What Every Clinician Should Know About Emerging New Antimicrobials

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Macrocycles are molecules with a ringed architecture ≥12 atoms. They are flexible and have very good binding activity to their site of activity. Their functional groups can interact across a wide range of binding sites without losing activity or being pushed off. They are very potent and very selective. Many have good solubility, lipophilicity, metabolic stability, and bioavailability. However, some, such as fidaxomicin and rifaximin, are not very well absorbed. Kathleen M. Mullane, DO, PharmD, University of Chicago, Chicago, Illinois, USA, discussed the emerging macrocycles and their mode of action.

The classic macrolides inhibit synthesis of proteins in bacteria by binding to 23S ribosomal RNA of the 50S ribosomal subunit. Glycopeptides bind to the pentapeptides of the peptidoglycan monomers in the bacterial cell wall, preventing polymerization. Rifampin inhibits bacterial DNA-dependent RNA polymerase, thereby blocking the elongating RNA molecule. Fidaxomicin, the only macrocycle classified by the Clinical and Laboratory Standards Institute, is a transcription inhibitor that interferes with the function of RNA polymerase at a different site than do the rifamycins. Macrocycles are exclusively derived from natural products then modified to enhance activity, reduce resistance, and increase tolerability.

Lipiarmycin is a new macrocyclic consisting of an 18-membered lactone antibiotic produced by the actinomycete species. Lipiarmycin has excellent bactericidal activity against *Mycobacterium tuberculosis* and lacks cross-resistance to standard antituberculosis drugs [Kurabachew M et al. *J Antimicrob Chemother* 2008].

Fidaxomicin is an isomeric mixture of stereoisomers of lipiarmycin A4 and tiacumicin B (95%). It inhibits bacterial RNA polymerase at a specific site in the switch region and has no cross resistance with rifampin. Binding in the switch region interferes with essential conformation change, inhibiting RNA polymerase loading of DNA to RNA. A bactericidal with a narrow spectrum of action, fidaxomicin is mainly confined to the GI tract following oral administration and it has minimal systemic absorption. High fecal concentrations are achieved with 24 hours of dosing, while plasma concentrations are low. Fidaxomicin inhibits production of toxins A and B, and further *Clostridium difficile* sporulation—something not seen with vancomycin, metronidazole, or rifaximin. The inhibitory effect on sporulation may contribute to fidaxomicin's superior performance in sustaining clinical response and reducing recurrences of *C. difficile* infection [Babakhani F et al. *Clin Infect Dis* 2012].

The microflora-sparing properties of fidaxomicin were examined in 2 large randomized clinical trials comparing vancomycin versus fidaxomicin for the treatment of *C. difficile*. While vancomycin and fidaxomicin were equally effective in resolving the symptoms of *C. difficile*, fidaxomicin was able to preserve greater diversity of microflora, sparing the Bacteroidete and Fermicute families of organsisms. Sparing these organsisms is important to the gut microbiome and may be 1 of the reasons that fidaxomicin is associated with a lower likelihood of CDI recurrence than vancomycin [Louie TJ et al. *Clin Infect Dis* 2012; Cornely OA et al. *Lancet Infect Dis* 2012]. Further data analysis from these 2 trials found fixdaxomicin was significantly more effective than vancomycin in patients taking concomitant antibiotics for other concurrent infections [Mullane KM et al. *Clin Infect Dis* 2011], in cancer patients, and in individuals with stage 3 or greater chronic kidney disease.

Some new macrocyclic compounds in development include the RNA polymerase inhibitor ripostatin, which also targets the switch region. Others include the bicyclolides EDP-322 and EDP-420, CB-183,315 (cyclic lipopeptide), and semisynthetic lipoglycopeptides dalbavancin and oritavancin with their long elimination half-life and activity against Gram-positive organisms.

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