Future uses of newer macrolides

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TWO NEW MACROLIDE ANTIBIOTICS HAVE RECENTLY BECOME available for clinical use in the United States – clarithromycin and azithromycin (which is an azalide). Only clarithromycin is currently available in Canada. Both of these new compounds have in vitro activity comparable to that of older macrolides such as erythromycin with the addition of activity against *Haemophilus influenzae*. In addition, both clarithromycin and azithromycin have been shown to have activity against uncommon and difficult to treat pathogens such as various protozoans, spirochetes, *Helicobacter pylori* and atypical mycobacteria.

HELICOBACTER PYLORI

H pylori is the subject of growing interest. It is a spiral-shaped bacterium found in the antrum of most patients with inflammatory gastroduodenal lesions (1). It is generally accepted as a cause of chronic active gastritis. Its importance in the pathogenesis of duodenal ulcers remains unclear. Although *H pylori* has not been established as an unequivocal cause of duodenal ulcers, there is persuasive evidence from treatment trials that eradication of *H pylori* infection changes the natural history of peptic ulcer disease in patients with duodenal or gastric ulcers (2-4). There are currently no firm recommendations for antimicrobial therapy of *H pylori*. When therapy is considered, it usually comprises bismuth subsalicylate and two antimicrobial agents such as tetracycline and metronidazole. Alternatively, ampicillin or amoxicillin has been used in place of tetracycline.

Although many antimicrobials appear effective against *H pylori*, all attempts at monotherapy have been ineffective. In fact, there is usually marked resistance to the antimicrobial at the end of therapy. Clarithromycin and azithromycin have excellent in vitro activity against *H pylori* (5). Clarithromycin is two to four times more active than erythromycin or azithromycin. Azithromycin has been studied as monotherapy of *H pylori*. All pretherapy isolates were susceptible. However, 10 of the 12 post therapy isolates demonstrated high level resistance to azithromycin and one was moderately resistant. Therefore, azithromycin may be useful in combination therapy, but it should not be used as monotherapy for eradication of *H pylori*. Clarithromycin appears to be the only drug studied which proved effective as monotherapy in eradication of *H pylori* (7). However, the study was very small and further clinical studies are indicated before clarithromycin can be recommended for therapy of eradication of *H pylori*.

MYCOBACTERIUM SPECIES

Clarithromycin and azithromycin have also been found to be more active in vitro than expected against several species of mycobacteria. This is extremely important since new drugs are desperately needed, especially for infections due to *Mycobacterium avium* complex (MAC). MAC is a ubiquitous organism and it is estimated that MAC may eventually infect most patients positive for the human immunodeficiency virus (HIV) (8,9). Although there are no data that show that treatment of MAC will change the ultimate outcome in

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acquired immunodeficiency syndrome (AIDS) patients, further studies are needed to determine if survival is improved. It is evident, however, that symptoms of MAC infection are improved with effective therapy and, therefore, the quality of life may be improved (10).

The ability of clarithromycin and azithromycin to concentrate in intracellular spaces where MAC exists make these drugs attractive choices. Indeed, both clarithromycin and azithromycin have been shown to be effective in the treatment of MAC infection in beige mice and human data are currently being compiled (11). A preliminary study by Dautzenberg et al demonstrated that clarithromycin had consistent activity against MAC in patients with MAC bacteremia (12). A study by Young et al (13) also demonstrated that azithromycin as a single oral agent was effective in AIDS patients with MAC bacteremia.

A recent randomized study evaluated the efficacy and safety of clarithromycin in the treatment of disseminated MAC (14). One hundred and eight patients were randomized to receive either 500, 1000 or 2000 mg of clarithromycin twice daily. An interim analysis of the first 72 patients demonstrated a significant log decline in colony-forming units of MAC in the blood over three months. In vitro resistance to clarithromycin developed in 16 of these patients. This study appears to indicate that clarithromycin is highly active against MAC bacteremia in patients with AIDS, but should not be used as a single agent because of the emergence of resistance.

There are currently studies underway to evaluate the use of clarithromycin and azithromycin in combination with other antimycobacterial agents for the treatment of disseminated MAC and as single agents for prophylaxis of MAC disease.

Another mycobacterium, *Mycobacterium chelonae*, is also of growing interest because of the marked antimicrobial resistance of this organism. Although a much less common infection than MAC, many therapies are ineffective for this organism. The therapies that are effective, such as amikacin, are potentially toxic. *M chelonae* is very susceptible to clarithromycin, which is much more active than erythromycin or azithromycin. Wallace has reported a single drug protocol of patients with disseminated skin disease caused by *M chelonae* treated with clarithromycin (15).

Approximately half the patients treated became asymptomatic and the other half had almost total resolution of their skin nodules. There is also reason to believe that clarithromycin and azithromycin may have potential use in the treatment of *Mycobacterium leprae*, an enormous problem worldwide. Both clarithromycin and azithromycin appear to be bactericidal when used as monotherapy in the treatment of leprosy in the mouse foot pad model and in preliminary human studies (16-18).

Neither clarithromycin nor azithromycin have much activity against *Mycobacterium fortuitum* or *Mycobac-*

terium tuberculosis (19). Therefore, it is unlikely that they will be of much benefit in the treatment of infections due to these organisms.

However, they may be of potential use in the treatment of other mycobacteria such as *Mycobacterium kansasii*, *Mycobacterium marinum* and *Mycobacterium xenopi* (20,21).

TOXOPLASMOSIS

Toxoplasmosis is the most common opportunistic infection of the central nervous system in patients with AIDS. It appears that the incidence of cerebral toxoplasmosis is declining possibly due to trimethoprim-sulphamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia (22). Clarithromycin and azithromycin, as well as another macrolide, roxithromycin, appear to be very active against *Toxoplasma gondii* in mouse models (23-25). The addition of minocycline to clarithromycin appears to be synergistic and in one study was superior to clarithromycin alone (26). In a small clinical trial of 13 AIDS patients with acute cerebral toxoplasmosis, clarithromycin in combination with pyrimethamine given for six weeks appeared to be well tolerated and very effective (27). Further studies are indicated.

SPIROCHETES

Clarithromycin and azithromycin have excellent in vitro activity against several spirochetes including *Treponema pallidum*, *Borrelia burgdorferi* and *Leptospira* species. Alder et al were able to demonstrate that clarithromycin had significant activity against *T pallidum* in infected hamsters (28). Azithromycin has been used in patients with primary and early secondary syphilis with apparent success in preliminary studies (29).

Lyme disease is probably the most common tick-borne infectious disease in the United States. It is due to infection with *B burgdorferi*. This organism is exquisitely susceptible to a number of macrolides including erythromycin, azithromycin and clarithromycin. The rate of killing of *B burgdorferi* is significantly better with azithromycin and clarithromycin than with erythromycin and beta-lactam antibiotics (30). Clarithromycin and azithromycin have been shown to be very effective in animal models of Lyme disease. In a limited human study, azithromycin given for seven days appeared to be as effective as amoxicillin given for 21 days for the treatment of Lyme disease (30).

VIRULENCE-MODIFYING PROPERTIES

Of additional interest is the ability of macrolides to modify bacterial virulence factors. There is evidence that azithromycin is able to inhibit production of Gram-negative exotoxins at subinhibitory concentrations. Molinari et al were able to demonstrate that azithromycin inhibited the enzymatic activities and pigment production of 10 strains of *Pseudomonas aeruginosa* (31).

Erythromycin and clarithromycin were unable to modify expression of these virulence factors in the same strains. Different classes of antimicrobial agents have been shown to alter host defense mechanisms. Clarithromycin appears to improve chemotaxis and intracellular killing of polymorphonuclear leukocytes (32). Natural killer activity also appears to be increased in the presence of clarithromycin. Therefore, it appears that clarithromycin exerts a lasting stimulatory effect in some functions of cell-mediated immunity in healthy volunteers and ill patients.

SUMMARY

Both clarithromycin and azithromycin are likely to have extended uses in the future. Both newer macrolides clearly have a role in the therapy of disseminated MAC disease in AIDS patients. New macrolides may also prove to be effective in the treatment of other mycobacterial diseases, especially *M chelonae* and *M leprae*. It is likely they may also have a role in the treatment of toxoplasmosis, *H pylori* and Lyme disease.

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