

FUNGAL OSTEOMYELITIS

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Abstract

Fungal osteomyelitis is a rare and potentially life threatening condition. Current management of fungal osteomyelitis involves the prolonged administration of antifungal agents and multiple surgical procedures. This review was designed to discuss the development of an osteoconductive biodegradable carrier or bone delivery system that could release therapeutic concentrations of antifungal agents over time because of the challenge to achieve desirable drug concentrations at the bone infection site coupled with potential patient noncompliance with current oral or injectable therapies, as well as the overall cost of care. Bone delivery systems utilize biocompatible, bioresorbable ceramic materials that could be impregnated with antimicrobial agents. Ceramics have been used successively with antibacterial agents for decades, but antifungal impregnated biodegradable systems need to be explored as an efficient and safe option for treating fungal osteomyelitis in the clinical setting.

Key words: fungal osteomyelitis, drug delivery systems, fluconazole, micafungin, amphotericin, biodegradable bone delivery system.

1. INTRODUCTION

The principles of antimicrobial therapy will be the primary objective for this discourse. It is anticipated that the incidence of fungal osteomyelitis, now considered rare, will increase in the foreseeable future as the expanding patient (both immunocompetent and immunocompromised) population are deliberately exposed to risk factors (indwelling central venous catheters, immunosuppressive and corticosteroid therapy during organ transplantation, parenteral nutrition, aggressive cancer chemotherapy, broad spectrum antibiotics, (re)placement of implants and various types of surgical procedures) as a mandatory stipulation of adequate healthcare by today's established Standard-of-Care (Wilson, 2003). Invasive fungal infections proceed insidiously for weeks to months, setting the stage for hematogenous spread to organs, including bones. A fungal organism may take days to weeks to be identified by the clinical laboratory, such that prolonged management (irrigation solutions, debridement and antimicrobial therapy) is inevitable. Serious fungal infections must be treated intravenously with cidal agents that

penetrate bone tissue. Antimicrobial agents (including antifungal agents) generally do not penetrate bone tissue to any great extent. Additionally, perfusion of tissue does not occur in areas of the body that are not vascularized, such as occurs with (in) necrotic tissue. This compounds the problem of treating intravenously with systemic antimicrobials. Until the recent advent of the echinocandins (such as micafungin, MFG), the polyene antifungal, amphotericin B (AMB), was the only fungicidal drug available. However, AmB is not well tolerated by patients because of its adverse side effect profile (primarily nephrotoxicity). Although the liposomal AmB formulations are generally considered safer for use, they are not completely devoid of adverse effects. Adequate initial treatment involves the use of intravenous administration (for a minimum of two (2) weeks) of a fungicidal therapeutic agent. The polyene antifungal AmB still surpasses the echinocandins in its broader spectrum of activity against yeast and molds. While some triazoles such as fluconazole (FCZ) are better tolerated by patients, they are fungistatic and therefore not appropriate as initial therapy to treat invasive fungal infections. Triazoles are administered orally for long-term fungal suppression after initial treatment with an intravenous agent. Recently, it has been found that FCZ is fungicidal when combined with cyclosporine (Cruz, Goldstein, Blankship, Del Poeta, Davis, Cardenas et al., 2002). This synergism remains to be explored by clinicians as a strategy to enhance the efficacy of FCZ. Additionally, the echinocandins and the polyene antifungal agents are not formulated as oral dosage forms. In this scenario, patient compliance may present another dilemma to the medical practitioner, as oral antifungal agents must be administered for months (possibly years) to ensure adequate suppression of the organism. The challenge to achieve desirable drug concentrations at the infection site coupled with potential patient noncompliance, and the overall cost of care (from weeks to months) may be best overcome using a bone delivery systems (BDS). Bone delivery systems utilize biocompatible, bioresorbable ceramic materials that can be impregnated with antimicrobial agents. Ceramics have been used successively with antibacterial agents for decades, but antifungal impregnated biodegradable BDSs need to be thoroughly investigated.

1.1 Microbial Colonization

Bones do not normally support microbial colonization. Microbial colonization of bone may occur when microbes adhere to a surface and begin to undergo processes that evade the defenses of the host (Wilson, 2003; Moholkar et al., 2006). In the early (acute) stages of colonization, the host defense system may be able to limit and/or kill the microbe. However, under certain conditions the microbe may resist host defenses, such as occurs when the size of the inoculum is larger than the threshold levels, host defense mechanisms are impaired, the tissue in which the microbe is colonized is traumatized or necrotic, and the surface (or tissue) is inanimate (acellular, dead bone and foreign bodies, biomaterials or implants).

Microbes reach the bone or implant surface (foreign body) by direct contamination, contiguous spreading or hematogenous seeding. The interaction between the bone surface and microbe is facilitated by van der Waals forces, creating irreversible adhesion receptor crosslinks with the surface (Moholkar et al., 2006). The microbe in a biologic environment can form a glycoprotein slime layer on inert surfaces and a biofilm enclosed colony of sessile microbe forms. Biofilms that form on inert or nonviable surfaces are not easily penetrated by antimicrobial therapy (Trampuz and Widmer, 2006).

A variety of yeasts and molds have been implicated in osteomyelitis. These include *Acremonium* (Keynan, Sperecher and Weber, 2007), *Aspergillus* (Holmes, Osterman and Tullos, 1988; Bridwell, Campbell and Barenkamp, 1990) and *Coccidioidomycosis* of the spine (Lewicky, Roberto and Curtin, 2004), *Blastomycosis* of bones and joints (MacDonald, Black and MacKenzie R, 1990; Oppenheimer, Embil, Black, Wiebe, Limerick, MacDonald, et al., 2007), *Cryptococcus* of humeral bone and spine (Gumbo, Hakim, Mielke, Siwji, Just-Nubling and Ismail, 2001; Goldshteyn, Zanchi, Cooke and Agha, 2006), *Onchomycosis* of toenail (Murray and Dawber, 2002) and *Scedosporium prolificans* of the ankle (Gosbell, Toumasatos,

Yong, Kuo, Ellis and Perrie, 2003). *Candida albicans* infections have resulted subsequent to (total hip or knee) arthroplasty (Marra, F., Robbins, G.M., Masri, Duncan, Wasan and Kwong, 2001), prosthetic arthritis (Merrer et al; Lerch, 2003), injection drug use (IDU; Miller, 2001), spondylodiscitis (Garbino, Schnyder, Lew, Bouchuiguir-Wafa and Rohner, 2003), and other infections of the sternum (Petrikkos, Skiada, Sabatakou, Antoniadou, Dosios and Giamarellou, 2001; Malani, McNeil, Bradley and Kauffman, 2002) and vertebrae (Khazim, Debnath and Fares, 2006). Non-*albicans* species (*C. krusei*, *C. tropicalis* and *C. glabrata* in particular) of *Candida* have been documented as well (Eisen, MacGinley, Christensson and Woods, 2000). Despite the publication of observational studies and case reports in the medical literature, fungal osteomyelitis is considered a relatively rare or uncommon disease.

Candida albicans, the most common species of yeast, is a normal commensal often found in the respiratory, gastrointestinal and genitourinary tracts; skin and other mucous membranes of humans (Ostrosky-Zeichner et al., 2002). It can be found on animate and inanimate surfaces, and objects in the community and in the health care environment. Invasive candidiasis can be caused by fungal colonization (mainly by injudicious use of broad spectrum antibiotics), interruption of defense barriers (through the skin, epithelial, and mucous membranes as in surgery or IDU) and loss of immune control mechanisms (such as monocytes, polymorphonuclear cells, lymphocytes, complement, cytokines and immunoglobulins are all components of the immune response to fungal infection). Hematogenous dissemination of candidiasis can spread to virtually any organ including bones and joints (Khazim et al., 2006). Hence, candidiasis is the fourth leading cause of nosocomial blood-stream infections in the United States and can cause invasive disease in the setting of reduced host defenses (Edmond, Wallace, McClish, Pfaller, Jones and Wenzel, 1999; Zaoutis, Argon, Chu, Berlin, Walsh and Feudtner, 2005).

Invasive rhinocerebral mucormycosis (IRM) is a rare and often fatal opportunistic fungal infection seen in immunocompromised hosts (HIV and hematologic malignancies) with rapid progression to death. Jacobs, Wood, Du Toit and Esterhuizen (2003) investigated the eradication of invasive mucormycosis using micafungin by contrasting two patients, both with acute leukaemia and mucor infection that was diagnosed with biopsy. One patient failed AmB therapy and succumbed to the infection. The other received successful autologous bone marrow transplantation approximately six (6) months after diagnosis with leukemia. Relapse occurred after this procedure and the patient received another allograft after reinduction and consolidation. In a year's time another relapse occurred and remission was achieved but fever ensued. The patient was treated with AmB intravenously and oral itraconazole (fungistatic agent). At this stage invasion of the maxillary sinus with mucormycosis was diagnosed on biopsy. Micafungin was used with gradual reduction of facial pain and clinical resolution after one month, confirmed with histologic investigation and microbiological cultures. Micafungin was readministered at the time of (another) chemotherapy and matched unrelated allograft, because of the potential for recrudescence. The patient succumbed to the multiple organ dysfunction that ensued subsequent to neutropenic sepsis from the severe inflammatory response syndrome. There was however, no evidence of systemic mycosis. The echinocandins have been used to treat invasive aspergillosis, sometimes in combination with AmB. Since it was previously shown that micafungin prevents adhesion to yeast (Borg-von Zepelin et al., 2002), an implant impregnated with a fungicidal agent could have been used, to prevent such a devastating disease.

1.2 Management of Osteomyelitis

The management of osteomyelitis relies on a combination approach of debridement, soft tissue coverage, and antimicrobial therapy (Cooper et al., 2001; Berendt et al., 2002; Wilson, 2003; Moholkar et al., 2006). The physical condition of the host is assessed and treated accordingly (with nutrition, smoking cessation, diabetes therapy, medical or surgical management of vascular disease) to minimize morbidity.

Then the disease is staged (type 1 to 4) and the offending organism is identified to determine appropriate antimicrobial therapy.

The management of bone infection (microbial osteomyelitis) may also necessitate irrigation solutions, surgical debridement, external fixation, and bone grafting (Schmidt et al., 1995). The antimicrobial agent must penetrate the bone, be nontoxic, convenient to administer and cost effective. These characteristics are achieved using a systemically (intravenous) administered agent for a minimum of at least 2 weeks. The duration of therapy may extend for months based on the severity of the infection, particularly if osteomyelitis is chronic, often because dissemination has occurred. Antimicrobial therapy does not obviate the need for removal of necrotic tissue, particularly in the absence of a viable blood supply. The void left after debridement may need to be filled with a suitable bone substitute for restoration of normal bone function. The use of biodegradable or resorbable synthetic materials is a viable surgical option to replace lost bone, as the porosity of the implanted material allows ingrowth of vascularized tissue, thereby eliminating the need for additional surgery (as nonbiodegradable material may need to be removed with a subsequent surgical procedure) and transmission of infectious disease (as the potential for infection exists with each surgical procedure). The ceramic material used must be biocompatible and osteoconductive to allow the body's natural bone making process to eventually replace implanted material. Though slow resorption is not necessarily a hindrance, complete resorption is desirable for long bones.

1.3 Drug Distribution and Metabolism

Antifungal agents used in the management of fungal osteomyelitis are usually injected (eradication of yeast) and/or consumed orally (for longterm suppression of infection). An orally ingested drug must first be absorbed via the gastrointestinal tract, before it can reach the plasma, unlike the injected drug which goes directly into the circulation. Distribution to tissues from the plasma depends on plasma protein binding, blood flow to tissues, and interaction with adipose tissue and membrane barriers. Amphotericin is lipid soluble and binds to human plasma and plasma albumin (lipoproteins) when injected (Bekersky, Fielding, Dressler, Lee, Buell and Walsh, 2002). Fluconazole is soluble and circulates in plasma mainly as free drug, with 14% bound to plasma proteins (Humphrey, Jevons and Tarbit, 1985; Groll et al., 1998). Micafungin is water soluble and binds highly (99.5%) to plasma (Hebert, Smith, Marbury, Swan, Smith, Townsend et al., 2005).

Drugs are distributed and eliminated from the body via the kidneys, bile, skin and/or feces in a hydrophilic and polar state (Park, 1996). However, many drugs are hydrophobic and non-polar, and must be converted into a hydrophilic and polar state to be eliminated. Elimination is facilitated by pathways, which change a hydrophobic, non-excretable, active drug to an excretable, inactive, water soluble drug. This process usually occurs in phases (I and/or II). Phase I reactions include oxidation, reduction and hydrolysis; oxidation (catalyzed by the cytochrome P450 [CYP] system) being the most important. The metabolites formed from phase I reactions may be less active, highly reactive or toxic. Hence, they are further processed by phase II enzymes or conjugation reactions (glucuronidation, sulfation, acylation, methylation, and conjugation with glutathione), which confer hydrophilicity. The CYP and other phase I enzymes are generally present in smaller amounts than phase II enzymes. When the amount of phase I enzymes are decreased, as may occur in deficiency states, the metabolites from phase II reactions may not be formed and drug elimination may be inhibited. Therefore phase I reactions are considered the rate limiting step in drug metabolism.

1.4 Conclusion

The use of drug delivery systems (DDSs) can be used as a treatment alternative. The main objective of a (DDS) is to deliver a drug effectively, to achieve greater efficacy by avoiding fluctuations in plasma drug levels, and to minimize toxicity compared to conventional formulations. These systems can be utilized for the delivery of antimicrobial agents, particularly those which are plagued with complications, such as Amphotericin B (AmB). To be continued in Part II.

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