Daptomycin Favored over Vancomycin For Skin Infections

A study comparing the relative costs and clinical efficacy of treatment of complicated skin and skin structure infections (cSSIs) with either daptomycin (Cubicin for Injection, Cubist Pharmaceuticals) or vancomycin (Vancocin, Eli Lilly/ViroPharma) found that a shorter duration of therapy tipped the balance in favor of daptomycin, the newer agent. Among patients whose infections resolved completely, the median duration of intravenous (IV) therapy was four days with daptomycin and seven days for vancomycin.

Susan Davis, PharmD, Assistant Professor of Pharmacy at Wayne State University in Detroit, Michigan, and her colleagues noted that in 2004, according to the most recent surveys sponsored by the Centers for Disease Control and Prevention (CDC), cSSIs were the primary diagnosis in approximately 562,000 hospital discharges in the U.S., with an average length of stay of 4.7 days. Significant increases in cost of care have accompanied the growing prevalence of methicillin-resistant Staphylococcus aureus (MRSA) infection in both hospital and community settings.

Daptomycin, which was approved by the FDA in 2003, is a novel lipopeptide antibiotic indicated for treatment of cSSIs caused by susceptible bacterial strains of gram-positive Strep-tococcus species and S. aureus, including MRSA. Speaking in a teleconference briefing coinciding with the publication of the study in Pharmacotherapy, senior investigator Michael Rybak, PharmD, MPH, Professor of Pharmacy and Director of Anti- Infective Research at Wayne State University, said that the open-label study evaluated clinical and economic outcomes in an acute-care setting (Detroit Receiving Hospital, a level 1 trauma center) among patients admitted with these infections. Daptomycin-treated patients (n = 53) were compared with vancomycin-treated historical controls (n = 212) matched in a 1:4 ratio.

Patients in the prospective arm received IV daptomycin 4 mg/kg every 24 hours for at least three days but for not more than 14 days. Controls received vancomycin for at least three days according to a dosing nomogram achieving trough concentrations of 5 to 20 mcg/mL (average, 13 mcg/mL). Additional treatment with aztreonam (Azactam, Elan), tobramycin (Tobradex, Alcon), or metronidazole (Flagyl, Pfizer) was permitted when gram-negative or anaerobic coverage was needed. After 72 hours, patients could be switched to oral antimicrobial regimens at the discretion of the primary physician. Similarly, patients could be switched to nafcillin (Unipen, Wyeth) if methicillin-susceptible S. aureus (MSSA) infection was identified. Both clinical and economic data were collected. Clinical outcomes for these patients were determined by an investigator who was blinded to the treatment drug and to the suspected or cultured organism.

S. aureus, the most common organism isolated in each group, was found in 51% of the daptomycin patients and in 79% of the vancomycin patients (P < 0.001). MRSA was also found more often in patients receiving vancomycin (75%) than in those receiving daptomycin (42%) (P < 0.001). The difference, Dr. Rybak explained in an interview, was that his hospital’s policy required vancomycin to be used only for MRSA or suspected MRSA. If patients had a streptococcal infection or an infection caused by MSSA, they were switched to a beta-lactam.

In the prospective study, patients could continue with daptomycin if they had any type of gram-positive, streptococcal, staphylococcal, MRSA, or MSSA infection. Therefore, it is more likely that historical control patients receiving vancomycin would have had S. aureus infection, probably MRSA.

Neither group experienced any antimicrobial-related adverse events or deaths. Although all patients in both groups achieved clinical success by the end of therapy, a significantly higher proportion of patients who received daptomycin achieved clinical success by the third and fifth days. Furthermore, a significantly greater proportion of these patients (77%; n = 41) achieved clinical cure at the end of inpatient antimicrobial therapy, compared with the vancomycin patients (42%; n = 89) (P < 0.001).

This association remained significant after the investigators controlled for the presence of MRSA, comorbidities, or surgical procedures related to infection management. The median duration to achieve clinical cure was three days shorter with daptomycin (four days; range, 2–10 days) compared with seven days with vancomycin (range, 3–19 days) (P < 0.001).

Patients receiving daptomycin needed a shorter median duration of IV antimicrobial therapy (four days; range, 3–13 days) versus a median duration of seven days for vancomycin (range, 3–14 days) (P < 0.001). The antibiotic-related length of stay for the daptomycin patients was a median of four days (range, 3–13 days, and the median duration with vancomycin was eight days (range, 3–19 days) (P < 0.001).

Clinically and molecularly defined community-associated MRSA was identified in 45 patients (15 receiving daptomycin; 30 receiving vancomycin). All of the patients achieved clinical success by the end of therapy, but the clinical success rate on the third day was higher with daptomycin (93% in 14 of 15 patients) than with vancomycin (57% in 17 of 30 patients) (P < 0.05).

Costs for were higher for IV daptomycin (median, $666; range, $500–$1,660) than for vancomycin (median, $124; range, $23–$650). The difference between therapy with daptomycin and with vancomycin was reduced when all inpatient antimicrobials were taken into account (daptomycin, median $678;
vancomycin, median $256). However, it was the total cost of hospitalization, with a median of $5,027 (range, $4,225–$17,090) for daptomycin and a median of $7,552 for vancomycin (range, $4,386–$19,944) \( P < 0.01 \) that moved the balance in favor of daptomycin.

The authors concluded that daptomycin could speed the time to resolution of cSSSIs and could bring about significant reductions in the duration of IV therapy and in associated costs of hospital care. Dr. Rybak put daptomycin’s higher acquisition cost in perspective:

> We often only think of the acquisition cost of antimicrobials, but the overall cost of patient therapy should also be considered. Drug acquisition cost is actually only a small percentage of the overall treatment cost of a hospital stay for infection.

He also voiced concern over growing antimicrobial resistance to vancomycin:

> Resistance to any antimicrobial is a possibility as long as the antimicrobial is in use. We tend to see changes in susceptibility to antimicrobials over time, especially when we rely on only a few antimicrobials for a particular pathogen, as we have with vancomycin for many years; in fact, we are now approaching the 50-year mark in 2008. We’ve had a good run with vancomycin for many years, but we are losing susceptibility. We have several new agents, daptomycin being one that we should use so that we don’t have to rely solely on vancomycin.

## Recombinant Human Thrombin Less Immunogenic Than Bovine-Derived Thrombin During Surgery

The FDA’s approval of a topical recombinant human thrombin of rDNA origin in January 2008 was based on a pivotal clinical trial showing that rThrombin (Recothrom, ZymoGenetics) was as efficacious as, but less immunogenic (antigenic) than, bovine-derived thrombin (bThrombin) for control of hemorrhage during surgery.

The lead investigator for the phase 3 trial, William C. Chapman, MD, Professor of Surgery at Washington University in St. Louis, Missouri, pointed out that excessive blood loss in surgery, physical trauma, or burn injuries might not be attributable to larger or smaller vessels (and therefore is not addressable by suture ligation or electrocautery) but might result from diffuse bleeding from raw surfaces. In such cases, enhanced hemostatic control can be achieved through the use of topical agents that are designed to increase concentrations of thrombin at the site of injury.

Topically applied hemostatic agents derived from plasma have been used for more than 30 years. One current stand-alone bovine plasma product (Thrombin-JMI, King Pharmaceuticals) is available in the U.S., as are several human plasma-derived thrombins as components of fibrin sealants (e.g., Baxter’s Tisseel and Haemacure’s Hemaseel).

Safety concerns with bThrombin have arisen out of reports of antibody development and reports of antibody cross-reaction to homologous human proteins that have led to significant bleeding disorders. About 20% of patients treated with various bThrombin preparations developed antibodies against bovine coagulation factors (e.g., thrombin and factor V). The use of thrombin derived from human plasma also entails the potential risk of transmission of blood-borne pathogens.

Dr. Chapman said that in a phase 2 study of rThrombin, which contains no human plasma components, researchers observed no increases in antibody development, compared with a placebo control.

A phase 3 trial included patients who were undergoing liver resection, peripheral arterial bypass, and spinal and dialysis access surgery.\(^2\) The objective of this randomized, double-blind trial was to compare the efficacy, safety, and antigenicity of rThrombin and bThrombin as adjuncts to hemostasis. The trial was conducted at 34 medical centers in the U.S. The primary efficacy endpoint was the time to hemostasis; secondary endpoints included the incidence and severity of adverse events, laboratory abnormalities, and development of antibodies to the products studied.

In this blinded study, bThrombin 1,000 units/mL or rThrombin 1,000 U/mL was applied to bleeding sites in combination with an absorbable gelatin sponge; 411 patients received the study drug, and 401 patients completed the study (203 receiving bThrombin, and 198 receiving rThrombin). The patients’ median age was approximately 60 years, and 47.5% were women. Surgeries were spinal in approximately 30% of patients, hepatic in about 30%, peripheral arterial bypass in 20%, and arteriovenous graft in about 20%.

Hemostasis was achieved within 10 minutes for 95% of patients in each treatment group. Among the 5% not achieving hemostasis within 10 minutes, additional treatment (i.e., usually consisting of more of the study drug) enabled hemostasis in about 85% of cases. Overall complications, including the mortality rate from surgery, adverse events, and laboratory abnormalities, were also similar between both groups.

However, differences in antibody development (i.e., seroconversion or more than a unit change of 1 titer) were significant; 43 bThrombin patients (21.5%) developed antibodies, compared with three rThrombin patients (1.5%) \( P < 0.0001 \). None of the three patients in the rThrombin group had abnormal coagulation laboratory results, bleeding, thromboembolism, or hypersensitivity.

Patients who developed anti-bThrombin antibodies had an increased incidence of bleeding and thromboembolic events, hypersensitivity, and abnormal activated partial thromboplastin time (aPTT), compared with patients in the bThrombin group without antibodies in a post hoc analysis. Among the three patients in the rThrombin group who tested positive for antibodies, no coagulation, bleeding, thromboembolism, or hypersensitivity was reported.

Nearly all patients (205 of 206 receiving bThrombin and 204 of 205 receiving rThrombin) experienced at least one adverse event in the 30-day follow-up period. Events in both groups occurred at a similar rate, with maximum severity usually moderate (56% with bThrombin, 52% with rThrombin).

Complications at the incision site were the most common events in 63% of the bThrombin group and in 63% of the rThrombin group. Treatment-related events were rare and affected 1% of bThrombin patients and 3% of rThrombin patients.

Two bThrombin patients and one rThrombin patient died, but no deaths were attributed to the study drug.

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Dr. Chapman concluded that bThrombin and rThrombin had comparable efficacy when used in conjunction with a gelatin sponge as a topical adjunct for surgical hemostasis. Safety profiles were similar for the two patient groups, but the rate of antigenicity associated with rThrombin was notably decreased.

In an interview, he replied that the risk of infection with carefully screened blood bank products was “quite small, but not zero.” He explained:

> If we now have recombinant proteins that allow us not to have to utilize either bovine, other animal, or human products with potential for infection—with all other factors being equal, the recombinant is likely to be the safer choice.

Dr. Chapman also noted that other recombinant hemostatic products have had a “great track record and great acceptance.”

**REFERENCE**

