

Anti-inflammatory activity of macrolides: a new therapeutic potential?

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The important role played by macrolides in the chemotherapy of infectious diseases is well established, but there is still much speculation about their anti-inflammatory potential. A review of in-vitro and ex-vivo studies reported in the literature shows that macrolides have potentially relevant immunomodulatory effects. In-vitro data suggest that erythromycin A derivatives have a direct effect on neutrophil function and the production of cytokines involved in the inflammation cascade. The ex-vivo results indicate that short-term administration of macrolides may enhance the immune response while long-term administration results in immunosuppression. Further research is required to improve our understanding of the therapeutic activity of macrolides.

Introduction

Macrolides are a long-used class of antibiotics which still play an important role in the chemotherapy of infectious diseases. Their activity in infections caused by intracellular pathogens was the basis for the development in the 1980s of new derivatives with improved tolerance, antimicrobial activity and pharmacokinetics.^{1–3} However, the possibility that the intracellular accumulation (a characteristic of this family) of these drugs⁴ also alters host cell functions has recently triggered a new interest in their therapeutic potential in clinical settings other than infections.^{5,6}

In particular, the interference of macrolides with the natural effectors involved in antimicrobial defences and inflammation is an area under active investigation.⁷ Such research is part of the larger, complex investigation of the immunomodulatory activity of antimicrobial agents^{8–10} which aims to improve the use of antimicrobials in infectious diseases associated with immunodeficiencies and exaggerated inflammatory responses. On the other hand, the therapeutic activity of some antimicrobials, such as chloroquine, cyclines and ansamycins, in clinical settings other than infections, particularly inflammatory diseases, has been clearly established.^{11–13} The aim of this review is to focus on the anti-inflammatory potential of macrolides, from the clinical data to the hypothetical mechanisms underlying this activity.

Our understanding of the pathophysiological processes involved in the beneficial and detrimental aspects of the inflammatory response has greatly improved in the past

few years. Detailed information on the various and intricate humoral and cellular effector systems may be obtained from some excellent reviews.^{14–18}

Clinical studies

The question of whether macrolides can attenuate inflammatory responses was first raised over 20 years ago.^{19–21} In particular, erythromycin and troleandomycin were shown to affect favourably the clinical status of patients with severe steroid-dependent asthma. The steroid-sparing effect of these drugs and their inhibition of theophylline clearance were postulated to contribute to their beneficial action in the treatment of asthma. However, mechanisms other than drug interactions may explain the beneficial effects of erythromycin alone or in combination with corticosteroids in the treatment of asthma and chronic obstructive pulmonary diseases. For example, Miyatake *et al.*²² observed that long-term administration of low-dose erythromycin reduced airway hyper-responsiveness in asthma.

Empirical clinical experience and one clinical study suggest that erythromycin is useful in decreasing mucus secretion in diseases such as acute and chronic bronchitis and asthma.²³ A similar effect has been demonstrated recently in patients with chronic bronchitis and bronchiectasis receiving clarithromycin.²⁴ This is supported by the in-vitro studies of Goswami *et al.*,²⁵ who reported that erythromycin reduced spontaneous and histamine-

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stimulated secretion of glycoconjugate by human airways. This effect was additive to that of dexamethasone. Tamaoki *et al.*²⁶ observed that pretreatment with roxithromycin or erythromycin resulted in a dose-dependent inhibition of goblet cell secretion and mucosal infiltration of neutrophils after interleukin 8 (IL-8) inhalation in guinea pigs. The newer macrolides are also effective in the treatment of acute exacerbation of chronic bronchitis and community-acquired pneumonia, diseases characterized by the frequent isolation of *Haemophilus influenzae*, a pathogen specifically adapted to colonize and damage the lower respiratory tract. Recently, Khair *et al.*²⁷ suggested that macrolides may decrease the detrimental effect of the host response to this organism.

The most intriguing and exciting feature of the therapeutic non-antibacterial potential of macrolides has been developed recently in Japan, where these antibiotics have been shown to be effective in treating diffuse pan-bronchiolitis (DPB). DPB is a disease of adults, prevalent in Japan, although some rare cases have been described in North America and Italy. The disease is characterized by chronic inflammation of the respiratory bronchioles and the infiltration of chronic inflammatory cells.²⁸ It progresses insidiously and results in respiratory failure caused by repeated episodes of respiratory infections, especially *Pseudomonas aeruginosa* infections. In Japan, several studies have examined the effects of empirical treatment of DPB with erythromycin. The clinical effectiveness of oral erythromycin is well established²⁹⁻³¹ but its pharmacological activity is unknown. However, all data support the hypothesis that the efficacy of erythromycin depends on mechanisms other than bactericidal activity. In particular, polymorphonuclear neutrophils (PMN) seem to play a crucial role in the deterioration of patients with DPB: excessive influx of these cells, which would result in localized production of detrimental oxidants and proteolytic enzymes, has been suggested as the cause of airway destruction.

Most studies have shown that the bronchoalveolar lavage (BAL) fluids of patients with DPB contain a high density of neutrophils and increased elastolytic-like and neutrophil chemotactic activities, neutrophil elastase, leukotriene B₄ (LTB₄) and IL-8. Lung function parameters were improved parallel to the decrease of these immunological dysfunctions after administration of erythromycin 600 mg/day for 3–12 months.³²⁻³⁴ Clindamycin, piperacillin or ampicillin taken as comparators were ineffective both on clinical symptoms and immunological parameters. Erythromycin has been the drug most extensively used in this context, but recently Shirai *et al.*³⁵ compared the efficacy of erythromycin (400 or 600 mg) with that of roxithromycin (150 or 300 mg) and clarithromycin (200 or 400 mg) given for 2 months or longer to patients with DPB or bronchiectasis: all three drugs were found to behave similarly, with a clinical efficacy in DPB of 86% (roxithromycin), 79% (erythromycin) and 67%

(clarithromycin), and in bronchiectasis >50% for all these drugs. In addition, azithromycin has been used successfully in DPB.³⁶ Kadota³⁷ and Sakito *et al.*³⁸ have reported recently that roxithromycin (150 mg/day for 1–12 months) was as effective as erythromycin (600 mg/day for 2–24 months) in improving the clinical status of DPB patients and reducing the number of neutrophils in BAL fluid as well as the amount of IL-1 β , IL-8 and the chemo-attractant LTB₄. The expression of the adhesion molecule macrophage-activating complex-1 (MAC-1) on peripheral neutrophils of DPB patients was significantly reduced after macrolide therapy.³⁷ Extensive clinical trials are required to determine whether there is a significant difference in the therapeutic activity of the erythromycin A derivatives. Interestingly, josamycin and other 16-membered ring macrolides are not beneficial in DPB patients.

The basis for this differential therapeutic activity of erythromycin A derivatives and 16-membered ring macrolides is unknown, but studies *in vitro* (see below) have also shown some differences in the modulation of phagocyte functions by these two subgroups of macrolides.

Animal models

One of the earliest studies showing an effect of erythromycin *in vivo* on immune parameters was carried out by Nelson *et al.*³⁹ Mice were challenged by aerosol with *Proteus mirabilis* or *Staphylococcus aureus* and injected intravenously with erythromycin 50–100 mg/kg. The number of total lavaged lung cells and, particularly, of PMN was decreased in erythromycin-treated mice; in parallel, pulmonary bactericidal activity was decreased for *P. mirabilis* but not for *S. aureus*. The authors proposed that this inhibitory activity could be the cause of bacterial superinfections in erythromycin-treated patients. However, a decreased neutrophilia in BAL of DPB patients may help reduce PMN-induced alveolar destruction. Similarly, Kadota *et al.*³³ reported that intratracheal injection of lipopolysaccharide (LPS) in mice promoted the accumulation of PMN in BAL fluid. Erythromycin (2 mg) given intraperitoneally 2 h before challenge markedly suppressed the intrapulmonary accumulation of PMN. IL-8-induced neutrophilia in BAL fluid was also diminished by erythromycin administration. A similar effect was described by Tamaoki *et al.*⁴⁰ in a model of endotoxin-induced vascular leakage and neutrophil accumulation in rat trachea. In this model, the efficacy of roxithromycin (10 mg/kg/day for 7 days) was equal to that of erythromycin. In addition, Mikasa *et al.*⁴¹ observed that long-term administration of erythromycin (10 mg/kg for 28 days) was as effective as dexamethasone in reducing intraperitoneal extravasation and neutrophil accumulation in a model of zymosan-induced peritonitis.

Other animal models have demonstrated the anti-inflammatory effectiveness of macrolides; for example, erythromycin proved beneficial in various acute mouse ear inflammation models.⁴² Recently, roxithromycin was also shown to be as active as indomethacin in rats in reducing hind-paw oedema induced by poly-L-arginine, slightly less effective in the L-carrageenan hind-paw oedema model and the croton oil-induced ear oedema, and not active in a chronic inflammation model.⁴³ Interestingly, only roxithromycin (not clarithromycin or azithromycin) exerted a relevant anti-inflammatory activity comparable to that of nimesulide in a model of carrageenan-induced paw oedema in rats.⁴⁴

Mechanisms of action

Although there is now abundant literature on the anti-inflammatory potential of macrolides, the underlying mechanism has not been elucidated. Given the complexity of the inflammatory response and the multiple effectors and targets involved, it is likely that these drugs act at different steps by identical or different mechanisms. The aim of in-vitro and ex-vivo studies for animals and humans has been to determine the targets of macrolide activities.

Since phagocytes and their products (oxidants, enzymes and cytokines) are key effectors in inflammation, most studies have been directed at the analysis of the modulation of their functional activities by macrolides.^{7,45} Other groups have investigated the possible macrolide-induced alteration of cytokine production.

Studies *ex vivo*

The immunomodulatory activity of macrolides in humans—the analysis *ex vivo* of immune parameters from patients or volunteers receiving macrolides—has been little explored. Anderson *et al.*⁴⁶ reported that a single oral dose of erythromycin stearate 500 mg increased PMN migration in healthy volunteers. This stimulatory effect of erythromycin (500 mg tds for 4 days) was also observed in six patients with persistently abnormal PMN chemotaxis and a history of chronic or recurrent bacterial infections.⁴⁷ Co-trimoxazole (500 mg bid for 4 days) was not effective in this system. Controversial results were provided by Torre *et al.*,⁴⁸ who observed that the ingestion of erythromycin ethylsuccinate (750 mg tds), josamycin (500 mg tds), miokamycin (600 mg bid), roxithromycin (150 mg bid) or rokitamycin (400 mg bid) for 4 days by healthy volunteers decreased PMN chemotaxis. Other studies showed that a single dose of roxithromycin 300 mg given to healthy volunteers enhanced PMN functions *ex vivo*,⁴⁹ whereas repeated doses of 300 mg/day for 7 days were associated with decreased production of oxidant by PMN in five out of six individuals.⁵⁰ Erythromycin (500 mg/day) did not alter any parameter of PMN functions. In an early study,

Martin *et al.*⁵¹ also noted that erythromycin (250 mg qds for 7 days) did not modify the oxidative response of PMN from healthy volunteers. A major problem for ex-vivo analyses of *in vivo*-induced modification of phagocyte functions is the possibility of drug efflux during cell isolation. Recently, using a technique in whole blood which does not require neutrophil isolation, Wenisch *et al.*⁵² have observed that a single oral dose of azithromycin (20 mg/kg) reduced neutrophil phagocytosis and oxidant production, whereas clarithromycin (8–12 mg/kg) slightly reduced phagocytosis only and roxithromycin (8–12 mg/kg) did not alter any parameter. Further studies are required, particularly in healthy individuals and patients receiving long-term treatment with macrolides, before any significant conclusions can be drawn.

Modification of cytokine production by macrolides has been explored mainly in animals. In general, short-term (7–28 days) administration of macrolides resulted in an enhanced immune response, whereas long-term treatment was associated with a decreased response. This was shown with erythromycin and roxithromycin which induced and increased production of IL-1, IL-2 and TNF- α by mouse cells stimulated *ex vivo*^{53–57} when the drugs were given for 7–28 days, whereas administration of roxithromycin for longer periods (42 days) caused a significant decrease of IL-1 and IL-2 production.^{56,57} IL-5 production was reduced throughout the test period (days 7–28). Fewer studies have been conducted in humans. Erythromycin given for 5 days (600 mg/day) increased IL-1 α and tumour necrosis factor γ (TNF- α) production by blood monocytes stimulated with phorbol myristate acetate (PMA) or interferon γ (IFN- γ)⁵⁸ and the mononuclear cells of individuals receiving azithromycin for 3 days (500 mg/day) released an increased amount of IL-2 receptor after PMA and phytohaemagglutinin (PHA) stimulation.⁵⁹ In a preliminary study,⁶⁰ erythromycin treatment (250 mg tds for 4 weeks) was associated with a decreased amount of IL-8 in the sputum of four adults with cystic fibrosis. The secretion of IL-8 by IL-1 β -stimulated alveolar macrophages of two individuals receiving erythromycin (600 mg/day) for 4 weeks was less than values obtained before treatment.³⁸ As indicated above, long-term treatment with erythromycin A-derived macrolides also decreases the production of IL-1 β and IL-8 in the BAL fluid of DPB patients.^{34,38}

Studies *in vitro*

Erythromycin A derivatives directly inhibit in-vitro oxidant production by phagocytes.^{61–66} Although most studies have been conducted with roxithromycin, data now show that all erythromycin A derivatives, including azithromycin and clarithromycin, but not the 16-membered ring macrolides, are endowed with this inhibitory property.^{67,68} The inhibitory effect of macrolides is time-dependent and may be obtained with a low concentration

(10–20 mg/L) achievable therapeutically at least in tissues. The mechanisms underlying this activity are still unclear. Perry *et al.*⁶⁹ suggested that roxithromycin inhibited phosphatidate phosphohydrolase, an enzyme that hydrolyses phosphatidic acid into diacyl glycerol, an activator of protein kinase C, whereas Mitsuyama *et al.*⁶⁶ proposed that protein kinase A is involved in the antioxidant activity of erythromycin. Further work is still required to clarify the neutrophil target of macrolides and the chemical structure involved in macrolide-induced inhibition. All erythromycin A derivatives impair oxidant production and, in parallel, promote neutrophil degranulation,^{70,71} suggesting that a common step in the transductional pathways involved in both functional activities is altered by this subgroup of macrolides. Preliminary data from our laboratory have shown that erythromycin A derivatives directly activate phospholipase D,⁷² while inhibiting the phosphatidate phosphohydrolase in a time- and concentration-dependent manner.

Other phagocyte functional activities modified by macrolides include chemotaxis, but, depending on the technique used to assess this parameter, both an increase and an inhibition of this function have been described.⁷

Macrolides interfere with cytokine production *in vitro*. Spiramycin (10–50 mg/L) and, to a lesser extent, erythromycin, but not roxithromycin, increase IL-6 release by LPS-stimulated human monocytes without affecting IL-1 α , IL-1 β and TNF production by these cells.⁷³ In contrast, Takizawa *et al.*⁷⁴ demonstrated that erythromycin and clarithromycin were able to suppress IL-6 production by IL-1 α -stimulated bronchial epithelial cells as well as IL-6 mRNA expression. In addition, Brennan *et al.*⁶⁰ reported that erythromycin but not roxithromycin decreased the production of IL-6 and IL-8 by an IL-1-stimulated epithelial cell line; similarly, Khair *et al.*²⁷ demonstrated the inhibitory effect of erythromycin (0.1, 1 mg/L) on the expression and release of IL-6 and IL-8 by cultured human bronchial epithelial cells after stimulation with *H. influenzae* endotoxin or IL-1 β . Various studies have also shown that erythromycin moderately impaired IL-8 production by pseudomonas-stimulated (not IL-1 β -stimulated) neutrophils without altering that of macrophages³⁴ and that erythromycin, roxithromycin and clarithromycin (but not josamycin or midecamycin) significantly reduced IL-8 production by LPS-stimulated THP-1 cells.⁷⁵ Josamycin, midecamycin and clarithromycin have also been reported to decrease, in descending order, the production of IL-2 by LPS-stimulated human monocytes.⁷⁶ Recently, the same group⁷⁷ reported that clarithromycin decreased TNF- α , IL-1 α , IL-1 β , IL-1 receptor antagonist (IL-1 ra) and granulocyte macrophage colony stimulating factor (GM-CSF), depending on concentration, while it increased IL-10 production by LPS-stimulated human monocytes, suggesting that macrolides may modify acute-phase inflammatory cytokines. TNF- α production by LPS-stimulated human

Table I. Clinical efficacy of macrolides as anti-inflammatory agents and effect on immune parameters

	Effective drugs	Immune parameter decrease
Demonstrated clinical efficacy ^{29–38} diffuse panbronchiolitis bronchiectasis	erythromycin, roxithromycin, (clarithromycin, azithromycin ^d) long-term, low-dose administration	(in BAL fluid) neutrophilia, elastase, chemotactic activity, IL-8, IL-1 β and LTB ₄
Other clinical uses ^{23–26} asthma COPD acute exacerbation of chronic bronchitis Potential clinical use ⁸⁶ cystic fibrosis	erythromycin (and other macrolides) erythromycin (and others?)	airway hyperresponsiveness (<i>in vitro</i>) mucus secretion (<i>in vitro</i> , <i>in vivo</i>) IL-8 (sputum)

BAL = bronchoalveolar lavage.

^aStudies with clarithromycin and azithromycin have been limited.

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Table II. The anti-inflammatory activity of macrolides in animal models and effect on immune parameters

Models	Macrolides	Immune parameter decrease
Bacterial challenge (aerosol)	erythromycin	PMN accumulation in lung and lung bactericidal activity
LPS, IL-8 intratracheal	erythromycin, roxithromycin	PMN in BAL fluid
Zymosan-induced peritonitis	erythromycin	PMN intraperitoneal
Poly-L-arginine	roxithromycin, indomethacin ^a	oedema
L-Carrageenan	roxithromycin, nimesulide ^a	

^aThese two had equivalent effectiveness.

monocytes was reported to be decreased by erythromycin.⁷⁸ Clarithromycin and erythromycin suppressed IL-1 production by LPS-stimulated peritoneal macrophages of mice, with clarithromycin having a stronger effect,⁷⁹ and the supernatant of mouse splenocytes cultured in the presence of roxithromycin for 7 days suppressed the production of TNF- α by LPS-stimulated macrophages, an effect probably due to IL-4 production.⁵⁵

Additional effects

Other effects of macrolides on host cells have been described. For instance, Tamaoki *et al.*⁸⁰ showed that erythromycin, roxithromycin and clarithromycin, but not ampicillin or cefazolin, attenuated neurally mediated contraction in airway smooth muscle. The authors suggested that macrolides could decrease the exocytotic release of acetyl choline. Nagai *et al.*⁸¹ reported that roxithromycin specifically inhibited the growth of HL 60 cells partly by inducing the formation of multinucleate cells, and Aoshiba *et al.*⁸² observed that erythromycin, roxithromycin, clarithromycin and midecamycin (10 mg/L) shortened neutrophil survival by accelerating apoptosis. The authors proposed that apoptosis would limit the ability of neutrophils to damage tissues by directly inhibiting their capacity to release potentially harmful products. Finally, Keicho *et al.*⁸³ demonstrated that erythromycin promoted the differentiation of monocytes to macrophages.

Summary and future prospects

The macrolides have some potentially useful immunomodulatory effects (Tables I–III). It is still not possible to identify precisely the cellular targets of these molecules, or the cascade of events stimulated by macrolide administration. The difficulties of the analysis, as stressed elsewhere,^{8,9} reside primarily in our incomplete understanding of the functioning of the immune system, both under homeostatic and pathophysiological conditions. Furthermore, the models currently available for the

analysis of drug-induced immunomodulation are far removed from the situation *in vivo*; for example, isolated cells and cell lines of different origins, in different states (resting, activated or elicited) and suspended in artificial medium; inter-species differences in immune responses, chronobiology, metabolism; healthy individuals versus infected/non-infected patients. The complex effects of any xenobiotic on the host must take into account its peculiar pharmacokinetic profile and pharmacological actions, as well as the homeostatic and pathological interactions of the various host systems in response to the environment.

With respect to the macrolides, it is clear that their pharmacokinetics are a key feature both in terms of their antimicrobial activity and their modulatory effect on host cell functions.⁸⁴ Critical targets of the macrolides appear to be the phagocytes and, particularly, the neutrophils, which accumulate these drugs and probably participate in their targeted delivery. Phagocytes and their products—cytokines, oxidants and enzymes—are chief effector cells in inflammatory diseases including bronchiectasis, DPB and chronic bronchitis, diseases that respond favourably to macrolide administration (see above). All *in-vitro* data (the only possible approach to the understanding of the mechanism of drug-induced alteration) reinforce the hypothesis of a direct effect of macrolides on neutrophil function (decreased oxidant production, apoptosis) and on the production of the cytokines involved in the inflammation cascade (decreased production of IL-1, IL-6, IL-8, TNF and increased production of IL-10 and, possibly, IL-4). Not all the macrolides have been assessed in this context, but at the present time it seems that only erythromycin A derivatives are endowed with these *in-vitro* anti-inflammatory properties. From the *ex-vivo* results reported in the literature, there appears to be some agreement that short-term administration of macrolides (for infection) results in enhancement of the immune response (a possible benefit in the treatment of infectious diseases), while long-term administration (in animals and DPB patients) results in immunosuppression. The key desired effect lies somewhere between these two thera-

Table III. Anti-inflammatory activity of macrolides and possible immune parameters affected

Study	Macrolides	Immune parameters	
		decreased	increased
PMN functions <i>in vitro</i> <i>ex vivo</i>	erythromycin derivatives erythromycin derivatives	oxidant production oxidant production?	degranulation; chemotaxis? chemotaxis?
Cytokines <i>in vitro</i> humans	erythromycin, clarithromycin erythromycin, roxithromycin, and clarithromycin clarithromycin	IL-6 IL-8 IL-1 α , IL-1 β , TNF- α , GM-CSF, IL-1ra TNF- α	IL-10
animals <i>ex vivo</i> humans	erythromycin clarithromycin–erythromycin roxithromycin–erythromycin erythromycin (5 days) azithromycin (3 days) erythromycin (4 weeks)	IL-1 TNF- α	IL-4?
animals	erythromycin, roxithromycin (≤ 28 days) roxithromycin (42 days)	IL-8 IL-5 IL-1, IL-2	IL-1 α , TNF- α IL-2r IL-1, TNF- α , IL-2, IL-4, IFN- γ

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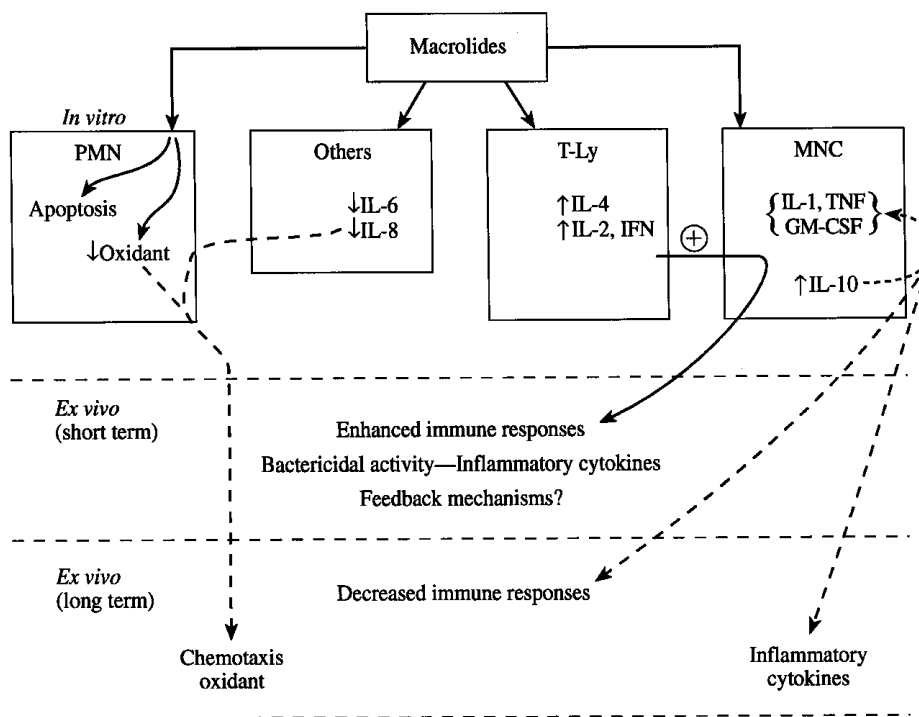


Figure. Proposed immunomodulatory activities induced by macrolides (derived from *in vitro* and *ex vivo* data).

peutic schemes and has not yet been identified. It is likely that long-term administration, which would result in greater cellular accumulation, triggers mechanisms other than those obtained at lower concentrations. A possible cascade of events derived from *in-vitro* to *ex-vivo* data is proposed in the Figure. Not all the components of this puzzling system have yet been identified or even, in some cases, assessed. For instance, the cellular expression of the various adhesion molecules, which plays an unambiguous role in the migration of neutrophils to inflammatory sites, has been little explored in the presence of macrolides. Khair *et al.*²⁷ have reported that the secretion of soluble ICAM-1 by *H. influenzae* endotoxin-stimulated human bronchial cells was suppressed by erythromycin (0.1–10.0 mg/L) and that this drug decreased the adherence of PMN to stimulated human endothelial cells. MAC-1 expression on peripheral neutrophils of DPB patients was reduced after macrolide therapy.³⁷

The potential use of macrolides as anti-inflammatory agents is still in its infancy. Much work remains to be done *in vitro* to determine the chemical pathways involved. Recently, Kobayashi^{30,31} suggested that the sugar moieties of macrolides, but not the lactone ring, were important for the efficacy of these drugs against diseases associated with the formation of biofilms. Similar conclusions have been reached by my own group⁸⁵ with regard to the direct effects of macrolides on neutrophil function. This is the first step in the elucidation of the structure–activity relationships of new macrolides (or of any new anti-inflammatory agent). The second important aspect of the

investigation *in vitro* is the characterization of the cellular targets of macrolide action. Whereas such laboratory investigations are currently being done with regard to neutrophils, study of the effect of macrolides on lymphocytes or monocytes still remains largely theoretical. It is necessary to identify the transduction pathway modified by macrolide molecules and perhaps to define a common cellular structure involved in transduction systems for different cell types. The immunosuppressants rapamycin and FK 506 would be suitable examples; they are structurally related to the macrolides and are targeted to the proteins of the FK 506-binding protein (FKBP) family which are of paramount importance both in eukaryotic and prokaryotic cells.

Although many fundamental aspects of macrolide–host cell interactions still remain to be elucidated, the future looks hopeful. In 1984, the prognosis of patients with DPB was very poor: the 5 year survival rate was only 26% for patients infected with *P. aeruginosa* and 55% for all other types of DPB. Since erythromycin has become the common therapy for DPB, the 10 year survival rate for all types of DPB has increased to 94%.^{30,31} These unexpectedly favourable results are encouraging the initiation of clinical trials of macrolides in cystic fibrosis, a congenital disease that has clinical and pathophysiological similarities to DPB.⁸⁶ They should also stimulate the fundamental research required to solve the problems outlined above and lead to the availability of new and safer anti-inflammatory drugs in the twenty-first century.

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