When a Paradoxical Increase in Serum Galactomannan Antigen during Caspofungin Therapy Is Not Paradoxical after All

To the Editor—Klont et al. [1] describe a paradoxical increase in serum aspergillus galactomannan index (GMI) during caspofungin treatment in a patient with invasive aspergillosis (IA) who ultimately recovered and suggest that initial GMI increases may be related to the echinocandins mode of action and that GMI monitoring in patients undergoing caspofungin treatment patients may not indicate progressive IA.

This paradoxical effect, however, is neither observed clinically [2] nor consistently present in experimental IA (table 1) [3–10] because 5 of 8 such studies do not show this effect [3, 7–10], and the remaining 3 give conflicting results. One study suggested a paradoxical effect at a dosage of 2 mg/kg per day of micafungin (MICA-2), rather than at 0.5 or 1 mg/kg per day (MICA-0.5 and MICA-1, respectively) [4], and an increased GMI at MICA-2 treatment, despite improved survival and decreased pulmonary lesion scores (PLS). However, the improved survival rate was modest (30% rabbits treated with MICA-2 vs. 0% untreated rabbits), and lung weight, a parameter of organism-mediated pulmonary injury (OMPI), was unaffected. A study of caspofungin dosages of 1, 3, and 6 mg/kg per day (CAS-1, CAS-3, and CAS-6, respectively) [5] reported survival advantage and a decrease in OMPIs, despite elevated GMI. However, the improved survival rate was minimal (22% treated rabbits vs. 5% untreated rabbits), and the effect on OMPIs did not depend on the dose; lung weight decreased with CAS-1 and CAS-6 (not CAS-3), and PLS was lower only with CAS-1 (but not CAS-3 or CAS-6). Infiltrate scores were not reduced at any dose. Similar findings were reported in another study with minimal survival improvement with single agent anidolafungin (2 of 6 treated rabbits vs. 0 of 15 untreated rabbits) [6]. Of note, a strong correlation between GMI and the number of colony-forming units per gram of tissue was observed in all studies, suggesting that GMI is truly reflective of fungal burden [3–10].

That paradoxical GMI increases result from the mode of action of echinocandins [1] is refuted by prominent correlations between quantitative lung tissue Aspergillus DNA (Q-PCR or RT-PCR) and serum and lung GMI [7, 10], and between decreasing GMI and lung tissue RT-PCR with improved survival with CAS-4, but not with lower doses [7].

We submit that echinocandins have limited activity against IA in prolonged neutropenia (≥10 days), as indicated by the lack of survival benefit with MICA-0.5 and MICA-1 [4], the modest benefit with MICA-2, and the improved survival benefit and the decrease of the number of lung colony-forming units per gram and GMI with CAS-4 (not the lower doses) [7]. Thus, echinocandin-associated GMI increases reflect their limited activity against IA and are not paradoxical. On the basis of data shown here and the lack of paradoxical effect in patients undergoing caspofungin treatment [2], increasing GMI in patients undergoing echinocandin treatment should be considered evidence of progressive IA.

β-Glucan in the fungal cell wall, which is inhibited by echinocandins [1], triggers a pro-inflammatory response [11]. Therefore, the reduction in OMPIs and the modest survival advantage with echinocandins may result from suppression of the β1-3 d-glucan–induced inflammation [11], as suggested by the contrast between limited inflammation among mice treated with caspofungin and severe inflammation/abscess formation in untreated mice [8, 9] and by increasing the number of colony-forming units per gram or GMI among rabbits treated with echinocandin and untreated rabbits [3, 4]. This hypothesis supports the addition of echinocandins to other mold-active agents during immune recovery, when rapid resolution of neutropenia may cause clinical deterioration [12–14]. Echinocandins may lessen this inflammatory response and provide additional antifungal activity, particularly in the presence of neutrophils [7–9].

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Marisa H. Miceli and Elias J. Anaissie
University of Arkansas for Medical Sciences, Myeloma Institute for Research and Therapy, Little Rock, Arkansas

References

4. Petrakis V, Petraitie R, Groll AH, et al. Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neu-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Model (duration of treatment)</th>
<th>Treatment (dosage, mg/kg per day)</th>
<th>Fungal load</th>
<th>Galactomannan index</th>
<th>Organism-mediated pulmonary injury</th>
<th>Lung weight</th>
<th>Pulmonary lesion scores</th>
<th>Infiltrate score on chest CT</th>
<th>Survival</th>
<th>Paradoxical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3]</td>
<td>Neutropenic rabbits (&gt;10 days)</td>
<td>MICA (1, RAV /2.5), and the combination of both (MICA-RAV) started on days 1–12 after inoculation</td>
<td>ND versus UCs, except for MICA-RAV for lungs only (P &lt; .01)</td>
<td>ND for MICA vs. UCs, except for MICA-RAV combination (P &lt; .01)</td>
<td>ND for MICA at 0.5 mg/kg per day; modest decrease for MICA at 1 and 2 mg/kg per day (P &lt; .05); decrease for AmB (P &lt; .001)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>No</td>
</tr>
<tr>
<td>[4]</td>
<td>Neutropenic rabbits (&gt;10 days)</td>
<td>MICA (0.5, 1, and 2), AmB (1), and L-AmB (5) started on days 1–12 after inoculation</td>
<td>ND for MICA versus UCs; decrease in fungal load for AmB arm (P &lt; .01) and L-AmB arm (P &lt; .001) for lungs only</td>
<td>ND for MICA vs. UCs, but UCs were tested to day 9 after inoculation, and the CAS arm was tested to day 11 after inoculation; the index decreased with AmB and with L-AmB (P &lt; .001)</td>
<td>ND</td>
<td>ND for MICA at 0.5 mg/kg per day; decrease for MICA at 1 and 2 mg/kg per day (P &lt; .05); decrease for AmB, L-AmB (P &lt; .001)</td>
<td>ND</td>
<td>NA</td>
<td>ND</td>
<td>NA</td>
</tr>
<tr>
<td>[5]</td>
<td>Neutropenic rabbits (&gt;10 days)</td>
<td>CAS 1 prophylaxis started 4 days before to 12 days after inoculation</td>
<td>ND for CAS arm vs. UCs for lungs only</td>
<td>ND, but the UCs were tested until day 9 after inoculation and the CAS arm was tested until day 11 after inoculation</td>
<td>ND</td>
<td>Decrease (P &lt; .01)</td>
<td>ND</td>
<td>NA</td>
<td>Increase in survival rate for CAS arm (~50%, compared with 0% for UCs; P &lt; .001)</td>
<td>Yes after day 7 after inoculation (increase in deaths among UCs)</td>
</tr>
<tr>
<td>[5]</td>
<td>Neutropenic rabbits (&gt;10 days)</td>
<td>CAS (1, 3, and 6) and AmB (1) started on days 1–12 after inoculation</td>
<td>ND for CAS arm vs. UCs; decrease in fungal load for AmB arm vs. UCs (P &lt; .01) for lungs only</td>
<td>ND between all CAS dosages vs. UCs; decrease for AmB vs. UCs (P &lt; .01); ND between all CAS dosages vs. UCs with regard to negative culture results and fungal loads in BAL specimens; all BAL culture results were negative after receipt of AmB</td>
<td>ND</td>
<td>ND for CAS at 3 mg/kg per day; decrease for CAS at 1 and 6 mg/kg per day (P &lt; .05)</td>
<td>ND</td>
<td>ND for CAS at 3 and 6 mg/kg per day; decrease for CAS at 1 mg/kg per day (P &lt; .01)</td>
<td>ND for CAS at 1, 3, and 6 mg/kg per day</td>
<td>Modest increase in survival rate for CAS at 1, 3, and 6 mg/kg per day (72%, compared with 5% for UCs; P &lt; .001)</td>
</tr>
<tr>
<td>[6]</td>
<td>Neutropenic rabbits (&gt;10 days)</td>
<td>AFG (5 and 10), Vor (30), and the combination of Vor-AFG (5) or Vor-AFG (10) started on days 1–12 after inoculation</td>
<td>ND for AFG and Vor arms vs. UCs; fungal load was lower for the combination of AFG with Vor vs. AFG or Vor alone (P &lt; .05) and vs. UCs (P &lt; .01)</td>
<td>ND between the AFG arms and UCs; serum and lung index decreased with Vor and with AFG-Vor (P &lt; .05)</td>
<td>Decrease with Vor plus AFG at 5 mg/kg per day (P &lt; .01) statistics were not given for single agents vs. UCs</td>
<td>ND for CAS at 3 mg/kg per day; decrease for CAS at 1 mg/kg per day (P &lt; .01)</td>
<td>ND for CAS at 3 mg/kg per day; decrease for CAS at 1 mg/kg per day (P &lt; .01)</td>
<td>ND for CAS at 1, 3, and 6 mg/kg per day</td>
<td>Decrease with Vor plus AFG at 5 mg/kg per day; decrease with Vor plus AFG at 5 mg/kg per day; decrease with Vor plus AFG at 5 mg/kg per day (71%); rate for Vor plus AFG at 5 mg/kg per day, 71%; rate for Vor alone, 60%)</td>
<td>Unclear; there was a modest increase in survival, without statistics and with no data for AFG at 10 mg/kg per day</td>
</tr>
<tr>
<td>Group</td>
<td>Treatment Details</td>
<td>Data Provided</td>
<td>Statistics</td>
<td>ND for CAS arm at doses of 1, 2, or 3 mg/kg per day; serum and lung indices decreased with CAS at 4 mg/kg per day (P = .09)</td>
<td>Increase with CAS and AmB (P &lt; .001) higher survival rate for CAS 4, after neutrophil recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenic rats (10 days)</td>
<td>CAS (1, 2, 3, and 4) and AmB (1) started on days 1–10 after inoculation</td>
<td>Data not provided; statistics were not consistently given for RT-PCR findings for lung specimens, but there was a probable decrease with CAS-4 after neutrophil recovery</td>
<td>ND for CAS arm at doses of 1, 2, or 3 mg/kg per day; serum and lung indices decreased with CAS at 4 mg/kg per day (P = .09)</td>
<td>Increase with CAS and AmB (P &lt; .001) higher survival rate for CAS 4, after neutrophil recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenic mice (3 days)</td>
<td>CAS (0.5), AmB (1), L-AmB (1), and combination of CAS-AmB or CAS-L-AmB started on days 0–5 after inoculation</td>
<td>Statistics were not given, but there was a probable decrease for kidneys and lungs (but not the spleen) for CAS vs. UCs; pronounced decrease for kidneys, lungs, and spleen compared with other drugs and combinations</td>
<td>Statistics were not given, and ~75% of UCs were dead by day 5 after inoculation; no. of days to negative index after inoculation: L-AmB-CAS arm, 7; AmB plus CAS arm, 14; AmB and L-AmB arms, 21; and CAS arm, 28</td>
<td>Increase for CAS and other drugs (P &lt; .001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenic mice (3 days)</td>
<td>CAS (0.5), L-AmB (1), G-CSF, and combination of CAS-G-CSF or CAS-AmB-G-CSF started on days 0–5 after inoculation</td>
<td>Statistics were not given, but there was a probable decrease for kidneys and lungs with CAS; pronounced decrease for kidneys and lungs, compared with other drugs and combinations</td>
<td>Statistics were not given, and &gt;75% of UCs were dead by day 5 after inoculation; no. of days to negative index after inoculation: L-AmB or CAS plus G-CSF and all 3 drugs combined, 21; CAS alone, 28</td>
<td>Increase with CAS and other drugs (P &lt; .001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mice with CGD</td>
<td>MICA (10), AmB (1), and the combination MICA-AmB started on days 0–5 after inoculation</td>
<td>Data not provided; ND vs. UCs for Q-PCR of lung specimens</td>
<td>ND vs. UCs, but testing was done once (on day 5 after inoculation); animals on whom testing was done were killed on day 5 after inoculation</td>
<td>Increase with MICA and AmB (P = .003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** AFG, anidulafungin; AmB: deoxycholate amphotericin B; CAS, caspofungin; CGD, chronic granulomatous disease; G-CSF, granulocyte colony-stimulating factor; L-AmB, liposomal amphotericin B; MICA, micafungin; NA, not available for evaluation/not applicable; ND, no difference; RAV, ravuconazole; UC, untreated or suboptimally treated control subject; Vor, voriconazole.

* In serum, unless otherwise indicated.

b Dosage, 300 μg/kg per day.

**Replay to Miceli and Anaissie**

To the Editor—We thank Miceli et al. [1] for their response to our article in which they suggest that our observation of an unexpected increase of circulating galactomannan (GM) was due to failure of the infection to respond to caspofungin therapy rather than a paradoxical effect [2]. Our laboratory has >10 years of experience with GM detection in patients with hematological malignancy, and we have not previously observed such high levels of circulating antigen (figure 1). Unlike our patient, the patients described by Maertens et al. [3] received antifungal treatment prior to caspofungin therapy. One study presented by Miceli et al. [1] as evidence of the nonexistence of a paradoxical effect relates to combination antifungal therapy with another echinocandin (micafungin and ravuconazole) in an animal model for invasive aspergillosis (IA) and differs from our patient, who received primary monotherapy with caspofungin [4]. Two other studies mentioned also fail to exclude a paradoxical effect and cannot be compared with our case. First, the kinetics of GM in patients who experience chronic granulomatous disease are known to be different from those in hematological patients [5]. Second, the results by van Vianen et al. [6] have not been consistently found by other researchers. Wiederhold et al. [7] detected an increase in quantitative lung tissue Aspergillus DNA (by RT-PCR) in neutropenic mice with pulmonary aspergillosis after treatment with caspofungin, 4 mg/kg per day, compared with 1 mg/kg per day. Our clinical observation is supported by both an animal model [8] that was not referred to by Miceli et al. [1] and our own in vitro experiment, in which fungal biomass was correlated with the release of GM by the causative Aspergillus strain following exposure to caspofungin [2].

The lack of a consistent description of a paradoxical effect should not provide the

![Figure 1](https://academic.oup.com/cid/article-abstract/44/5/757/350449)

Figure 1. Frequency of peak galactomannan serum ratios in 22 hematology patients with proven and probable invasive aspergillosis. A case patient is a patient with invasive aspergillosis primarily treated with caspofungin who experiences a subsequent unexpected increase in galactomannan level (P = .03).