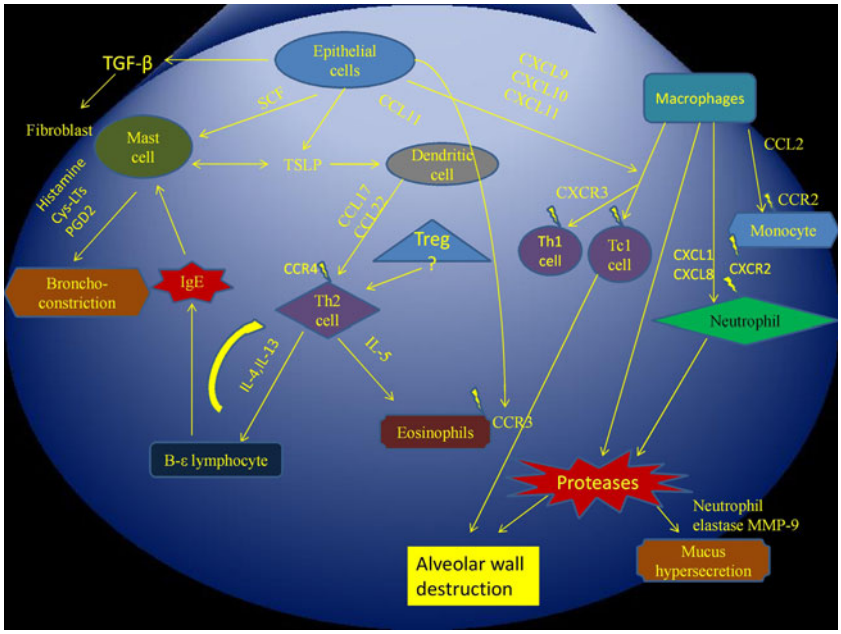


**Fig. 3** Mechanisms of respiratory tract inflammation (based on references [43–62])

Kumar et al. [37] described decreased myeloperoxidase (MPO) activity, malondialdehyde (MDA) and nitric oxide (NO) production, ultimately contributing to diminished acute lung injury during pulmonary infection. Macrolides accumulate within cells, suggesting that they may interact with receptors or second messengers responsible for the regulation of cell cycle and cellular immunity. An undesirable action of long-term therapy may thus be the induction of antimicrobial resistance. Non-antimicrobial macrolides are now being developed as potential immunomodulatory agents [17, 50–61]. In another enquiry, telithromycin inhibited the production of pro-inflammatory mediators and the activation of NF-kappaB in murine cells stimulated in vitro. This was documented in murine splenocytes and the murine macrophage cell line RAW 264.7. Spleen cells from BALB/c-untreated mice (the animal lacks a thymus, is unable to produce T-cells, and is therefore immunodeficient) and RAW 264.7 mouse leukaemic monocyte macrophage cell line (Abelson murine leukaemia virus-induced tumour) macrophages were cultured in the presence of telithromycin.

Proliferation and apoptosis (colourimetric assay) and cytokine production (enzyme immunoassay) of spleen cells in response to LPS and concanavalin A (Con A), and nitric oxide (NO) (colorimetric assay) and cytokine production by lipopolysaccharide-stimulated RAW 264.7 cells were determined [18]. In addition, telithromycin has been found to suppress TNF-alpha production [24]. Macrolides initially decrease, then increase, and finally suppress cytokine secretion from normal human bronchial epithelial cells. This is mediated through inhibition and activation of extracellular signal-regulated kinases (ERK) and subsequent reversible delay in cell proliferation, probably through ERK. Consistent with such actions, macrolides appear to reduce mucin production and neutrophil migration by interfering with ERK signal transduction [10, 20].

Various studies have shown that growth factors and their receptors play a pivotal role in airway epithelial repair processes. The immunomodulatory effects are miscellaneous. Among these growth factor receptors, the epidermal growth factor receptor (EGFR) receptor has been documented to modulate epithelial cell migration and proliferation [62]. Available evidence suggests that many of these effects are due to the inhibition of extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation and nuclear factor kappa B (NF-kappaB) activation. The potential indirect activation of the EGF receptor via ERK1/2 activation is in line with the realisation that early, but not late phase, ERK1/2 activation is not inhibited by anti-EGF receptor antibodies.

## Azithromycin

Azithromycin (AZM) administration has been found to be associated with markers of alternative macrophage activation. These markers include the surface expression of the mannose receptor, the upregulation of arginase 1 and a decrease in the production of proinflammatory cytokines. Additionally, AZM increased the number of CD11b(+) monocytes and CD4(+) T cells infiltrating the alveolar compartment. A predominant proportion of CD11b(+) cells were Gr-1 positive [Gr-1(+)]. Granted that the latter cells are known to be immunoregulatory, this outcome highlights the immunomodulatory potential of AZM. The differences corresponded to decreases in neutrophil influx into the lung parenchyma. At the same time, characteristics of peribronchiolar inflammation were changed (Table 1, Fig. 2), even

though clearance of infectious organisms was not affected. Hence, the immunomodulatory effects of AZM are associated with the induction of alternative and regulatory macrophage activation characteristics during infection. In summary, AZM has been hitherto demonstrated to decrease neutrophil influx, increase monocyte and CD11b cell influx into the airway compartment, induce macrophage activation and reduce production of proinflammatory cytokines, without any effect on bacterial clearance [8, 9, 22].

Moreover, AZM exposure significantly decreased glutathione S-transferases (GSTs) [63] in specific GSTT1 (gene 22q11.2 chromosome) and GSTM1 (gene 1p13.1chromosome) mRNA and protein expression in IB3-1 [a mutant cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel genotype of D508/W1282X] [64], restoring the levels to those observed in non-cystic fibrosis C38 cells, which also express lower levels of gamma-glutamyltransferase (GGT) activity than IB3-1. In tracheobronchial submucosal gland cell line 2CFSMEo cells, another CF cell line, AZM reduced GSTT1 by 45% and GSTM1 mRNA levels by 45% [65]. AZM reduced GST activity by approximately 25 and 40% in IB3-1 and 2CFSMEo cells respectively. GSTP1 was similarly expressed in all CF and non-CF cells and was unaffected by AZM. The anti-inflammatory cytokine IL-10 also downregulated GST activity at similar levels, implying a potential link between GST inhibition and the anti-inflammatory properties of AZM. In bronchoalveolar lavage of CF mice homozygous for the F508 del mutation, GSTM1 protein levels were hardly detectable after AZM treatment. The relationship between increased GST expression and activity, along with its reversal by AZM treatment, suggest that this drug may harbour novel antioxidant properties. It now remains to be elucidated whether decreased GST activity directly contributes to the anti-inflammatory properties of AZM or whether it is merely a marker of the oxidative status in CF cells [66].

AZM has been evaluated in three cystic fibrosis airway epithelial cell lines (IB3-1, human bronchial epithelial 16HBE14o-AS3 and 2CFSMEo cells) and two isogenic non-CF cell lines (C38 and human bronchial epithelial 16HBE14o-S1), in order to investigate whether it could reduce tumour necrosis factor alpha (TNF-alpha) mRNA and protein levels by real-time quantitative PCR analysis and enzyme-linked immunosorbent assay (ELISA) respectively. The effects on the DNA binding of nuclear factor (NF)-kappaB and specificity protein 1 (Sp1) were explored by ELISA. AZM did not alter the mRNA expression levels of interleukin-6, a proinflammatory molecule not differentially expressed in CF and isogenic non-CF cells. However, it reduced the levels of TNF-alpha. The latter effect may be, partly at least, attributable to the inhibition of NF-kappaB and Sp1 DNA binding [67]. Furthermore, the ability to ameliorate the noxious effects of lipopolysaccharide (LPS) was assessed in three different LPS-induced mouse inflammatory models. It turned out that azithromycin (at 10 and 100 mg/kg) significantly attenuated the increase in plasma TNF-alpha concentration induced by intraperitoneal LPS infusion [38]. However, studies have hitherto been equivocal in this disorder and only topical administration has demonstrated safety and effectiveness [68–71].

## Clarithromycin

The immunomodulatory properties of clarithromycin were evaluated using female B6C3F1 mice and a series of immune assays to evaluate the changes in innate and acquired cellular and/or humoral immune responses. Cell activity was modified with reduced production of elastase and oxidising agents [72]. These immunomodulatory effects appear to result from an interaction with transcription factors regulating the expression of cell genes. In addition, clarithromycin reduced bronchial mucosal secretion, as well as production of *Pseudomonas* bacterial biofilm (Table 2) [73].

Another work looked at the immunomodulatory effect of 3-day continuous administration of clarithromycin in experimental sepsis resulting from multidrug-resistant *Pseudomonas aeruginosa*. It was noted that clarithromycin significantly reduced TNF-alpha release from blood monocytes [19]. Moreover, the immunomodulatory activities of macrolide antibiotics were examined in human lung carcinoma A549 cells in vitro and in a specific-pathogen-free (SPF) mouse model of pneumonia induced by *Mucoplasma pneumoniae* antigen in vivo. Clarithromycin (CAM) decreased the number of macrolide-sensitive and macrolide-resistant *Mucoplasma pneumoniae* in the lungs of gnotobiotic mice. The latter are born through caesarean delivery to prevent even the natural contamination that occurs during the delivery process. Babies are removed from mothers in germ-free condition and immediately placed in a purely sterile environment for research purposes. Thus, in SPF mice, CAM ameliorated the pulmonary inflammation induced by *Mucoplasma pneumoniae* antigens [11].

## Erythromycin

The receptor activator of NF-kappaB ligand (RANKL) and its signal downstream nuclear factor-kappaB (NF-kappaB) are critical regulators of immune responses. There is a correlation with NF-kappaB expression, proliferation and apoptosis of human Jurkat T cells [74]. Real time polymerase chain reaction (RT-PCR) and Western blotting analysis confirmed that erythromycin (EMC) and its two derivatives (1 and 2) could inhibit the expression of NF-

kappaB mRNA and protein [8, 9, 22]. This dataset indicates that EMC and its derivatives exert immunomodulatory effects, presumably through an interaction with NF-kappaB expression, P-selectin, E-selectin, vascular cell adhesion molecule-1 (VCAM-1) mRNA upregulation/expression of intercellular adhesion molecule-1 (ICAM-1), macrophage infiltration, but also reduce the level of RANKL [74–76]. Moreover, EMC was evaluated on transforming growth factor (TGF)-beta /Smad signaling fibroblasts. EMC and new derivates inhibited fibroblast proliferation and collagen production in human lung fibroblasts induced by TGF-beta. Augmentation of Smad3 mRNA was induced by TGF-beta. Mothers against decapentaplegic homologue 7 or Smad7 mRNA and p-Smad2/3 were inhibited by TGF-beta [77].

Furthermore, another mechanism appears to be the inhibition of T lymphocyte proliferation. In addition, IL-2 and IFN-gamma levels are significantly decreased and IL-4, IL-5, IL-8 and IL-13 levels significantly increased after EMC treatment. Similarly, activator protein 1 (AP-1) and nuclear factor (NF)-kappaB are both reported to be involved in gamma-glutamylcysteine synthetase (gamma-GCS) expression [78]. Thus, EMC can influence the oxidant-antioxidant equilibrium in human bronchial epithelial (HBE) cells, indicating an emerging option for the development of new drugs to target inflammatory diseases. In another work [79], T cell subsets including CD3+, CD4+ and CD8+ cells were evaluated after stimulation with concanavalin A (Con A) and phytohemagglutinin (PHA). CD8+ cells were more responsive to Con A compared to PHA. EMC therapy did not make a significant difference to the SIs when stimulated with PHA. CD3+, CD4+ and CD8+ cells in absolute numbers and CD4+/CD8+ ratios were not different among those harvested at three study points. These results did not support prolonged EMC administration in chronic diseases [79].

### Roxithromycin

Others have examined the in vitro effects of roxithromycin (RXM) on the release of inflammatory mediators from alveolar macrophages (AM) and neutrophils. RXM concentrations were significantly increased in the bronchoalveolar lavage cells of treated patients. In vitro experiments testify to an inhibitory effect of RXM on IL-8 release from AM and neutrophils [12]. Interleukin-8, neutrophil elastase and leukotriene B4 contributed to the neutrophilic inflammation in the airways of subjects with chronic lower respiratory tract infections, and the clinical effects of RXM may be attributed to the suppression of excess release of chemotactic mediators from inflammatory cells [12, 80]. Moreover, RXM at pharmacological concentration suppressed IFN-gamma production of CD45RA(−) T cells stimulated with immobilised anti-CD3, but not that of unfractionated T cells. RXM also preferentially suppressed IL-2 production of immobilised anti-CD3-stimulated CD45RA(−) T cells. Thus, RXM may preferentially suppress IFN-gamma production of memory T cells, but not that of naive T cells, so that this agent may be considered an emerging immunomodulator for the treatment of various autoimmune disorders with deranged CD45RA(−) T cell function [81]. RXM strongly inhibits the expression of VEGF mRNA and the production of VEGF. Furthermore, RXM suppresses activation of transcription factors AP-1 and SP-1, which represent critical factors in VEGF transcription in TNF-alpha-stimulated HPDL cells. In addition, it significantly inhibits TNF-alpha-induced c-Jun N-terminal kinase activation (JNP) and marginally inhibits extracellular signal-regulated kinase (ERK)1/2 activation, but not p38 mitogen-activated protein kinase activation. The inhibition of TNF-mediated VEGF and induction of Ets-1 suggest the potential therapeutic utility of RXM in chronic inflammatory conditions [81, 82].

Finally, recent data suggest that macrolides may have a beneficial immunomodulatory and/or neuroprotective effect on neuroimmunological and neurodegenerative diseases including multiple sclerosis, diabetic nephropathy and amyotrophic lateral sclerosis [21]. The anti-inflammatory properties were also investigated through different routes of administration namely inhalation and topical administration (for atopic dermatitis) [69, 71, 75, 83]. Thus, their immunomodulatory potential is being increasingly appreciated (Tables 1, 2).

## From bench to bedside: clinical applications of macrolides in respiratory diseases

### Macrolides and COPD

Airway and lung parenchyma inflammation are now known to play an important role in chronic obstructive pulmonary disease (COPD) [84]. Both neutrophil and eosinophil activation and recruitment have been observed, while several inflammatory mediators are involved in the inflammatory cascade [85]. From a practical viewpoint, patients with frequent exacerbations exhibit increased airway inflammation and a more rapid decline in lung function. Due to the growing understanding of the importance of inflammation in the pathogenesis of COPD, studies have focused on the development of methods suitable for the study of inflammation in such patients. Several biomarkers are measurable in sputum, bronchoalveolar lavage, bronchial biopsies, exhaled breath and blood [86, 87]. Neutrophils are the most widely represented cells in sputum samples from COPD patients and their number relates to the degree of airway obstruction and rate of FEV1 decline. Inflammatory

mediators involved in neutrophil recruitment are elevated in sputum from COPD patients and increase further during exacerbations [86, 87].

The ability of macrolides to influence airway inflammation has been known for many years. Macrolides exert anti-inflammatory and immunomodulatory actions through manifold mechanisms, such as inhibition of inflammatory cell chemotaxis, cytokine synthesis, adhesion molecule expression and reactive oxygen species production in COPD [40, 47, 88–99]. Enquiries into inflammatory biomarkers have yielded conflicting results, mainly due to the different times of drug administration. Indeed, both increase and decrease of biomarkers have been reported [93, 100–113]. However, differences have even been observed with the same type and duration of macrolide administration, so that further clarification is eagerly awaited. Several studies have demonstrated a reduction in exacerbations and stabilisation/increase in respiratory capacity (Table 2) [93, 100–113]. Several other studies have yielded such results regarding sputum/exacerbations reduction, improvement in pulmonary function test, pathogen count and cytokine inflammatory levels [47, 99]. The longest period of time that macrolides have ever been used in COPD patients is 1 year and the largest dose is 1,000 mg/week. Pulmonary function tests did not improve after this time. Severe gastrointestinal adverse effects have not been observed, but this appears to have been due to the low dose administered. The most common adverse effect observed was macrolide antibiotic resistance. In light of this evidence, it remains to be addressed whether prolonged macrolide administration could induce resistance to macrolides, ultimately leading to a reduction of their positive effect [50–53, 58–61, 114]. This concern arises from the recognised frequent colonisation of the respiratory tract of these patients by various pathogens.

Two parameters should be taken into account in terms of COPD exacerbations: (1) Pharmaceutical: treatment with tiotropium, long-acting b2-agonists and/or inhaled corticosteroids has shown a reduction of approximately 20–25% in the rate of exacerbations. (2) Bacterial: persistence of bacteria after antibiotic treatment is associated with persistent bronchial inflammation [115–117]. Additionally, presence of bacteria in the airway (bronchial colonisation) is associated with more frequent and severe exacerbations [118], and presence of a persistent pathogen after completion of antibiotic therapy is significantly associated with shorter infection-free period [119]. Taken together, this evidence prompts the hypothesis that vigorous antibiotic treatment to effectively eradicate bacteria may prevent recurrence, at least during the first months after the exacerbation, in harmony with the "fall and rise" hypothesis of bronchial bacterial infection [120].

Changes in serotype of infecting strains could offer a satisfactory explanation for late recurrence [121]. Attempts have also been made to identify any differences in outcomes among fluoroquinolone, levofloxacin, clarithromycin and other antibiotics [107, 122–132]. A significantly better bacterial eradication with levofloxacin compared to clarithromycin has been reported; however, no significant differences were noted in the exacerbation-free interval. This is in contrast with previous studies with gemifloxacin [133] and moxifloxacin [134]. Finally, the use of the exacerbation-free interval as the primary outcome takes into account the unique characteristics of exacerbations in COPD. This is important because most research on antibiotics in exacerbations of chronic bronchitis has been modelled on pneumonia studies. The two conditions, however, should not be interchangeably studied together. Indeed, the chance of bacterial infection as a cause of exacerbation decreases in patients with better lung function (such as those with acute pneumonia), granted that those with sufficient airway function are able to expectorate bacteria-containing mucosa and protect the respiratory tract from infections [135].

## Macrolides and asthma

Patients with asthma carry a greater risk of developing infections due to rhinoviruses, and the associated symptoms are more intense and persistent than among healthy subjects [136]. Viral and bacterial infections are the main cause of asthma exacerbations, but inadequate treatment is also important. Viral infection induces a host inflammatory response characterised by a predominantly neutrophilic infiltration, along with other cells, notably eosinophils, CD4þ and CD8þ cells, and mast cells. During this process, proinflammatory cytokines and chemokines, including IL-6, IL-8, IL-16, eotaxin, RANTES ("regulated on activation, normal T expressed and secreted," also known as cymokine ligand 5-CCL5), IP-10 and vascular endothelial growth factor (VEGF), are significantly increased [137–141]. Similar to viruses, atypical bacteria also induce bronchial inflammation by inducing the secretion of cytokines on the part of nucleated cells in peripheral blood [142] and alveolar macrophages [143–145]. In turn, bronchial epithelial cells induce the expression of TNF-α, IL-8, IFN-γ and nuclear factor kb (NF-kb), as well as the activation of the latter. In mice [146], both *Mucoplasma pneumoniae* and *Chlamydia pneumoniae* have been found to cause bronchial hyperresponsiveness (BHR) and inflammation [48, 147–155].

Several studies have evaluated different macrolides administered either short-term or long-term, with or without corticosteroids and montelukast, in terms of their efficacy in reducing exacerbation rates and stabilising/increasing respiratory capacity (Table 2) [44, 136, 140, 155–170]. Kutlin et al. [166] assessed macrolide treatment with levofloxacin and obtained positive results. Ogawa et al. [159] observed

that roxithromycin promoted lymphocyte apoptosis in *Dermatophagoides*-sensitive asthma patients. Low concentrations of roxithromycin (1–500 ng/ml) augmented the early, but not the late, phase of apoptosis in *Dermatophagoides farinae*-stimulated peripheral blood mononuclear (PBM) cells. High concentrations of this agent (at 1 μg/ml, 6 μg/ml being the maximum serum level) augmented both the early and late phases of apoptosis. Furthermore, in an acute model of allergic airway inflammation, the differential modulation of Th1 and Th2 cytokines was inhibited with rapamycin, SAR943 (32-deoxorapamycin), IMM125 [a hydroxyethyl derivative of D-serine (8)-cyclosporine], and budesonide by intratracheal instillation 1 h prior to allergen challenge. Thus, the effectiveness of these drugs, at least in such models, could be documented [171]. The protective effect of RXM was also evaluated on airway responsiveness to the sulpyrine provocation test. Shoji et al. [172] addressed the question of whether this protective activity is associated with a reduction in aspirin-induced excretion of urinary leucotriene E4 (u-LTE4). The latter is important as a marker of cysteinyl leucotriene overproduction that participates in the pathogenesis of aspirin-intolerant asthma. It produced positive effects in inhibiting hyper-responsiveness.

The favourable effects of macrolides have also been tested in non-infectious asthma, and clarithromycin was successful in reducing neutrophilic airway inflammation in refractory asthma [45, 173]. Moreover, clarithromycin treatment in asthmatic patients could reduce airway oedema, which may lead to airway tissue shrinkage and cause an artificial increase in the number of blood vessels. In this fashion, clarithromycin may be seen as protecting the airway [174]. Unfortunately, this positive effect was not sustained beyond a period of 2 years, and the positive effect of macrolides was not observed in all studies [167, 172, 173, 175–177]. Amayasu et al. [163] and Kostadima et al. [164] failed to present any improvement in respiratory capacity, but sputum reduction and eosinophilic control were achieved. In the investigation by Nelson et al. [175], a severe reduction in bone density was observed due to high dose of methylprednisolone, and in a further study abnormal function tests were observed [176]. Concern surrounds whether lung function tests were carried out by the same physician or according to ERS/ATS guidelines [178]. Evidence for reduced bronchial hyper-responsiveness has also been obtained after treatment with erythromycin, roxithromycin and azithromycin, although in these studies no positive effects were observed in pulmonary function tests [160, 170, 179]. Simpson et al. [173] reported favourable outcomes for quality of life (QoL). No gastrointestinal adverse effects were noted, but it should borne in mind that doses were very low, in comparison to works studying other respiratory diseases. However, most studies in asthma were carried out in children, and therefore doses had to be altered accordingly, although they were appropriate for body-mass index. Add-on inhaled AZM administration has proved successful in improving local bacterial control by means of anti-inflammatory and immunomodulatory effects [150]. Hersperger et al. [180] administered MLD987 based on the concept that T-helper cells of the Th2 phenotype are of paramount importance in the pathogenesis of asthma through numerous cytokines. A locally active T-cell modulator, MLD987, was given by inhalation, orally or intravenously. MLD987 is a potent immunosuppressant that inhibits the activation, proliferation and release of cytokines from T-cells with IC (50) values in the low nanomolar range. Inhaled administration reduced systemic side effects, lending support to the view that MLD987 has the potential to serve as an alternative to inhaled glucocorticosteroids for the long-term therapy of asthma [180]. Finally, there is in vitro experience that macrolides could induce bronchodilation [43].

## Macrolides and cystic fibrosis

Cystic fibrosis (CF) is the most common autosomal recessive life-shortening disease in the Caucasian population. It affects all exocrine glands, most importantly the lung, pancreas, liver and testis. CF lung disease is characterised by exaggerated inflammatory response and chronic airway infection, mainly with *Staphylococcus aureus*, *Haemophilus* spp. and *Pseudomonas aeruginosa* [181]. Infection and inflammation result in progressive bronchiectasis and, ultimately, in respiratory failure [182–184].

There are several theoretical reasons why macrolides could be disease-modifying agents in CF. First, airway inflammation is recognised as a major factor in the pathogenesis of lung disease in CF [182–186]. Macrolides at high doses have been shown to retard the decline of lung function in CF [187, 188]. Secondly, macrolides reduce sputum viscoelasticity and airway adhesion of *P. aeruginosa* [189–191]. Moreover, they reduce inflammatory response in CF [36, 86, 192–194]. Several studies using macrolides either in short-term or in long-term administration have provided positive results regarding reduction of exacerbations and stabilising or increasing respiratory capacity (Table 2) [52, 67, 195–228]. In contrast, only a few studies have failed to show positive outcomes in respiratory capacity [202, 215, 220]. Wolter et al. [220] also reported positive results regarding the QoL of patients receiving macrolides. Saiman et al. [222] noted more frequent adverse effects in comparison to other studies, but it should be mentioned that this was the largest multicentre study with the highest doses (250–500 mg AZM, three times weekly). Hansen et al. [202] and Pirzada et al. [212] have shown that weight gain was an additional positive factor for overall survival. Furthermore, a study in

mice with CF showed airway epithelial cells to exhibit upregulation of MIP-2 and KC responses to LPS, and azithromycin failed to downregulate these responses. Conversely, in CF cells, AZM increased KC and TNF-a expression under non-stimulated and LPS-stimulated conditions respectively. In non-CF cells, AZM enhanced LPS response to MIP-2 and IL-10. It was observed that airway epithelial cells contributed to the dysregulation of the immune processes in CF. Azithromycin rather stimulated cytokine expression in CF airway epithelial cells [229].

Another study looked at the induction of ATP binding cassette (ABC) proteins, which are involved in chloride transport and have been proposed as a possible mechanism of the beneficial effects of AZM in CF. This work focused on the effects of AZM on mRNA and protein expression of multi-drug resistance-associated protein 1 (MRP1) and multi-drug resistance protein 1 (MDR1). Interestingly, findings did not support the hypothesis of induction of ABC transporters by AZM [204]. Moreover, an association between increased glutathione S-transferase (GST) expression and activity, alongside its reversal by AZM treatment in vitro and in vivo, suggested novel antioxidant properties for this drug. Further research is warranted to ascertain whether decreased GST activity directly contributes to the anti-inflammatory properties of AZM or is rather a marker of the oxidative status in CF [66]. Classical and alternative macrophage activation in response to LPS from *Pseudomonas aeruginosa* has also been investigated. AZM downregulated inflammatory cytokine production by classically activated CF alveolar macrophages [230]. AZM can be used for cystic fibrosis with positive results; nevertheless the optimum dosage and time administration are still under investigation.

## Macrolides and bronchiectasis

Bronchiectasis is a common disease in the Asia-Pacific region. It leads to chronic sputum production and recurrent exacerbations. Bronchiectasis is largely idiopathic, its pathogenesis comprising infective, inflammatory and enzymatic components. Treatment is unsatisfactory and clinical trials are sparse. Antibiotic therapy is complex and includes short-term empirical treatment for acute exacerbations, and long-term oral, nebulised or i.v. therapy [231, 232]. In some patients, long-term prophylactic antibiotic treatment is vital to prolong the exacerbation-free period, although this may not be free from adverse effects and induction of antibiotic resistance [233].

Several studies with short-term or long-term macrolides have looked at respiratory capacity (Table 2) [234–242]. These have shown important beneficial actions of macrolides, including downregulation of proinflammatory cytokines via an effect on nuclear transcription factors, reduction in adhesion molecule expression, suppression of inducible nitric oxide synthase (iNOS), reduced neutrophil chemotaxis and degranulation, inhibition of neutrophil elastase, cytoprotection against bioactive phospholipids, improvement in the rheological properties of mucus, reduction in bronchial hyper-reactivity, inhibition of *Pseudomonas aeruginosa* biofilm formation, potential modulation of neutrophil death by apoptosis pathways, and airway remodelling [242]. Tsang et al. [240] failed to demonstrate such effects with EMC even at a dose of 500 mg. Cymbala et al. [237] and Tsang et al. [239] showed no efficacy in reducing sputum concentration or improving respiratory capacity [237, 239, 242–244]. Tsang et al. [239] and Davies et al. [243] demonstrated reduced exacerbation rates in their patient studies, and this result was not dose dependent. Koh et al. [244] also presented reduced airway responsiveness. Davies et al. [243] found abnormal PFT results, which led to premature study discontinuation. Again, it may be questioned whether lung function tests were reproduced by the same physician or according to ERS/ATS guidelines [178]. Macrolide trials in bronchiectasis are limited in number, size of study population, and length of treatment and follow up. However, there is consistent evidence of a decrease in exacerbation frequency and sputum volume. These findings would need to be confirmed in larger series with longer follow-up and meticulous assessment of adverse effects to define a role for macrolides in bronchiectasis treatment.

## Macrolides and bronchiolitis

Diffuse panbronchiolitis (DPB) is a chronic airways disease predominantly affecting East Asians and represents a distinctive sinobronchial syndrome with characteristic radiologic and histologic features. Bronchiolitis obliterans syndrome (BOS) is the leading cause of death in lung transplant recipients. It has recently been noted that the progression of BOS in lung-transplant recipients might be inhibited by macrolides [245–258]. BOS may be classified into fibroproliferative and neutrophilic, the latter responding to AZM, the former being refractory [259–264]. In these patients, macrolides have presented beneficial results in improving respiratory capacity [245, 246]. Shirit et al. [250] did not demonstrate improvement in respiratory capacity. Khalid et al. [265] also presented data that macrolide administration complicated bone marrow transplantation. In addition, positive results of macrolide treatment were observed in the reduction of neutrophils in BAL samples. Again, the results of long-term use regarding patient survival are thus far inadequate. Respiratory capacity tends to remain stable after long-term treatment and does not improve beyond 2 years. Studies have so far not been extended beyond 1 year and so interpretation of

overall patient survival needs to be done with caution. Additional studies of at least 5 years are needed to provide a more convincing answer [253]. Studies using macrolide treatment and assessing respiratory capacity and exacerbations are summarised in Table 2 [266, 267].

## Macrolides and viral infections

The mechanisms of virus-induced respiratory effects have received considerable attention. Recent studies have shown that the high mortality rate of influenza virus infections is a consequence of an overactive inflammatory response. Typically, severity of infection is closely related with virus-induced cytokine dysregulation. Importantly, influenza infections are characterised by the appearance of "cytokine storms," i.e. extreme production and secretion of numerous pro-inflammatory cytokines. This is responsible for the development of lethal clinical symptoms, such as massive pulmonary oedema, acute bronchopneumonia, alveolar haemorrhage, reactive haemophagocytosis and acute respiratory distress syndrome. Numerous in vitro, in vivo and clinical studies have established that viruses are potent inducers of various cytokines and chemokines [TNF-alpha, interferon (IFN)-gamma, IFN-alpha/beta, IL-6, IL-1, MIP (macrophage inflammatory protein)-1, MIG (monokine induced by IFN-gamma), IP (interferon-gamma-inducible protein)-10, MCP (monocyte chemoattractant protein)-1, RANTES, IL-8] [268–274].

There is recent evidence that macrolides could be used in combination with oseltamivir to prevent secondary infections by bacteria in patients severely affected by the novel H1N1 viruses, such as A/California 04/09 and similar strains [275]. Macrolides could interfere with the influenza virus replication cycle, resulting in the inhibition of virus production from infected cells [276], mainly by inhibiting intracellular haemagglutinin HA0 proteolysis [277]. Based on existing evidence, macrolides may be considered for exacerbations, yielding some promising results [275–283]. However, confirmation in larger series, as well as delineation of their precise role, is still awaited.

## Macrolides and cryptogenic organising pneumonia

Cryptogenic organising pneumonia (COP) generally responds well to corticosteroids. There are some data on the immunomodulatory properties of certain macrolides as an alternative to corticosteroids in mild disease or as adjuvant to standard therapy. The factors associated with a poor prognosis in organising pneumonia (OP) cases remain unclear, although OP patients with autoimmune aetiology may have poorer outcomes [15, 284, 285]. Little is known about alternative immunosuppressive agents in corticosteroid-resistant OP [286–290]. Published data indicate that macrolide efficiency in these patients relies mostly on improvement of respiratory capacity and BAL normalisation. Add-on macrolides have been used in refractory cases with various outcomes, but treatment experience is still lacking and more experience is desirable [285, 291–293].

## Adverse effects of macrolides

When macrolides are administered at larger doses or reach higher serum concentrations, the incidence of adverse effects sometimes increases, necessitating trial discontinuation [225, 294, 295]. The side effects differ among individual macrolides and between young and old adults. The reason for these differences is unclear, but it has been suggested that auditory impairment is more common with high-dose azithromycin (1.5 g/5 days) and erythromycin (≥3 g/day) [296], while hepatitis is more frequent with high-dose clarithromycin (1,000 mg twice daily), and gastrointestinal discomfort is common to both AZM and EM [271, 295, 297, 298]. In addition, age and low body weight have been linked with more prevalent adverse events [299, 300]. Recent studies with intravenous azithromycin have shown minimal side effects with doses as high as 4 g, suggesting that gastrointestinal symptoms are likely related to a direct effect of the drug on the gastrointestinal tract rather than high tissue levels [301]. The latter are likely responsible, however, for the temporary auditory impairment noted in some patients. Hearing impairment has previously been noted with macrolide use [296, 302]. This has generally been related to high-dose erythromycin (≥3.0 g/day) and AZM (600 mg/day) [303].

The most common side effects may be summarised as follows:

1. Gastrointestinal: Gastrointestinal complaints have been mainly reported in patients receiving EM, CAM and AZM [294, 304]. This side effect is related to serum level. Dose-limiting gastrointestinal side effects were also higher when doses of 4,000 mg/day were used [61, 294, 305–307]. Hepatotoxicity may occur, as manifested by an increase in liver enzymes or cholestasis [294, 308]
2. Ototoxicity: Ototoxicity is typically reversible, sensorineural and bilateral, with hearing loss involving the lower frequencies. Hearing impairment has usually been bilateral, symmetrical and reversible. The small number of cases of EM-related hearing impairment in which audiograms were obtained have involved alteration at all frequencies, but with the greatest changes at speech frequencies rather than high frequencies [296]. This has been reported for EM, AZM and CAM [294, 303]. When AZM was reduced to 300 from 600 mg/day, ototoxicity was reversed. Paradoxically, replacement of AZM with CAM in one study led to reversal in ototoxicity [309].

3. Cardiac toxicity: Macrolides have a twofold potential effect on the QT interval: (1) intrinsic prolongation, i.e. prolongation of the repolarisation period of the action potential by blocking the HERG potassium channels [303] and (2) inhibition of the metabolism of other proarrhythmogenic drugs by acting on cytochrome P450 in the liver. Co-administration of EM and other inhibitors of cytochrome P450 resulted in a five-fold increase in cardiac sudden death rates [310]. During the 1987–2000 period, 156 deaths were attributable to macrolides, according to the U.S. Food and Drug Administration [102, 311–313]. In practice, special care must be taken when administering macrolides, especially intravenous EM, to elderly patients and those with heart failure. In female patients older than 80 years with cardiac comorbidity or using other pro-arrhythmogenic drugs, ECG follow-up should be considered to monitor QT prolongation during macrolide administration. There are no studies correlating dose-dependent side effects to ECG abnormalities.
4. Other rare adverse effects: Urticaria, rash and neutropenia have been described. All are reversible after treatment cessation [309].
5. Resistance: Macrolide resistance has increased considerably over the last decade [50–57]. Three mechanisms may be responsible for the increase in macrolide resistance. First, isolates with intrinsic resistance to macrolides may prevail as susceptible ones are eradicated. Second, resistance may be acquired through one- or multi-step mutation. Third, resistant isolates may be acquired through cross-infection from other patients. A significant association between macrolide prescription and local resistance has also been observed in several studies [57–61]. Moreover, macrolide resistance is determined by two mechanisms, namely by active drug reflux encoded by *mef* genes (M phenotype) or by ribosomal target modifications by *erm a–b* genes, which reduce macrolide affinity to the ribosomal target site. In most studies, respiratory capacity has improved or at least remained stable after macrolide treatment, but the positive outcome was temporary due to the development of macrolide resistance. The longest period of positive outcome in respiratory capacity was observed at 1 year; in long-term studies, a decline was observed in the second and third years of follow-up. This observation was correlated with emergence of cross-resistance to 14-, 15- and 16-membered macrolides, lincosamides and group B streptogramins (MLSb phenotype). MLS resistance can be expressed either constitutively (cMLS phenotype) or inducibly (iMLS phenotype) [314–317]. This may be the longest period that is required for acquired resistance/changes in the serotype of the infecting strains [52, 53, 121].

A way to monitor these changes in the clinical setting could be a simple technique such as induced sputum. Reduction of neutrophils and neutrophil elastase in sputum suggests the positive outcome of macrolide therapy as observed by He et al. [101], but this was not observed in another study by Seemungal et al. [100]. In order to control exacerbations in several respiratory diseases, three parameters have to be managed: (a) presence of bacteria in the airway (bronchial colonisation) [118], or (b) the presence of a persistent pathogen at the end of antibiotic therapy [115, 119]. Therefore, prompt bacterial eradication has to be made with addition of quinolones [122, 133], in harmony with the "rise and fall" hypothesis of bronchial bacterial infection [120], even though this may lead to later recurrence [121]. Numerous studies in respiratory diseases have demonstrated induced resistance to macrolides [52, 53, 318].

Macrolides preserving their anti-inflammatory effects with little antibacterial effect should now be created. Positive outcomes achieved with these agents when administered in small doses have been reported, but without proper assessment of induced resistance on short- or long-term follow-up [239, 240]. Thus, it is conceivable that clinicians might add new immunomodulatory drugs of the macrolide family to their armamentarium in the near future. Immunomodulatory macrolide antibiotics without antibacterial properties may be developed by modifying the molecular structure of the atoms attached to the macrocyclic ring [319]. These purely immunomodulatory macrolides could circumvent bacterial resistance. This has already been explored in tetracyclines, which also have anti-inflammatory properties. Chemically modified tetracyclines, with no antibacterial actions, induce an anti-inflammatory response by modulating cytokine and matrix metalloproteinase secretion [320–324]. However, only in vitro and animal studies have been performed to investigate the effect of chemically modified tetracyclines. To our knowledge, no phase 1 studies are yet available describing the efficacy and safety of purely immunomodulatory drugs, and such progress is desired before final conclusions are drawn.

6. Drug interaction with theophylline: In several studies, macrolides (EM, rokitamycin, dirithromycin) dose-dependently affected theophylline plasma concentration. The magnitude and time course of this interaction in patients with congestive heart failure and COPD may differ considerably from that reported in healthy volunteers, prompting a 25% dose reduction of theophylline in some patients [325–328].
7. Combination with statins: The combination of macrolides with statins is not advisable, since it may lead to rhabdomyolysis [41, 42].

## Conclusions

Macrolides are a group of antibiotics that inhibit bacterial protein synthesis. They are used to treat infections caused by Gram-positive bacteria, *Streptococcus pneumoniae*, and *Haemophilus influenzae* infections, such as respiratory tract and soft-tissue infections. Macrolides have also been shown to be effective against *Legionella pneumophila*, mycoplasma, mycobacteria, some rickettsias and chlamydia. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin and they usually do not cause allergic reactions. Moreover, macrolides possess anti-inflammatory and immunomodulatory actions extending beyond their antibacterial activity. Indeed, they downregulate the inflammatory cascade, they attenuate excessive cytokine production in viral infections and they may reduce influenza-related exacerbations. In respiratory diseases, macrolides have so far manifested variable efficacy. Overall, they appear to induce an increase in respiratory capacity and exacerbation-free period, but many issues need to be further addressed. Therefore, randomised controlled clinical trials involving larger patient samples are warranted to confirm whether these actions are of substantial clinical relevance. We mainly need to define dose and duration of administration, but also which macrolide might prove superior in each condition. Moreover, trials should be carried out in influenza-related exacerbations, to further delineate the promising results shown by macrolides in such circumstances. After more than 30 years, these agents still hold a vital place in our therapeutic armamentarium. Looking into the future, there is some ground for speculation that the role of macrolides in the treatment of respiratory diseases may be enhanced by creating agents with a profound anti-inflammatory effect and little antibacterial effect.

**Conflicts of interest** Nothing to declare.

**Author contributions** P.Z. and N.P. conceived and wrote the manuscript. E.C. assisted in the explanation and presentation of the multiple anti-inflammatory/immunomodularlatory properties. I.K., E. M. and K.Z. provided useful insights.

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