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Review Article

The role of roxithromycin in the treatment of respiratory tract infections: a comprehensive overview

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ABSTRACT

Respiratory tract infections (RTIs) represent a substantial global health burden. Antibiotics, including macrolides like roxithromycin, are frequently prescribed to treat these infections. Roxithromycin exhibits bacteriostatic and bactericidal properties by disrupting bacterial protein synthesis. It has a better pharmacokinetic profile than erythromycin and demonstrates satisfactory tissue penetration and distribution. In addition to its antimicrobial action, roxithromycin displays anti-inflammatory properties, modulates neutrophilic actions, reduces pro-inflammatory cytokines, and inhibits mucus secretion and synthesis. These mechanisms contribute to its efficacy in treating a spectrum of RTIs, including sinusitis, pharyngotonsillitis, chronic rhinosinusitis, pneumonia, and bronchiectasis. Clinical studies have consistently demonstrated the effectiveness and tolerability of roxithromycin. Overall, roxithromycin offers a multifaceted approach to target both the microbial and inflammatory components of RTIs. Hence, this review aims to provide an overview of the pharmacokinetics and pharmacodynamics, as well as the efficacy and tolerability of roxithromycin in treating RTIs.

Keywords: URTIs, LRTIs, Roxithromycin, Chronic rhinosinusitis, Post-antibiotic effect, Anti-inflammatory effect

INTRODUCTION

Respiratory tract infections (RTIs) represent substantial sources of morbidity, mortality, and productivity loss on a global scale.[1] RTIs are one of the most common reasons to seek consultation with a general practitioner in outpatient settings.[1-4] Every year, millions worldwide are diagnosed with RTIs, which are responsible for around 4 million deaths across all age groups.[5]

RTIs can be further categorized into infections affecting the upper and lower respiratory tracts.[1,2] Upper RTIs (URTIs) include conditions such as the common cold, laryngitis, pharyngitis/tonsillitis, rhinitis, rhinosinusitis, and otitis media.[1,3] On the other hand, lower RTIs (LRTIs) include conditions like bronchitis, bronchiolitis, pneumonia, and tracheitis.[1,3]

RTIs are usually either viral or bacterial in origin. When the origin is bacterial, *S. pneumoniae*, non-typical *H. influenzae*, and *Moraxella catarrhalis* commonly cause acute otitis media, acute bacterial rhinosinusitis, and acute exacerbations of chronic bronchitis. *S. pyogenes* are typically involved in acute pharyngotonsillitis. Lastly, *Bordetella pertussis*, *C. pneumoniae*, or *Mycoplasma pneumoniae* are common culprits in cases of acute bronchitis and community-acquired pneumonia (CAP).[2]

Antibiotics are frequently prescribed for RTIs in both adults and children in primary care settings.[1] Among

them are macrolides, which have been used medically for more than six decades.[6] Macrolides are characterized by a macrocyclic lactone ring and are categorized as 14-, 15-, or 16-membered depending on the number of carbon atoms present in their structure.[7]

Erythromycin, the first macrolide identified, was isolated from the soil bacterium *Streptomyces erythraeus* and was initially used in clinical settings in 1952. Early use of macrolides was considered an effective alternative to penicillin for individuals with penicillin allergies or those afflicted by penicillin-resistant bacterial infections. Subsequent generations of macrolides resulted through chemical modifications to erythromycin, expanding their range of effectiveness, enhancing pharmacokinetic/ pharmacodynamic attributes, and mitigating adverse reactions.[7] Initially, macrolides were used for treating gram-positive bacterial infections; however, their usage expanded significantly following Kudoh's report that described the immunomodulatory properties of macrolides for the first time in 1987.[7,8] Kudoh's study demonstrated the effectiveness of macrolides, particularly erythromycin, in improving the survival rate of patients with diffuse panbronchiolitis.[8] Subsequent trials confirmed these favorable effects not only for erythromycin but also for other 14-membered ring macrolides like clarithromycin and roxithromycin.[9]

Roxithromycin is an ether oxime derivative of erythromycin, exhibiting *in vitro* activity similar to erythromycin.[10] Clinical studies have validated the potential of roxithromycin for treating a range of infections, including RTIs like CAP, atypical pneumonia, and ear, nose, and throat (ENT) infections.[11]

The present review provides a comprehensive overview of the pharmacokinetic and pharmacodynamic properties of roxithromycin and its use in treating RTIs.

MECHANISM OF ACTION, ANTIMICROBIAL SPECTRUM, PHARMACOKINETICS, AND OTHER PROPERTIES

Mechanism of action

Roxithromycin interacts with the 50S bacterial subunit of the 70S ribosome, consequently disrupting bacterial protein synthesis.[10-12] Roxithromycin exhibits bacteriostatic properties at low concentrations and is bactericidal at higher concentrations.[12]

Antimicrobial spectrum

Roxithromycin exhibits an *in vitro* antibacterial spectrum similar to that of erythromycin. The antimicrobial spectrum of roxithromycin is given in Table 1.

Pharmacokinetics

The pharmacokinetics of roxithromycin have been investigated in both healthy volunteers and patients needing antibiotic treatment, including those with renal or hepatic impairment.[10-12] The pharmacokinetic parameters are presented in Table 2.

Post-antibiotic effect

The sustained suppression of in-vitro bacterial growth following the withdrawal of antibiotics is called the post-antibiotic effect (PAE).[11] Kuenzi et al conducted a study involving several bacteria including *H. influenzae*, *S. aureus*, *S. pyogenes*, and *S. pneumoniae*.[13] Experiments revealed that the duration of PAE was influenced by both the drug concentration and the duration of exposure (Table 3). Roxithromycin had similar PAEs *in vitro* as erythromycin and the clindamycin.[13]

Tissue penetration

Roxithromycin has been demonstrated to penetrate sinonasal tissues significantly more than nasal mucosa. In a study by Siu et al it was found that while the minimum inhibitory concentration (MIC) necessary for treating bacterial species associated with chronic rhinosinusitis (CRS) was therapeutic in tissue and serum, it did not reach effective levels in mucus.[14]

Accumulation in polymorphonuclear leukocytes and macrophages

Antibiotic uptake by phagocytes is imperative for their efficacy against intracellular pathogens. The accumulation of roxithromycin has been reported to be increased in polymorphonuclear leukocytes (PMN). In a study by Hand et al the ratio of antibiotic concentration inside the cells to its concentration outside (C/E ratio) for roxithromycin was considerably high at 34 in comparison to other antibiotics like imipenem, cefotaxime, trimethoprim, and metronidazole. This uptake of roxithromycin into phagocytes was identified as an active process and exhibited saturation kinetics characteristic of carrier-mediated membrane transport systems.[15]

The intracellular accumulation and subcellular distribution of ^{14}C-labeled roxithromycin and erythromycin in macrophages and PMN have been studied. Roxithromycin showed higher accumulation compared to erythromycin, with concentration ratios ranging from 14 (in PMN) to 190 (in alveolar macrophages). It has a reversible uptake that is unaffected by anaerobic conditions or aminoglycosides giving it a significant advantage over other antimicrobial agents.[16]

Table 1: The antimicrobial activity spectrum of roxithromycin.

Microorganism	Sensitivity/potency to roxithromycin	Compared to other antibiotics
Gram-positive		
S. aureus (excluding MRSA strains)	Sensitive[11]	-
Staphylococcus epidermidis[10]	Sensitive[11]	Less potent than erythromycin[10, 11]
Streptococci (Groups A, B, and C, *S. pneumoniae*)	Susceptible[10,11]	Comparable to erythromycin, clindamycin, cefaclor and amoxicillin
Gram-negative		
Moraxella catarrhalis	Potent activity[10,11]	Similar to erythromycin and clarithromycin
Hemophilus influenzae	Borderline activity[10]	
Others		
Chlamydia pneumoniae	Susceptible	-
Mycoplasma pneumoniae	Susceptible	Activity similar to erythromycin and spiramycin but more potent than doxycycline[10]

Table 2: Pharmacokinetic parameters for roxithromycin.

Parameters	Findings for roxithromycin
Absorption	
Absolute bioavailability after oral administration[12]	~50%
Mean plasma concentration (after 2 hours of dose)[10,11]	150 mg dose: 6.6-7.9 mg/L 300 mg dose: 9.1 to 10.82 mg/ L
AUC (mg/L·h)[11]	150 mg: 72.6 to 81 300 mg: 116.5 to 132
AUC[10]	16.2-fold greater than erythromycin (250 mg)
Distribution	
Tissue and tissue fluid penetration (Mean peak tissue or fluid concentration (mg/kg or mg/L**,** sampling time after 150 mg dose)[11]	Adenoid (1 h): 13.3 Maxillary sinus mucosa (4 h): 4.15 Middle ear fluid (12 h): 0.93 Tear fluid (2 h): 4.8 Tonsils (6 h): 2.7 Lung tissue (6 h): 5.6 Bronchial aspirate (4 h): 3.1
Protein binding[11]	Binding to albumin: Weak and nonspecific (around 15.6 to 26.7%) Binding to α1-acid glycoprotein: Strong and saturable Maximum binding to serum proteins: 96.4% at concentrations of 2.5 mg/L Binding to lipoproteins: 7 to 11% Binding to globulins and erythrocytes: Little or no binding
Metabolism and excretion	
Plasma clearance[10]	Dose- or plasma concentration-dependent
Elimination[11]	Unchanged roxithromycin: Urine: 50%, feces: 55% Descladinose derivative: Urine: 25%, feces: 22% Demethylated derivative: Urine: 5%, feces: 7%
Elimination half-life[10, 11]	8.4 to 15.5 hours

Table 3: Post-antibiotic effect of roxithromycin.

Microorganism	Drug	Concentration (no. of times×MIC)	Exposure time (hours)	PAE duration (hours)
***Streptococcus pneumoniae*[13]**	Roxithromycin	2-3×MIC	1-2	2.6-4.4
		5-10×MIC	1-2	7-9
		2-3×MIC	6	6.3
	Erythromycin	2-3×MIC	1-2	3.2-5.3
		5-10×MIC	1-2	6.3
	Clindamycin	2-3×MIC	1-2	2.5-4.9
		5-10×MIC	1-2	6.9

Continued.

Microorganism	Drug	Concentration (no. of times×MIC)	Exposure time (hours)	PAE duration (hours)
***Streptococcus pyogenes*[13]**	Roxithromycin	0.5-1×MIC	1	1.5
		0.5-1×MIC	6	1.5
		5-10×MIC	6	6-7
	Erythromycin	5-10×MIC	6	6-7
	Clindamycin	5-10×MIC	6	4.5-5.5
***Staphylococcus aureus*[13]**	Roxithromycin	0.5-1×MIC	1-6	1.5-2.5
		5-10×MIC	1-6	2.5-5.2
***Hemophilus influenzae*[13]**	Roxithromycin	1×MIC	2	Insignificant
	Erythromycin	10×MIC	1-2	2.4
	Clindamycin	10×MIC	1-2	1.2

Note: MIC, minimum inhibitory concentration.

Anti-inflammatory action

Macrolides exhibit anti-inflammatory action by decreasing the pro-inflammatory cytokines like interleukin-5 (IL-5), IL-6, and IL-8, suppressing the oxidative burst and degranulation of neutrophils, and enhancing phagocytosis.[17-19]

Effect on neutrophilic action: Lipopolysaccharides (LPS) are major constituents in the cell wall of gram-negative bacteria and can interact with cellular mediator systems involving neutrophils, resulting in inflammatory responses in the respiratory system.[18] Furthermore, neutrophil adhesion and the upregulation of intracellular adhesion molecule (ICAM) expression occurs in response to LPS.[19] Modulation of neutrophilic action by macrolides is the most widely recognized in the bronchial and sinus mucosa.[17] Some of these actions are given in the Figure 1.

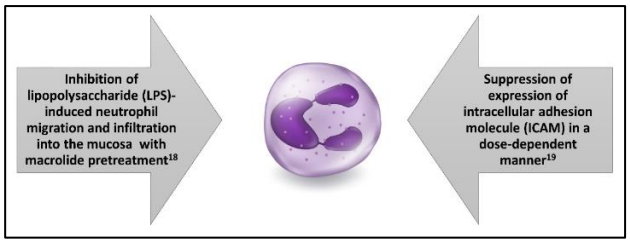

Figure 1: The action of macrolides on the neutrophils.

Reduction of IL-8

IL-8 is a potent pro-inflammatory cytokine with neutrophil chemoattractant properties. IL-8 acts both as a target for and a product of neutrophils. Macrolides are believed to reduce IL-8 production by suppressing transcription factors.[19]

Effect on nitric oxide

Nitric oxide (NO) plays a crucial role in various normal physiological airway functions but can also function as an inflammatory mediator. Macrolide therapy has been shown to suppress the release of NO from pulmonary macrophages following immune complex injury.[20]

Immunomodulatory effects

LRTIs: Nakamura et al investigated the clinical and immunoregulatory effects of long-term macrolide antibiotic therapy in ten patients with chronic LRTIs (CLRTI). The study found that IL-8, neutrophil elastase, and leukotriene B4 contribute to neutrophilic inflammation in CLRTI patients, and the clinical effects of roxithromycin result from the suppression of the excessive release of chemotactic mediators from inflammatory cells (Figure 2). [21]

Figure 2: Clinical and immunoregulatory effects of long-term therapy.

Note: RXM, roxithromycin.

URTIs: Studies in patients with CRS revealed that roxithromycin demonstrates a notable decrease in the counts of macrophages, neutrophils, and eosinophils, as well as reductions in concentrations of various inflammatory markers including neutrophil elastase, eosinophil cationic protein (ECP), CC-chemokine ligand-5 (CCL-5), interleukin-1beta (IL-1beta), IL-6, IL-8, interferon-gamma (IFN-gamma), tumor necrosis factor-

alpha (TNF-alpha), myeloperoxidase (MPO), and alpha-macroglobulin in nasal secretions. [22]

In-vitro sensitivity

A study was conducted to evaluate resistance patterns in common respiratory pathogens, such as *S. pneumoniae*, *S. aureus*, *K. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, in 50 patients with RTIs. Roxithromycin showed higher sensitivity to isolated organisms compared to amoxicillin. Even in cases where samples were resistant to amoxicillin and amoxicillin-clavulanic acid combination, roxithromycin remained sensitive for *S. pneumoniae* isolates, making it a viable alternative for managing both URTIs and LRTIs in the community.[23]

The European committee on antimicrobial susceptibility testing

According to the breakpoint tables for interpretation of MICs and zone diameters version 14.0, valid from 2024-01-01, the MIC breakpoints (mg/l) for *Streptococcus* groups A, B, C, and G for roxithromycin for susceptibility is ≤0.5 mg/l.[24]

EFFECT ON MUCUS SECRETION AND SYNTHESIS

Mucus secretion

Roxithromycin has demonstrated the ability to inhibit IL-8-mediated mucus releases. Additionally, macrolides have been observed to decrease goblet cell secretion in response to LPS in animal studies. In CRS, macrolides have been found to improve mucus clearance and production.[25]

Mucus synthesis

The elasticity and viscosity of airway mucus are largely determined by high-density mucin (MUC) glycoproteins.[26] Major components of airway mucus include MUC4, MUC5AC, and MUC5B. Macrolides inhibit the expression of MUC5AC mRNA in response to LPS through a mechanism similar to the suppression of IL-8. Similar effects have been observed in the nasal mucosa.[27]

EFFICACY AND SAFETY OF ROXITHROMYCIN

The efficacy and safety of roxithromycin have been studied in both URTIs and LRTIs.[10, 11]

Studies on URTIs

Sinusitis: Elevated and sustained concentrations of roxithromycin have been demonstrated within maxillary sinus tissue in individuals diagnosed with sinusitis. In a study conducted in patients with acute or recurrent sinusitis, roxithromycin (150 mg BID) and amoxicillin and clavulanic acid combination (625 mg TID) demonstrated satisfactory clinical efficacy (Table 4). Out of the 52 patients who underwent sinus puncture to isolate causative organisms, 48 were found to harbor pathogens susceptible to both antibiotics. However, roxithromycin was better tolerated than amoxicillin and clavulanic acid combination (Table 4).[28]

Low-dose roxithromycin has been demonstrated to enhance the aeration of all four sinuses markedly and decrease neutrophil and IL-8 levels in the nasal discharge of patients with chronic sinusitis.[28] Findings from one study indicated a significant decrease in all symptoms of chronic sinusitis and improvement even in cases where *H. influenzae* was detected.[29] In another study, a low dose of roxithromycin was demonstrated to have a prolonged curative effect on chronic sinusitis.[30]

Cumulative evidence suggests that roxithromycin was effective and well-tolerated in treating acute and recurrent sinusitis as well as chronic sinusitis.[28-30]

Chronic rhinosinusitis: A placebo-controlled study assessed the efficacy of roxithromycin (150 mg daily) for CRS over 3 months. The study revealed statistically significant improvements in various parameters including sino-nasal outcome test (SNOT)-20 score, nasal endoscopy findings, and saccharine transit time (STT) in patients receiving roxithromycin (Table 4). Furthermore, the effect of roxithromycin based on the IgE level of the patients was evaluated. Roxithromycin resulted in reductions in STT ($p<0.01$), SNOT-20 ($p<0.01$), nasal endoscopic scoring ($p<0.01$), and IL-8 levels in the post-treatment nasal lavages ($p=0.02$) in patients with low IgE, and in STT ($p=0.04$) in those with high IgE. These results indicated the efficacy of roxithromycin in CRS, particularly among patients with lower levels of IgE, reinforcing the *in vitro* evidence supporting their anti-inflammatory properties.[31]

URTIs/ ENT infections: A multicenter study compared the efficacy and safety of roxithromycin (300 mg OD) with amoxicillin/clavulanic acid tablets (875+125 mg BID). Patients enrolled were diagnosed with ENT diseases, including acute otitis media (85%), pharyngotonsillitis (31%), and rhinosinusitis (11%). Roxithromycin exhibited similar effects in reducing signs and symptoms compared to amoxicillin/clavulanic acid but with improved compliance due to its once-daily dosing regimen (Table 4).[32]

In another study, the efficacy and tolerability of roxithromycin (300 mg OD) were compared to clarithromycin (250 mg BID) in patients with URTIs, such as sinusitis, pharyngotonsillitis, and otitis media. Roxithromycin exhibited better efficacy, particularly in cases of otitis media and pharyngotonsillitis, as well as better clinical response and tolerability compared to clarithromycin (Table 4).[33]

Studies on LRTIs

Pneumonia: An open-label randomized study conducted across three outpatient clinics compared roxithromycin and cefixime for the treatment of uncomplicated CAP. *S. pneumoniae* was the most frequently isolated pathogen from sputum in 26 cases (43%), while mixed organisms were detected in 18 cases (30%). Additionally, *Staphylococcus aureus*, *H. influenzae*, or *M. catarrhalis* were found in 11 out of 60 patients. Atypical pathogens were identified through serology in 7 cases within the roxithromycin group and 3 cases within the cefixime group. roxithromycin, administered at a daily dosage of 300 mg, was effective and well-tolerated for empirical treatment of mild to moderate CAP (Table 5).[34]

In another study, the efficacy and tolerability of erythromycin, clarithromycin, and roxithromycin were evaluated. The clinical success rates with the three macrolides did not differ significantly; however, clarithromycin and roxithromycin were better tolerated than erythromycin (Table 5).[35]

Mycoplasma pneumonia: Macrolides are reported to be effective in treating mycoplasma pneumonia. In an open trial, roxithromycin was also found to be clinically effective in treating mycoplasma pneumonia.[36]

Bronchiectasis: Roxithromycin effectively alleviates clinical symptoms of patients with bronchiectasis. Study conducted on patients with, once-daily administration of roxithromycin demonstrated favorable effects on clinical outcomes, including symptom relief and improvements in quality of life. None of patients receiving Roxithromycin reported any adverse effects (Table 5).[37]

In another study, the efficacy of roxithromycin was evaluated in children diagnosed with bronchiectasis. Roxithromycin demonstrated significant improvement in the sputum purulence scores as well as sputum leucocyte count by the sixth week of treatment (Table 5). After 12 weeks, roxithromycin therapy increased the geometric mean of provocative cumulative dose producing a 20% fall in forced expiration volume (FEV1, PD20) (Table 5). Thus, roxithromycin could potentially decrease airway responsiveness in patients with bronchiectasis and improve airway reactivity.[38]

LRTIs: The efficacy and tolerance of roxithromycin (300 mg OD) were compared with clarithromycin (500 mg BID) in patients with LRTIs, such as chronic bronchitis and pneumonia. Both roxithromycin and clarithromycin demonstrated efficacy in treating LRTI; however, roxithromycin was better tolerated, offering the added benefit of a once-daily dosage regimen (Table 5).[39]

Studies on RTIs including URTIs and LRTIs

Findings from non-comparative studies demonstrated clinical cure rates ranging from 84-100% for roxithromycin in treating RTIs.[11]

The efficacy of roxithromycin was assessed in an interim analysis of a study conducted in eight countries, involving a large group of patients with URTIs and LRTIs, and roxithromycin was effective in managing these infections in general practice.[40]

In another study, the efficacy and tolerability of roxithromycin (150 mg BID) were evaluated in 96 patients with URTIs and LRTIs and compared to amoxicillin-clavulanic acid (500 mg/125 mg TID). Both drugs were equally effective in the treatment of RTIs, but roxithromycin was tolerated better (Table 6).[41]

Another study, a meta-analysis of twelve clinical studies, investigated the efficacy of roxithromycin (300 mg OD) in 4297 patients with RTIs, among whom 384 (8.9%) were identified to have *H. influenzae* as causative pathogen.

Roxithromycin exhibited response rate comparable to amoxicillin/clavulanic acid and greater than erythromycin (p=0.03). Roxithromycin was more effective in treating pneumonia in direct comparison studies (Table 6). This study supports the empirical use of roxithromycin in RTIs where *H. influenzae* is potential pathogen.[42]

DOSAGE AND ADMINISTRATION

Adults

For adults, the recommended dosage of roxithromycin is 300 mg per day, which can be administered using one of the following dosage regimens: Roxithromycin 300 mg tablets: one tablet daily, or roxithromycin 150 mg tablets: one tablet twice daily or two tablets once daily. For atypical pneumonia, the recommended dosage is 150 mg taken twice daily. The typical duration of treatment ranges from five to ten days, varying based on the indication and individual clinical response. Streptococcal throat infections necessitate at least ten days of therapy for effective treatment.[12]

Special populations

The dose is the same for the elderly and patients with renal impairments. For patients with documented cirrhotic liver disease, the recommended dosage is one tablet of roxithromycin 150 mg taken once daily.[12]

Pediatric population

In the pediatric population, roxithromycin is typically administered twice daily at a dosage of 5 to 8 mg/kg/day. For children weighing 40 kg and above, the recommended regimen consists of one 150 mg tablet of roxithromycin in the morning and another in the evening.[12] The treatment duration ranges from five to ten days, depending on the specific indication and the patient's clinical response. For Streptococcal throat infections, a ten-day course of therapy is recommended. It is imperative to strictly adhere to the prescribed treatment duration, and should not exceed ten days.[12]

Table 4: Efficacy and safety of roxithromycin in upper respiratory tract infections.

Conditions	Study design; patients	Intervention; comparator; duration	Outcomes			
			Parameters	**Roxithromycin**	**Placebo**	**Comparator**
Acute and recurrent sinusitis[28]	Open randomized trial; n=60	Roxithromycin-150 mg BD for 10-14 days; Amoxicillin-clavulanate-625 mg TID for 10-15 days	Satisfactory response	93.1% (27/29)	-	88.8% (24/27)
			Tolerability	3.4% (1/29; p<0.05)	-	25.9% (7/27)
Chronic sinusitis[30]	Open trial; n=30	Low-dose (150 mg) of roxithromycin; 3 months	Subjective and objective symptoms	Improvement in postnasal drip and nature of discharge in ≥80% of patients. All symptoms significantly decreased (p<0.001) Headache decreased (p<0.05)	-	-
Chronic rhinosinusitis[31]	Double-blind; placebo-controlled trial; n=64	Roxithromycin 150 mg OD (n=29); vs placebo (n=35); 3 months	Mean SNOT-20 score	Pre-treatment, 2.75; At 12 weeks, 2.35; p<0.01	Pre-treatment, 2.83; At 12 weeks, 2.88; p-NS	-
			Mean nasal endoscopy	Pre-treatment, 3.2; post-treatment, 2.6; p<0.01	Pre-treatment, 3.0; post-treatment, 2.9; p-NS	-
			STT (min)	Pre-treatment, 11.5; post-treatment, 8.2; p<0.01	Pre-treatment, 10.9; post-treatment, 11.3; P-NS	
ENT infections[32]	Multicenter, randomized open-label study; n=100	Roxithromycin 300 mg OD (n=50) vs amoxicillin-clavulanate 875 + 125 mg BD (n=50); 7 days	Satisfactory overall clinical response (%)	82%	-	78%
			Patients with gastrointestinal side effects (%)	4%	-	12%
URTIs[33]		Open comparison; n=200; roxithromycin 300 mg OD vs clarithromycin 250 mg BD for 9 days	Signs: resolution or improvement	Sinusitis: 90% (p<0.05) Pharyngotonsillitis: 100% (p<0.01), Otitis media: 98% (p<0.01)		Sinusitis: 69%, Pharyngotonsillitis: 77%, Otitis media: 79%
			Clinical response to treatment	Sinusitis: 87% (p<0.01), Pharyngotonsillitis: 96% (p<0.01), Otitis media: 90% (p<0.01)		Sinusitis: 66%, Pharyngotonsillitis: 77%, Otitis media: 61%
			Tolerability	4% (p<0.05)		12%

Note: BD-twice daily; ENT-Ear, nose, and throat; IL-8-Interleukin-8; NS-Not significant; OD-Once daily; SNOT-20- Sinonasal outcome test-20; STT-Saccharine transit time; TID-Thrice daily; URTIs-Upper respiratory tract infections.

Table 5: Efficacy and safety of roxithromycin in LRTIs.

Conditions	Study details	Intervention; comparator; patients; duration	Parameters	Outcomes		
				Roxithromycin	Placebo	Comparator
CAP[34]	Open, randomized study	Roxithromycin 300 mg OD (n=30); cefixime 400 mg OD (n=30); 8-10 days	Clinical cure rates	100%	-	94%
Mild pneumonia[35]	Open randomized trial	Clarithromycin 500 mg 12-hourly (n=29), Roxithromycin 150 mg 12-hourly (n=30), and erythromycin stearate 500 mg 6-hourly (n=27); 10 days	Clinical success rates (clinical cure or improvement)	82%; p=0.32	-	Clarithromycin: 89% Erythromycin stearate: 73%
			Clinical cure rates	64%; p=0.04	-	Clarithromycin: 75% Erythromycin stearate: 41%
			Adverse events	6.6%	-	Clarithromycin: 3.4% Erythromycin stearate: 18.5%
Mycoplasma Pneumonia[36]	Open trial	Roxithromycin; n=15	Clinical efficacy	Excellent: 6 cases, Good: 6 cases, and Fair: 1 case 92.3% efficacy rate	-	-
			Eradication rate	66.7%	-	-
Bronchiectasis[37]	Double-blind, placebo-controlled study	Roxithromycin 300 mg OD (n=14) vs placebo (n=14); 8 weeks	Improvement in symptom score (SS) (mean differance)	-1.66, p=0.005	-0.06, p=0.94	-
Bronchiectasis[38]	A placebo-controlled study in children	Roxithromycin 4 mg/kg BID, n=13) and placebo (n=12); 12 weeks	Sputum purulence scores (mean)	Baseline: 2.54 6th week: 1.77, p<0.05 12th week: 1.39, p<0.01	Baseline: 2.42 6th week: 2.17 12th week: 2.17	-
			Sputum leucocyte score (mean)	Baseline: 2.13 6th week: 1.62, p<0.05 12th week: 1.31, p<0.01	Baseline: 2.17 6th week: 1.92 12th week: 1.83	
			The geometric mean value (range of 1 SD) of PD20	Before treatment: 87.1 (47.3-160.4) BU After roxithromycin: 169.2 (83.2-344.2) BU; p<0.01	Before treatment: 74.2 (36.6-150.4) After treatment: 82.7 (41.8-163.7) BU; p>0.1	
LRTIs[39]	Open, randomized, parallel-group study; n=60	Roxithromycin 300 mg OD (n=25); Clarithromycin 500 mg BD (n=25); minimum duration of 3 days	Clinical response satisfactory	88%	-	80%
			Adverse events	3%	-	23.3%

Note: BD-Twice daily; BU-Breath units; CAP- Community-acquired pneumonia; LRTIs-Lower respiratory tract infections; OD-Once daily; TID- Thrice daily. Clinical cure rates are reported in % of patients.

Table 6: Efficacy and safety of roxithromycin in respiratory tract infections.

Conditions	Study details	Patients; intervention; comparator	Parameters	Outcomes	Comparator
RTIs[40]	Open trial	32,405 patients, including 18,020 with URTIs and 14,385 with LRTIs; Roxithromycin	Clinical resolution or improvement in URTIs	Acute pharyngitis/ tonsillitis: 97% Sinusitis: 96% Otitis: 96%	-
			Clinical resolution or improvement rates for LRTIs	Bronchitis: 97% Exacerbation of chronic bronchitis: 94% Pneumonia: 95%	
			Side effects	4%	-
RTIs[41]	Double-blind trial	Roxithromycin (150 mg BD, n=48); amoxicillin-clavulanate (500 mg/125 mg TID, n=48)	Clinical response	96%	95%
			Adverse events	4%	17%
RTIs[42]	12 studies meta-analysis	Roxithromycin (n=331; 268-150 mg BID, 63-300 OD); various other antibiotics (n=53)	Overall clinical response (per protocol)	87%	All comparators: 77% Erythromycin: 50% Amoxicillin/clavulanic acid: 80%
			Clinical response on an 'intention-to-treat' (ITT) basis	78%	All comparators: 70% Erythromycin: 45% Amoxicillin/clavulanic acid: 86%
			Overall clinical response (ITT) for *H. influenzae*	81%	70%
			Efficacy in cases of pneumonia, with *H. influenzae*	93% (p=0.02)	53%
			Efficacy in cases of pneumonia, sinusitis, and otitis media	79% (p>0.05)	70%

CONCLUSION

With the global burden of RTIs causing significant morbidity and mortality, the need for effective treatments is important. Roxithromycin presents itself as a promising therapeutic option in the management of RTIs. It has demonstrated bacteriostatic and bactericidal properties and exhibits a favorable pharmacokinetic profile with satisfactory tissue penetration.

Beyond its antimicrobial actions, roxithromycin exhibits anti-inflammatory effects, which further enhance its efficacy in treating a wide range of respiratory infections. By modulating neutrophilic effects, reducing pro-inflammatory cytokines, and inhibiting mucus secretion, roxithromycin addresses not only the microbial aspect but also the inflammatory component of RTIs.

Clinical studies have consistently demonstrated that roxithromycin is effective and well-tolerated, and provides comparable or better outcomes to other antibiotics commonly used in RTIs. Its accumulation in immune cells like polymorphonuclear leukocytes and macrophages further enhance its potency against intracellular pathogens, contributing to its broad spectrum of activity.

Overall, roxithromycin is a valuable therapeutic agent, offering efficacy, tolerability, and favorable pharmacokinetic and pharmacodynamic properties in the treatment of RTIs.

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REFERENCES

1. Rogan M. Respiratory Infections, Acute. Int Encyclopedia Publ Health. 2017;332-6.
2. Van Eyk AD. Treatment of bacterial respiratory infections. South African Family Practice. 2019;61(2):8-15.
3. Reed KD. Respiratory Tract Infections: A Clinical Approach. Molecular Med Microbiol. 2015;1499-506.
4. Cooke J, Llor C, Hopstaken R, Dryden M, Butler C. Respiratory tract infections (RTIs) in primary care: narrative review of C reactive protein (CRP) point-of-care testing (POCT) and antibacterial use in patients who present with symptoms of RTI. BMJ Open Respir Res. 2020;7(1):e000624.
5. Chen AP, Chuang C, Huang YC, Wu PF, Huang SF, Cheng NC, et al. The epidemiology and etiologies of respiratory tract infection in Northern Taiwan during the early phase of coronavirus disease 2019 (COVID-19) outbreak. J Microbiol Immunol Infect. 2021;54(5):801-7.
6. Vázquez-Laslop N, Mankin AS. How Macrolide Antibiotics Work. Trends Biochem Sci. 2018;43(9):668-84.
7. Blondeau JM. Immunomodulatory Effects of Macrolides Considering Evidence from Human and Veterinary Medicine. Microorganisms. 2022;10(12):2438.
8. Pollock J, Chalmers JD. The immunomodulatory effects of macrolide antibiotics in respiratory disease. Pulm Pharmacol Ther. 2021;71:102095.
9. Lin X, Lu J, Yang M, Dong BR, Wu HM. Macrolides for diffuse panbronchiolitis. Cochrane Database Syst Rev. 2015;1(1):CD007716.
10. Markham A, Faulds D. Roxithromycin. An update of its antimicrobial activity, pharmacokinetic properties and therapeutic use. Drugs. 1994;48(2):297-326.
11. Young RA, Gonzalez JP, Sorkin EM. Roxithromycin. A review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. Drugs. 1989;37(1):8-41.
12. Roxithromycin. New Zealand Data Sheet. Available at: https://www.medsafe.govt.nz/profs/datasheet/a/ArrowRoxithromycintab.pdf. Accessed on 13 May 2024.
13. Kuenzi B, Segessenmann C, Gerber AU. Postantibiotic effect of roxithromycin, erythromycin, and clindamycin against selected gram-positive bacteria and *Haemophilus influenzae*. J Antimicrob Chemother. 1987;20(B):39-46.
14. Siu J, Klingler L, Wang Y, Hung CT, Jeong SH, Smith S, et al. Oral antibiotics used in the treatment of chronic rhinosinusitis have limited penetration into the sinonasal mucosa: a randomized trial. Xenobiotica. 2020;50(12):1443-50.
15. Hand WL, King-Thompson N, Holman JW. Entry of roxithromycin (RU 965), imipenem, cefotaxime, trimethoprim, and metronidazole into human polymorphonuclear leukocytes. Antimicrob Agents Chemother. 1987;31(10):1553-7.
16. Carlier MB, Zenebergh A, Tulkens PM. Cellular uptake and subcellular distribution of roxithromycin and erythromycin in phagocytic cells. J Antimicrob Chemother. 1987;20(B):47-56.
17. Cervin A, Wallwork B. Efficacy and safety of long-term antibiotics (macrolides) for the treatment of chronic rhinosinusitis. Curr Allergy Asthma Rep. 2014;14(3):416.
18. Tamaoki J, Takeyama K, Yamawaki I, Kondo M, Konno K. Lipopolysaccharide-induced goblet cell hypersecretion in the guinea pig trachea: inhibition by macrolides. Am J Physiol. 1997;272(1 Pt 1):L15-9.
19. Tamaoki J. The effects of macrolides on inflammatory cells. Chest. 2004;125(2):41S-50S.
20. Tamaoki J, Kondo M, Kohri K, Aoshiba K, Tagaya E, Nagai A. Macrolide antibiotics protect against immune complex-induced lung injury in rats: role of nitric oxide from alveolar macrophages. J Immunol. 1999;163(5):2909-15.
21. Nakamura H, Fujishima S, Inoue T, Ohkubo Y, Soejima K, Waki Y, et al. Clinical and immunoregulatory effects of roxithromycin therapy for chronic respiratory tract infection. Eur Respir J. 1999;13(6):1371-9.
22. Zimmermann P, Ziesenitz VC, Curtis N, Ritz N. The Immunomodulatory Effects of Macrolides-A Systematic Review of the Underlying Mechanisms. Front Immunol. 2018;9:302.
23. Shirsat A, Khandke DA, Patankar A. Comparison of the *in vitro* Sensitivity of Respiratory Pathogens to Roxithromycin, Amoxicillin and Amoxicillin+ Clavulanic Acid. The Indian Practitioner. 2017:11-5.
24. EUCAST. Available at: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_14.0_Breakpoint_Tables.pdf. Accessed on 5 March 2024.
25. Tamaoki J, Nakata J, Tagaya E, Konno K. Effects of roxithromycin and erythromycin on interleukin 8-induced neutrophil recruitment and goblet cell secretion in guinea pig tracheas. Antimicrob Agents Chemother. 1996;40(7):1726-8.
26. Rubin BK. Physiology of airway mucus clearance. Respir Care. 2002;47(7):761-8.
27. Shimizu T, Shimizu S, Hattori R, Gabazza EC, Majima Y. *In vivo* and *in vitro* effects of macrolide antibiotics on mucus secretion in airway epithelial cells. Am J Respir Crit Care Med. 2003;168(5):581-7.
28. Chatzimanolis E, Marsan N, Lefatzis D, Pavlopoulos A. Comparison of roxithromycin with co-amoxiclav in patients with sinusitis. J Antimicrob Chemother. 1998;41(B):81-4.
29. Gotfried MH. Macrolides for the treatment of chronic sinusitis, asthma, and COPD. Chest. 2004;125(2):52S-60.
30. Kimura N, Nishioka K, Nishizaki K, Ogawa T, Naitou Y, Masuda Y. Clinical effect of low-dose,

long-term roxithromycin chemotherapy in patients with chronic sinusitis. Acta Med Okayama. 1997;51(1):33-7.
31. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope. 2006;116(2):189-93.
32. Mira E, Benazzo M. A multicenter study on the clinical efficacy and safety of roxithromycin in the treatment of ear-nose-throat infections: comparison with amoxycillin/clavulanic acid. J Chemother. 2001;13(6):621-7.
33. de Campora E, Camaioni A, Leonardi M, Fardella P, Fiaoni M. Comparative efficacy and safety of roxithromycin and clarithromycin in upper respiratory tract infections. Diagn Microbiol Infect Dis. 1992;15(4):119S-22S.
34. Salvarezza CR, Mingrone H, Fachinelli H, Kijanczuk S. Comparison of roxithromycin with cefixime in the treatment of adults with community-acquired pneumonia. J Antimicrob Chemother. 1998;41(B):75-80.
35. Hatipoglu ON, Tasan Y. A comparative efficacy and safety study of clarithromycin, roxithromycin and erythromycin stearate in mild pneumonia. Yonsei Med J. 2000;41(3):340-4.
36. Kaku M, Kohno S, Koga H, Ishida K, Hara K. Efficacy of roxithromycin in the treatment of *Mycoplasma pneumonia*. Chemotherapy. 1995;41(2):149-52.
37. Juthong S, Eiamsa-ard S. Roxithromycin as Anti-Inflammatory Drug Improves Clinical Outcomes in Adult Patients with Bronchiectasis: A Double-Blinded Randomized, Placebo-Controlled Pilot Clinical Trial. J Health Sci Med Res. 2019;22;37(3):229-36.
38. Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: a double-blind, placebo-controlled study. Eur Respir J. 1997;10(5):994-9.
39. Tatsis G, Tsoukalas G, Boulbasakos G, Platsouka E, Anagnostopoulou M, Pirounaki M, et al. Efficacy and tolerance of roxithromycin versus clarithromycin in the treatment of lower respiratory tract infections. J Antimicrob Chemother. 1998;41(B):69-73.
40. Marsac JH. An international clinical trial on the efficacy and safety of roxithromycin in 40,000 patients with acute community-acquired respiratory tract infections. Diagn Microbiol Infect Dis. 1992;15(4):81S-4S.
41. Lousbergh D, Jochems G, Everaert L, Puttemans M. Roxithromycin versus amoxicillin-clavulanic acid in the treatment of respiratory tract infections. Diagn Microbiol Infect Dis. 1992;15(4):91S-5S.
42. Cooper BC, Mullins PR, Jones MR, Lang SD. Clinical efficacy of roxithromycin in the treatment of adults with upper and lower respiratory tract infection due to *Haemophilus influenzae*: a meta-analysis of 12 clinical studies. Drug Investigation. 1994;7:299-314.

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