In the Literature

Voriconazole and Breakthrough Zygomycosis


There have been, over the past several years, scattered published reports that describe the occurrence of infection due to zygomycetes occurring in patients while they were receiving voriconazole. As part of the Research on Adverse Drug Events and Report (RADAR) project, Trifilio and colleagues have now described such breakthrough infections in 56 patients seen at 13 cancer centers. The diagnosis was histologically confirmed in 70%. All but 2 patients had hematologic malignancies, and two-thirds had received hematopoietic stem cell transplants (HSCTs), one-half of which came from related donors.

The mean and median durations of voriconazole administration at the time of diagnosis were 80 and 50 days, respectively (range, 6–700 days). The diagnosis of zygomycosis was made a mean of 150 days after HSCT (median, 98 days; range, 11–925 days). Twenty-two patients had graft-versus-host disease; one-half of these cases were acute. The variability of conditioning and chemotherapeutic regimens made it impossible to make any conclusions regarding a relationship between these factors and the risk of infection. Treatment for zygomycete infection consisted of a lipid formulation of amphotericin B, given either alone (56%) or in combination with a second agent (29%), in 85% of patients. Only 11% of patients were treated with posaconazole. The mortality rate was 73%, with all deaths attributed to the zygomycosis.

Despite lack of US Food and Drug Administration approval, voriconazole is frequently used as prophylaxis and as empirical therapy in patients with neutropenia due to chemotherapy and/or in association with HSCT, and it appears to be an effective agent for these uses; for example, clinical experience suggests that voriconazole is an effective agent in prophylaxis for Aspergillus infection among HSCT recipients [1]—an unsurprising finding, given the efficacy of this triazole in the treatment of known invasive aspergillosis. The in vitro activity of voriconazole against the much less frequently encountered zygomycetes is, however, limited. Posaconazole, which has recently received US Food and Drug Administration approval for prophylaxis indications is, in contrast, significantly more active than voriconazole against these organisms in vitro. Thus, a recent analysis of 45 zygomycete isolates, including 19 Mucor isolates, 11 Rhizopus isolates, 8 Absidia isolates, 4 Cunninghamella isolates, 2 Syncphalastrum isolates, and 1 Rhizomucor isolate, found that the MIC90 of posaconazole was 1.0 μg/mL, whereas the MICs of both voriconazole and itraconazole were >16 μg/mL, as determined on the basis of the Clinical and Laboratory Standards Institute’s M38 method, with 24 h of incubation [2]. Furthermore, the use of posaconazole as salvage therapy with patients zygomycosis reportedly resulted in partial or complete responses in 60% of 91 patients, with an additional 21% maintaining stable disease [3].

The study by Trifilio and colleagues would have been more valuable if they had provided incidence data for patients who received voriconazole in addition to the data that they provided for patients who did not receive this agent. Furthermore, no information is provided with regard to the distribution of cases among the 13 reporting centers. Were they clustered at just a few sites, or was the occurrence of zygomycoses confined to just a few sites? The answers to these questions would help address the significance of the problem of infection with the zygomycetes. In 2 recently published randomized trials that examined the efficacy of posaconazole as prophylaxis in at-risk patients, there was a total of only 2 cases of zygomycosis among 587 recipients of comparator agents (mostly fluconazole), and there were no cases among 592 posaconazole recipients [4, 5]. Whether this incidence is sufficient to make a strong case for choosing posaconazole as the preferred prophylactic antifungal agent in these contexts is a matter that deserves additional analysis. In the mean time, the clinician should be aware of the possibility that a new infection that occurs in a severely immunocompromised patient receiving voriconazole could be due to a zygomycete.

References


Does Anti–Tumor Necrosis Factor Therapy Increase the Risk of Surgical Site Infection (SSI) in Patients with Rheumatoid Arthritis?

den Broeder AA, Creemers MCW, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti–tu-
Patients with rheumatoid arthritis and other diseases who receive treatment with agents that block the activity of TNF are at increased risk of developing intracellular infections with organisms such as *Mycobacterium tuberculosis* and *Histoplasma capsulatum*. There is concern that anti-TNF therapies, which have come into widespread use, may increase the risk of other types of infections as well, including postoperative SSI. In fact, a small retrospective study recently reported an increased risk of serious postoperative infections in anti-TNF recipients who have rheumatoid arthritis and who are undergoing orthopedic procedures [1]. In a much larger investigation, den Broeder and colleagues examined the risk factors for SSI in a retrospective, parallel-cohort study with a 1-year follow-up period.

In this study, the overall incidence of SSI after 1219 surgical procedures in 768 patients with rheumatoid arthritis was 4.5%. Only 22 of the 55 infections were, however, microbiologically confirmed. When stratified by the use of anti-TNF agents, SSI rates were 4.0% among the 1023 patients who had never received this therapy, 5.8% among the 104 patients who had discontinued anti-TNF therapy a mean of 5.6 drug half-lives before surgery, and 8.7% among the 92 patients who continued to receive such therapy at the time of surgery. The last group had actually received their last dose of anti-TNF therapy on average a mean of 1.9 drug half-lives before their surgical procedure was performed.

Multivariate analysis identified elbow or foot/ankle surgery and prior skin or wound infection as significant risk factors for SSI, whereas the use of sulfasalazine and, paradoxically, a longer duration of surgery were associated with reduced risk. Perioperative receipt of anti-TNF agents was not significantly associated with an increased risk of SSI (OR, 1.5; 95% CI, 0.43–5.2). Wound dehiscence, however, occurred more frequently among patients who continued to receive anti-TNF therapy, but not among those who discontinued it. The study was reported to have a power of 80% to detect an absolute risk of 18% (relative risk, 3.6) of infection when anti-TNF therapy was continued.

There were a number of confounding variables in this retrospective study that may not have entirely been accounted for by the logistic regression analysis; these include an increase over time in the frequency of surgical interventions and likely other factors related to the procedures. The use of anti-TNF therapies increased 3-fold over the course of the study, and there were differences in the specific agent used during that time as well. Nonetheless, the preliminary message that can be safely drawn from this study is that the use of anti-TNF therapies is not associated with a marked increase in SSI, but continuation of these therapies at the time of surgery may possibly be associated with problems in wound healing.

**Reference**


**Susceptibility to an Animal Trypanosome**


Humans are normally resistant to infection with *Trypanosoma evansi*, a parasite of domesticated mammals, such as cattle and water buffalo, in areas in Africa, South America, and Asia. Humans are also resistant to 1 of the 3 subspecies of *T. brucei*, *T. b. brucei*, as a consequence of the presence of a serum apolipoprotein L-1 (APOL1), which, when endocytosed by the trypanosome, creates pores in the lysosomal membrane, leading to the death of the organism. *T. b. rhodesiense* and *T. b. gambiense*, in contrast, have developed resistance to APOL1, and as a consequence, they are important human pathogens. An Indian cattle farmer was recently found to be infected with *T. evansi*, leading to the finding that his susceptibility to this infection was fortunately due not to a trypanosomal factor; rather, it was due to frame-shift mutations in both alleles of the gene that encodes APOL1, leading to absence of serum trypanolytic activity.

**Preventing Intravenous Catheter–Related Bloodstream Infection (BSI)**


Approximately 100 Michigan hospitals participated in a study evaluating the implementation of evidence-based interventions designed to prevent intravenous catheter-related BSI. The recommended procedures were hand washing, use of full-barrier precautions during the insertion of central venous catheters, cleaning of the skin with chlorhexidine, avoidance of the femoral site (if possible), and removal of unnecessary catheters. The intervention was associated with a reduction in the median rate of BSI from a baseline of 2.7 cases per 1000 catheter-days to 0 cases per 1000 catheter-days (P < .002) after 3 months. The mean rate also decreased from 7.7 cases per 1000 catheter-days to 1.4 cases per 1000 catheter-days (P < .002) after 16–18 months of observation.