

特別講演 2

A global perspective on macrolide use

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Introduction

Erythromycin A was first marketed in 1952 as an alternative therapy to β -lactam agents for the treatment of infections with Gram-positive cocci. During the 1990's clarithromycin and roxithromycin (not used in the US) were introduced and in 1994 azithromycin, a 15-member azalide antimicrobial, was introduced. These medications have an increased spectrum of activity, less frequent dosing, and a significant reduction in gastrointestinal side effects¹⁾.

Globally, 20% of the anti-infective market is held by macrolides with azithromycin having a 9% market share and clarithromycin an 8% market share in 2001. In the United States in 2002, macrolides accounted for 23.3% of antibiotic sales, quinolones 26.6%, cephalosporins 17.9%, and β -lactams 20.9% (Fig. 1). Between 1997 and 2001 there has been a 1.1% decrease in macrolide use worldwide, a 3.8% reduction in cephalosporin use, a 1.7% decrease in broad spectrum penicillin use, but a 12.6% increase in fluoroquinolone use. Overall there has been a 1.3% reduction in antibiotic use during these four years. Respiratory infections accounted for 41% of anti-infective drugs use in 2002 and in that same year antibiotics sales were 10.6 billion dollars in the United States (Fig. 2).

Immunomodulation and DPB

Interest in the immunomodulatory effects of macrolide antibiotics began in the 1960s with the observation that the 14-member antibiotic, troleandomycin, was an effective "steroid-sparing" agent when used to treat patients with severe asthma²⁾. It

has been 20 years since the immunomodulatory effects of macrolides were established for the treatment of DPB in Japan making these medications the treatment of choice for DPB³⁾. Because of this, erythromycin and clarithromycin are also widely used in Japan for the therapy of sinusitis and chronic obstructive pulmonary disease (COPD)⁴⁾.

In the 1980's erythromycin was first used for the treatment of diffuse panbronchiolitis (DPB) as an immunomodulatory agent. In the last two years, clarithromycin and azithromycin have been widely adopted as immunomodulatory agents for the treatment of cystic fibrosis and bronchiectasis in Europe and North America. There is a great deal of research underway to evaluate if these agents will also be effective for other chronic inflammatory airway diseases such as asthma, sinusitis, and chronic bronchitis. Of note is that antimicrobial resistance appears to have no effect on immunomodulatory activity.

There are insufficient data to demonstrate clinically significant differences in the efficacy of the different macrolide antibiotics as immunomodulatory agents with the exception that the 16-member macrolides, josamycin and spiramycin, appear to lack either mucoregulatory or immunomodulatory effects⁵⁾. There are fewer data on the use of azithromycin for the treatment of DPB as this medication was only introduced into Japan in 2000, but early work in cystic fibrosis (CF), suggests efficacy similar to that of clarithromycin.

Only in the last 8 to 10 years that these properties have been actively investigated outside of East Asia.

Fig. 1. Antibiotic sales in the US by class : Total Market : \$10.6 Billion

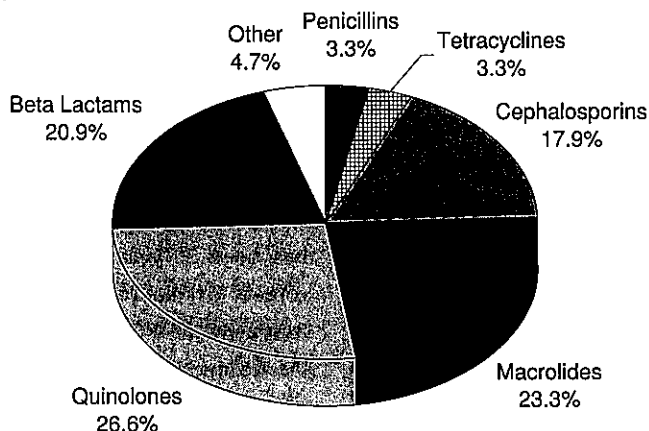
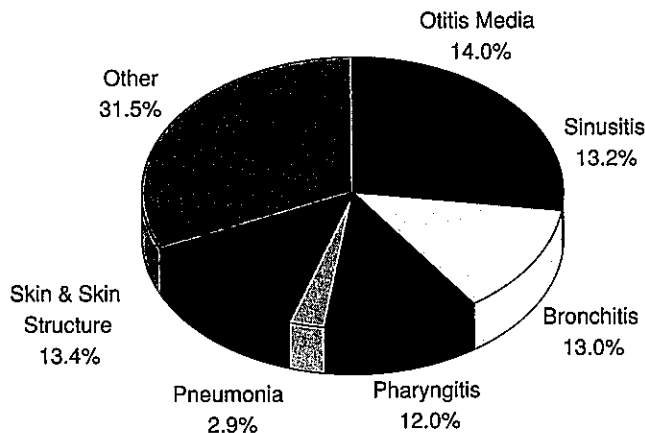


Fig. 2. Clinical Uses for Anti-Infectives



Respiratory infections account for 41% of all anti-infective drug use.

Source : Scott-Levin's PDDA 2002 ;

Combined Tab/Cap & Oral Suspension

In North America, there is intense interest in the use of macrolides as adjunctive therapy for the treatment of CF, asthma, COPD in the United States. Preliminary data strongly suggest impressive efficacy for the treatment of CF lung disease, similar to that seen in the therapy of DPB⁶⁾.

Cystic Fibrosis

The first published use of macrolide antibiotics for the treatment of CF was in a 16 year old Japanese

student who, in 1995, was reported to have significant improvement in pulmonary function with the use of erythromycin⁷⁾. The first controlled trial in the West was reported by JAFFE and colleagues in 7 children studied at the Royal Brompton Hospital who received azithromycin daily or least 3 months. These children had a mean 11% improvement in FEV1 and FVC. The group in London then conducted a prospective randomized, double blind, and placebo controlled crossover trial of azithromycin in subjects

with CF. During the 15 month trial half of the subjects enrolled had a relative improvement in FEV₁ of 10% or greater while on azithromycin. Those who did best were homozygous for the delta F508 gene mutation and greater improvements were seen in those patients not taking concomitant dornase alfa⁶⁾. The results of this study were confirmed by a large US study reported in 2003⁸⁾. On the basis of these studies the use of erythromycin or azithromycin as an immunomodulatory agent is now recommended for the treatment of patients with CF and decreased lung function.

COPD

VESTBO and colleagues showed in 1996 that patients with chronic mucus hypersecretion had an excess decline in pulmonary function and increased risk of hospitalization relative to those who did not⁹⁾. TAMAOKI and colleagues in Japan demonstrated that clarithromycin substantially reduces sputum expectoration in patients with COPD⁴⁾. Studies by Tagaya and colleagues show that even a short course of clarithromycin can reduce mucus hypersecretion in patients with chronic bronchitis¹⁰⁾. At the time of writing there is a trial of azithromycin underway for the treatment for chronic bronchitis being evaluated in the United States.

Sinus Disease.

Erythromycin or clarithromycin can decrease nasal secretion in patients with acute sinusitis¹¹⁾. Clarithromycin also reduces the concentration of inflammatory cytokines in the sinus mucosa and accelerates the resolution of chronic sinusitis¹²⁾. Japanese data suggest that clarithromycin can reduce the size of nasal polyps in patients with sinusitis and inflammatory sinusitis and polyposis¹³⁾. On the basis of these studies clarithromycin therapy is being used in the West for some patients with chronic inflammatory (non allergic) sinusitis.

Asthma

There has been a long standing interest in the use of macrolides for the treatment of asthma in the West. Troleandomycin was used as "steroid sparing" agent beginning in the 1970's but general use was limited because of side effects⁷⁾. Subsequent to this GOTFRIED conducted a placebo controlled trial evaluating a trial of clarithromycin 500 mg twice daily in 21 patients with steroid dependent asthma. Over the course of 6 weeks therapy, subjects had improved pulmonary function and decreased symptoms without any increase in the need for oral corticosteroids¹⁴⁾.

Macrolide resistance

Macrolide resistance comes in two main forms. Ribosomal resistance mediated by the *ermB* gene produces a higher level of resistance than efflux pump resistance mediated by the *mefA* gene. The United States and Europe have similar populations but there were approximately 169 million courses of antibiotics prescribed in the United States in 2001 in comparison to 234 million courses in Europe that year. Japan with a population 30% less had 284 million courses of antibiotics prescribed during 2001. Because macrolides have been used more extensively in the Far East, up to 90% of *Streptococcus pneumoniae* in Japan have been reported to be macrolide resistant, up to 50% resistance has been reported to Europe, and 10~30% resistance has been reported in North America.

Conclusion

The use of macrolide antibiotics as immunomodulatory agents for the treatment of chronic inflammatory airway disease has been widespread in Japan and Korea for at least 10 years. With recent studies in CF, it is anticipated that these drugs will gain more widespread use and acceptance in the West in coming years¹⁵⁾. If effective immunomodulatory agents without antibacterial properties (and thus without the risk of antimicrobial resistance) are

developed, and if macrolides are found to be effective for the treatment of chronic diseases like coronary artery disease, cancer, inflammatory bowel disease, inflammatory arthritis, and atopic dermatitis, their use could dramatically increase. Currently, North American physicians are more reluctant to prescribe chronic antibiotics, and insurance companies in the US often refuse to pay for antibiotics used as immunomodulatory drugs.

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