Introduction: Fusidic Acid Enters the United States

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The emergence of infections due to community-associated methicillin-resistant Staphylococcus aureus (MRSA) in the United States (and elsewhere in the world) during the past decade has brought the rather pedestrian spectrum of acute bacterial skin and skin structure infections (ABSSSIs) to a new level of concern [1]. Previously recommended oral antibiotics, such as oxacillin, cloxacillin, dicloxacillin, and cephalaxin, have no useful activity against MRSA. Unless infection with these organisms can be excluded clinically, empirical coverage for MRSA is indicated in many areas of the United States where the prevalence of community-associated MRSA exceeds 30%–50% [2]. Granted that many of the ABSSSIs caused by community-associated MRSA, such as small, uncomplicated abscesses, are relatively “benign” and may respond to surgical drainage alone, these organisms nonetheless are fully capable of causing severe disease including bacteremia with overwhelming sepsis, endocarditis, and metastatic abscesses in the setting of ABSSSI [3]. Given these facts, it is clear that there is a need for effective antimicrobial agents to treat ABSSSI, and such agents must include the 2 major organisms that cause this disease (S. aureus [including MRSA] and group A streptococci) in their spectrum.

Except for linezolid, to our knowledge, there have been no definitive randomized trials for oral agents currently being used to treat ABSSSI in the United States. Thus, there is a real need for additional data and for the development of more effective oral agents for these infections, not only in the skin but elsewhere in the body as well.

The growing importance of MRSA is reflected in the fact that the Infectious Diseases Society of America has just promulgated an extensive set of clinical practice guidelines for the treatment of MRSA infection in adults and children [4]. This comprehensive document reviews the major syndromes caused by MRSA and provides a set of logical therapeutic recommendations. The recommendations for oral therapy include clindamycin, trimethoprim-sulfamethoxazole, a tetracycline (doxycycline or minocycline), and linezolid. They also recommend that if coverage for both β-hemolytic streptococci and community-associated MRSA is desired, trimethoprim-sulfamethoxazole or one of the tetracyclines should be used in combination with a β-lactam, such as amoxicillin. Clindamycin or linezolid alone was also believed to be likely effective in this setting, despite the increasing rate of resistance to clindamycin. Notably, the use of rifampicin as a single agent or as adjunctive treatment for ABSSSI was not recommended.

Conspicuously absent from this list of recommended antimicrobial agents is an antibiotic that has been widely used throughout the world but never licensed in the United States—namely, fusidic acid. The reasons for it not having been licensed in the United States are likely due to marketing considerations rather than efficacy, because it has been used very effectively for the treatment of staphylococcal infections in many other countries. In addition to demonstrating effectiveness for the management of infections due to S. aureus (including MRSA), the drug has also had an excellent safety record. One of the primary issues that has been of concern

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where the drug has been widely used has been the emergence of resistance among staphylococci. For that reason, fusidic acid has sometimes been used in combination therapy—most commonly with rifampicin—when it appears to be highly effective and resistance emergence is low [5].

It is in the aforementioned setting that fusidic acid is being “resurrected” for potential use in the United States as it is currently being used elsewhere. The clinical studies of ABSSSI that have been performed have used a unique “front-loaded” dosing schedule, which is designed to promote efficacy (especially among pathogenic streptococci for which elevated minimum inhibitory concentrations are frequent) and minimize the likelihood of the development of resistance during therapy.

The articles in this supplement provide a comprehensive overview of fusidic acid and address the issue of resistance as well as its clinical efficacy and safety.

The first article in this supplement provides a background on the regulatory environment in which the drug is being subjected to during clinical trials. Subsequent papers provide data on the antimicrobial activity of fusidic acid and document the low prevalence of resistance to fusidic acid among MRSA isolates in the United States. Of note is the fact that the activity of fusidic acid against β-hemolytic streptococci is considerably less than that against staphylococci; for that reason, it will be important to examine the clinical results when the drug is used to treat ABSSSI due to group A streptococci. The mechanism of action of fusidic acid is unique in that it is the only clinically available antimicrobial agent that works by binding to elongation factor G (EF-G), preventing its release from the ribosome and thus inhibiting bacterial protein synthesis. There are several mechanisms of resistance to the drug in S. aureus. High-level resistance is usually caused by mutations in the gene encoding EF-G, fusA. Several transferable mechanisms of resistance, including fusB and fusC, result in low-level resistance.

S. aureus can persist intracellularly in phagocytic cells where the surrounding medium is acidic. As it turns out, fusidic acid penetrates well into phagocytes and demonstrates enhanced activity at a low pH. The intracellular activity of fusidic acid is similar to that of clindamycin and linezolid, but only fusidic acid accumulation is enhanced by low pH.

Data from phase 1 trials supporting a novel dosing schedule (1500 mg twice per day on day 1 followed by 600 mg twice per day for 10–14 days) provide the basis for a phase 2 clinical study of fusidic acid for ABSSSI. In a comparative phase 2 trial, the drug has been shown to be as effective as linezolid for the treatment of ABSSSI due to gram-positive organisms. Data on the safety of fusidic acid (including data retrieved from the available global literature published between 1962 and 2007) document the low prevalence of adverse effects associated with the drug, even when it has been used for long-term treatment of conditions such as osteomyelitis. The commercial and scientific rationale for the study and introduction of fusidic acid into the US market forms the basis for the concluding article in this symposium, which makes a strong argument for its addition to our therapeutic armamentarium against MRSA and other staphylococci in the United States, where clinicians have not previously had direct access to this valuable agent.

Acknowledgments

Financial support. This symposium was supported by a research grant from Cempra Holdings.

Supplement sponsorship. This article was published as part of a supplement entitled “Fusidic Acid Enters the United States” sponsored by Cempra Pharmaceuticals.

Potential conflicts of interest. R. C. M. has received a consulting fee and support for travel to meetings from Cempra for scientific advisory board work and has served as a consultant for Cubist, Pfizer, Merck, Novartis, Ortho, J&J, and Forest. G. R. C. has served as a consultant for Theravance, received support from Cubist Pharmaceuticals and Theravance, and serves as a consultant for Cerexa, Merck, Pfizer, Cempra, Polymedic, Nabriva, The Medicines Company, GSK, Trius, Durata, PRA, Furiex, Inimex, Innoccoll, Rib-X, Seachaid, Dr Reddy’s Laboratory, Tetraphase, Synereca, AstraZeneca, Achaogen, and Astellas.

M. L. G.: no conflicts.

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