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Macrolide Treatment and Personalized Medicine in Japan

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Abstract

Macrolides are known as antibiotics, but also have various actions, including immunomodulatory effects. Recently, they were suggested that effectiveness for acute infectious diseases, such as influenza and pneumococcal pneumonia by inhibited of cytokines and toxins in addition to chronic infectious diseases like mycobacterium and pseudomonas infection.

They show few allergic reactions and can contribute to more effective relief of symptoms and inhibition of the development of resistance to other antibacterial agents in Japan.

Keywords: Macrolide; Japan, Influenza; *Streptococcus pneumonia*; *Pseudomonas aeruginosa*

Introduction

Macrolides are classified as protein synthesis inhibitors in terms of their mode of action. After being taken up by a bacterium, macrolides bind to a subunit (50S) of the protein synthesis initiation complex (70S ribosome) and block its function, inhibiting the growth of the bacterium by blocking the elongation of protein chains. Therefore, macrolides generally are thought to show bacteriostatic antibacterial activity.

Specific macrolides, in the order of their development, include erythromycin, clarithromycin, and azithromycin. It can be considered that in this order their adverse effects are lower, half-lives are longer, and antibacterial activities are stronger.

Macrolides have the following characteristics (Table 1).

Antibacterial spectrum: Macrolides have antibacterial activity against most gram-positive, some gram-negative, and some anaerobic bacteria. Additionally, macrolides show strong antibacterial activity against mycoplasma, chlamydia, and legionella, and are first-line drugs for these atypical bacterial infections.

In addition to their antibacterial activity, macrolides have immunological activity, and are used long-term at low dosages for conditions such as chronic respiratory tract infections (for instance, diffuse panbronchiolitis).

Given 1) and especially 2), macrolides have attracted attention as a combination drug in severe pneumonia (including pneumococcal pneumonia) and in some viral diseases (influenza, etc.).

Macrolides also are considered unique antibacterial agents that differ greatly from β-lactam antibiotics in that:

Macrolides are used as alternative drugs in patients with penicillin allergies, and

Macrolides are used as typical drugs in the treatment of nontuberculous mycobacterial infection (mycobacterium avium complex (MAC), etc.).

1	Antibacterial	Especially for atypical pathogens
2	Immunomodulation	For chronic inflammatory diseases, including diffuse panbronchiolitis which is similar to cystic fibrosis
3	Immunomodulation	For acute infectious diseases, such as influenza and pneumonia due to ML-resistant *Streptococcus pneumoniae*
4	Substitute	For penicillin allergic patients
5	Anti-mycobacterium, such as *M. tuberculosis* and *M. avium* complex (MAC)	

Table 1: Action of macrolides.

Consequently, macrolides can be used for specific individuals to take advantage of these various characteristics, and thus it is no exaggeration to say that macrolides are one of the classes of antibacterial agents that can be used in the greatest number of patients.

Here, we give an overview focused particularly on features 1, 3 and consider the possibilities for even more targeted administration of macrolides, especially in Japan.

Broad antibacterial spectrum, including coverage of atypical bacteria

When patients are admitted with sepsis due to conditions such as severe pneumonia or bacteraemia, one can predict a poor prognosis even without knowing the causative agent, and there is a desire to start treatment with an antibacterial agent with the broadest possible range as empiric therapy to avoid antibacterial "leakage," so that treatment can begin as soon as possible.

In pneumonia, various guidelines suggest treatment with a penicillin as the first-line treatment. At the same time, in cases when the causative agent is unknown and there is suspected involvement of atypical bacteria such as mycoplasma, the guidelines provide a method

to identify the pathogen but, in the interim, recommend active use of a macrolide alone as the first-line treatment, or concurrent use of a macrolide with a penicillin, for comprehensive coverage in Japan [1-5].

This may be how macrolides are best used and where macrolides are particularly effective. It is a method of use that may be indicated in many relatively young patients with pneumonia who complain of a dry cough. with these combination methods, of course, if the causative agent or microorganism is identified and symptoms are stable, a switch should be made to a more optimal antibacterial therapy, including "de-escalation," to avoid the administration of unnecessary antibacterial agents. On a practical level, enough consideration also needs to be given to the fact that the susceptibility to macrolides of gram-positive bacteria, especially pneumococci, is very low in Japan. One must always keep in mind a balance with penicillin's, to which gram-positive bacteria are much more susceptible.

Long-term, low-dose administration in chronic respiratory tract infections

It is also now known that in chronic infections, macrolides have an immunological effect that acts on the individual and the bacteria, such as inhibiting the production of cytokines and biofilms, and it may be said that long-term, low-dose administration for conditions such as diffuse bronchiolitis is recognized as a solid method [5].

The targets at such times are known to be mainly gram-negative bacteria that tend to have drug resistance, typified by Pseudomonas aeruginosa, but macrolides also may be applicable in persistent infections with other bacteria. We had a patient with a pet dog who had a persistent infection with Pasteurella, which is known as a zoonotic infection, in whom remission of symptoms and image findings was achieved with long-term, low-dose administration of a macrolide [6].

A penicillin was initially used for acute exacerbations, but penicillin resistance gradually developed, and the number of acute exacerbations also increased. However, after starting long-term administration of a macrolide, the acute exacerbations decreased sharply. Of course, the *Pasteurella* detected from the patient had resistance to macrolides from the start of treatment, and it may be that this *Pasteurella* infection was controlled by the many mechanisms that have been reported in conditions, such as chronic *Pseudomonas aeruginosa* infection. Other than in similar chronic infections and in infections of the respiratory system, macrolides also may be applicable in individuals with infections from devices or catheters that cannot be removed or against infections in the field of orthopedic surgery, where long-term administration is often necessary.

Expectations as a combination drug for severe pneumonia and other conditions

Macrolides have previously been shown to have an immunomodulatory function. Further improvements in survival rates, especially in severe pneumonia, have been reported when macrolides are administered together with β-lactam antibiotics [7-10].

Compared with new quinolones, which have nearly the same antibacterial spectrum, a significantly higher effect is seen with macrolides [8]. This improved efficacy may result from the characteristic immunological mechanisms of macrolides, but further detailed investigations are needed. Ceccato et al. reported that combined β-Lactam/macrolide therapy showed the advantage for severe pneumonia, especially in patients with high inflammatory response (C-reactive protein, >15 mg/dL) and pneumococcal community-acquired pneumonia, rather than combined β-Lactam/fluoroquinolone therapy [9]. Addition of methylprednisolone to β-Lactam/macrolide were also suggested to have slightly benefit in severe pneumonia treatment not only by the antibiotic effects but also mediated through the inhibition of inflammatory molecules, such as Interleukin-6, Interleukin-8, and procalcitonin's [10].

Furthermore, it has been confirmed from basic investigations of pneumococcal infections, a known cause of pneumonia, that macrolides inhibit the production of the toxin pneumolysin that is produced by pneumococci [11]. Such actions would seem to be consistent with previous reports that many cases of clinical remission are observed with the administration of macrolides, even in cases of pneumococcal pneumonia from which macrolide-resistant pneumococci are detected [12]. Recently, the possibility was reported that patients treated with combination macrolides, even those who had macrolide-resistant pneumococcal pneumonia, had significantly lower rates of ICU admission and decreased exacerbations of image findings [13]. In cases of more severe pneumonia, especially when *Streptococcus pneumoniae* was revealed to be the causative agent, there is thought to be considerable advantage in the combined use of macrolides in individuals without waiting for drug susceptibility results, like other studies [9,10].

In association with *Streptococcus pneumoniae*, secondary pneumonia from influenza in winter is a major problem. We observed significant improvements in clinical symptoms of influenza (especially fever) not only with anti-influenza drugs but also with combination macrolides [14]. To date, there have been no specific reports detecting any significant difference in reduction of fever when macrolides are used, and it is still in controversial. Of course, macrolides themselves do not have any antiviral effect, but it may be possible that the inhibition of protein synthesis, including excessive cytokine production called as 'cytokine storm, by macrolides provides an advantage in severe influenza patients. Further investigations and more cautions will be needed for clinical use.

Macrolides also have been reported to have effects not limited to viruses as mentioned above but also in patients themselves, such as protection of ciliated epithelial cells of the respiratory tract. It may be that macrolides can be used in individuals depending on the season, for example, the influenza season, mainly in patients with some underlying disease of the lungs.

Conclusion

Possibility of inhibition of drug-resistant bacteria using macrolides in combination with other antibiotics

In terms of inhibiting drug-resistant bacteria with the combined use of antibacterial agents, the recommendation for 3 to 4 drug therapy rather than single-drug therapy with isoniazid or rifampicin for tuberculosis is typical. Looking at the field of acute medicine, however, the method of using macrolides in combination with penicillin's or with third- or fourth-generation cephalosporins with similar spectra (rather than, for example, the single carbapenems that tend to be widely used for severe pneumonia) may be desirable in terms of inhibiting the development of resistance.

In this review, we have presented possibilities for the various actions of macrolides that could be said to be unique, actual patient cases, and

research reports. Macrolides have relatively few adverse effects and do not induce allergic reactions. Thus, with adroit concomitant use in individuals and careful attention to interactions with other drugs, macrolides may be antibacterial agents that can contribute to more effective relief of symptoms and inhibition of the development of resistance to other antibacterial agents.

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