Current experience in treating invasive zygomycosis with posaconazole

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Abstract

The treatment of zygomycosis has two cornerstones, namely, surgery and antifungal drugs. In many patients, both need to be applied to achieve treatment success; without treatment, the mortality rate of zygomycosis approaches 100%. Because treatment options are limited, no well-designed randomized clinical trial has been conducted and data are predominantly derived from compassionate-use programmes or case reports. Amphotericin B (AmB) lipid complex (ABLC) was clinically evaluated for efficacy against zygomycosis in a single series and resulted in cure or improvement in 52% and in the stabilizing of disease in 20% of patients. Liposomal AmB (L-AmB) is frequently used, but no large series have yet been published. Posaconazole has demonstrated in vitro and in vivo activity against Zygomycetes. Two series demonstrated salvage treatment response rates of 60% and 79%, respectively. Antifungal combinations have not been evaluated thoroughly enough to warrant recommendations outside of clinical trials. Survival is usually associated with surgical debridement and improvement in underlying diseases. Currently, surgical debridement should be performed. Antifungal treatment should consist of either ABLC \( \geq 5 \) mg/kg once per day or L-AmB \( \geq 3 \) mg/kg once per day. When toxicity occurs or stable fungal disease is achieved, treatment can be switched to oral posaconazole 200 mg four times per day. If impaired kidney function is overt or expected on the grounds of, for example, uncontrolled diabetes, primary treatment of zygomycosis with posaconazole is an option.

Keywords: Diabetes mellitus, immunodeficiency, invasive fungal infection, mucormycosis, posaconazole, zygomycosis

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Introduction

Zygomycoses are the most common of the so-called ‘rare’ invasive fungal infections [1]. They represented >7% of such diseases in a large cohort of adult haematopoietic stem cell recipients [2].

Without treatment, the mortality rate of zygomycosis approaches 100% [3]. For mould infections as devastating as zygomycosis, it may even be reasonable to define the stabilizing of disease as indicative of successful treatment [4].

Zygomycetes are ubiquitous organisms. Although the most severely immunocompromised patients are most at risk, other patient populations are too. These populations are heterogeneous and range from patients with poorly controlled diabetes mellitus to those with contaminated traumatic wounds [5,6]. Peritoneal dialysis is another risk factor, in which zygomycetes peritonitis should be included in a differential diagnosis. An overview of cases published has recently been presented [7]. Nosocomial outbreaks related to construction work have been described, as have outbreaks caused by water damage within the rooms of a paediatric oncology ward, which led to two invasive infections and required control with an aggressive management plan [8].

Treatment Options for Zygomycosis

Although therapeutic options for invasive aspergillosis and invasive candidiasis have increased during the last decade, treatments for diseases caused by Zygomycetes remain very limited [9]. In general, four therapeutic options deserve consideration as part of a multimodal approach to therapy. One approach involves surgery and the other three rely on the different antifungal drugs that show activity against Zygomycetes. Most patients undergo surgical debridement, frequently prior to diagnosis of the nature of the infection. Extensive surgical debridement is difficult to achieve because important structures are often adjacent to necrotic tissues, particularly in sinu-nasal, rhino-orbital and, especially, cerebral involvement. As a consequence, surgery may at best yield a partial remission [4]. Some well-documented cases describe fungal organisms in repeat histology
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Age, years</th>
<th>Underlying condition</th>
<th>Risk factors</th>
<th>Fungal isolate</th>
<th>Organ involvement</th>
<th>Surgical resection, Y/N</th>
<th>Dose, mg/day</th>
<th>Duration, months</th>
<th>Combined with lipid-based amphotericin B</th>
<th>Outcome</th>
<th>References</th>
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<tbody>
<tr>
<td>Alexander et al.</td>
<td>2008</td>
<td>ND</td>
<td>ND</td>
<td>SOT</td>
<td>Apophysomyces elegans&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>800</td>
<td>ND</td>
<td>N</td>
<td>Failure</td>
<td>[18]</td>
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<td>Alexander et al.</td>
<td>2008</td>
<td>ND</td>
<td>ND</td>
<td>SOT</td>
<td>Rhizopus sp.</td>
<td>NA</td>
<td>NA</td>
<td>800</td>
<td>ND</td>
<td>N</td>
<td>CR</td>
<td>[19]</td>
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<td>Bethge et al.</td>
<td>2005</td>
<td>43</td>
<td>AML</td>
<td>Chemotherapy</td>
<td>Rhizopus sp.</td>
<td>Lung, thyroid, kidney</td>
<td>N</td>
<td>ND</td>
<td>~24</td>
<td>Y</td>
<td>PR</td>
<td>[20]</td>
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<tr>
<td>Bethge et al.</td>
<td>2005</td>
<td>63</td>
<td>AML</td>
<td>Chemotherapy</td>
<td>Rhizomucor sp.</td>
<td>Left calf, lung</td>
<td>N</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
<td>Died</td>
<td>[20]</td>
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<td>Brugere et al.</td>
<td>2005</td>
<td>46</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Surgical resection, Y/N</td>
<td>Mucor sp.</td>
<td>Lung</td>
<td>N</td>
<td>ND</td>
<td>N</td>
<td>Died</td>
<td>CR</td>
<td>[21,22]</td>
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<td>Chan et al.</td>
<td>2007</td>
<td>10</td>
<td>Aplastic anaemia</td>
<td>Antithymocyte globulin, cydospinor, corticosteroids</td>
<td>Rhizopus oryzae</td>
<td>Skin, subcutaneous tissue, muscle</td>
<td>Y</td>
<td>600</td>
<td>&gt;2</td>
<td>N</td>
<td>CR</td>
<td>[23]</td>
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<tr>
<td>de Decker et al.</td>
<td>2006</td>
<td>12</td>
<td>Post-traumatic fasciitis</td>
<td>None</td>
<td>Mucor sp.</td>
<td>Skin, muscle</td>
<td>Y</td>
<td>200</td>
<td>~5</td>
<td>Y</td>
<td>CR</td>
<td>[24]</td>
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<tr>
<td>Ferguson et al.</td>
<td>2007</td>
<td>43</td>
<td>Trauma</td>
<td>None</td>
<td>Apophysomyces elegans</td>
<td>Rhinocerebral</td>
<td>Y</td>
<td>800</td>
<td>6</td>
<td>N</td>
<td>CR</td>
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<td>Garbino et al.</td>
<td>2005</td>
<td>55</td>
<td>Trauma</td>
<td>Corticosteroids</td>
<td>Absidia sp.</td>
<td>Subcutaneous tissue</td>
<td>Y</td>
<td>800</td>
<td>6</td>
<td>N</td>
<td>CR</td>
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<tr>
<td>Gilman et al.</td>
<td>2007</td>
<td>7</td>
<td>Poorly controlled diabetes mellitus</td>
<td>None</td>
<td>Mucor sp.</td>
<td>Rhino-orbital</td>
<td>Y</td>
<td>600</td>
<td>&gt;1</td>
<td>Y</td>
<td>CR</td>
<td>[26]</td>
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<tr>
<td>Harada &amp; Lau</td>
<td>2007</td>
<td>54</td>
<td>NIDDM</td>
<td>Allogeneic SCT, GvHD, corticosteroids</td>
<td>Rhizopus nigricans</td>
<td>Lung, pleura</td>
<td>Y</td>
<td>800</td>
<td>34</td>
<td>N</td>
<td>CR</td>
<td>[27]</td>
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<tr>
<td>Leather et al.</td>
<td>2005</td>
<td>51</td>
<td>AML</td>
<td>Chemotherapy</td>
<td>Rhizopus sp.</td>
<td>Skin, subcutaneous tissue</td>
<td>Y</td>
<td>800</td>
<td>&gt;4</td>
<td>N</td>
<td>CR</td>
<td>[28]</td>
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<tr>
<td>Margo et al.</td>
<td>2007</td>
<td>54</td>
<td>Poorly controlled NIDDM</td>
<td>None</td>
<td>Histology</td>
<td>Rhino-orbital-cerebral</td>
<td>Y</td>
<td>800</td>
<td>&lt;8</td>
<td>Y</td>
<td>SD</td>
<td>[29]</td>
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<tr>
<td>Noethis et al.</td>
<td>2006</td>
<td>12</td>
<td>Poorly controlled diabetes mellitus</td>
<td>None</td>
<td>Rhizopus sp.</td>
<td>Rhino-orbital-cerebral</td>
<td>N</td>
<td>ND</td>
<td>15</td>
<td>N</td>
<td>CR</td>
<td>[31]</td>
</tr>
<tr>
<td>Rustar &amp; Cackerham</td>
<td>2006</td>
<td>22</td>
<td>ALL</td>
<td>Polycystic kidney disease</td>
<td>Rhizopus sp.</td>
<td>Rhinocerebral</td>
<td>Y</td>
<td>800</td>
<td>5</td>
<td>N</td>
<td>CR</td>
<td>[33]</td>
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<tr>
<td>Sorensen et al.</td>
<td>2006</td>
<td>10</td>
<td>Severe aplastic anaemia</td>
<td>Antithymocyte globulin, cydospinor, corticosteroids</td>
<td>Absidia corymbifera&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Rhino-orbital-cerebral</td>
<td>Y</td>
<td>800</td>
<td>&gt;6</td>
<td>Y</td>
<td>CR</td>
<td>[35]</td>
</tr>
<tr>
<td>Stark et al.</td>
<td>2007</td>
<td>42</td>
<td>CLL</td>
<td>Allogeneic SCT, GvHD, corticosteroids, mycophenolate mofetil</td>
<td>Rhizopus microsporus</td>
<td>Rhino-orbital</td>
<td>Y</td>
<td>800</td>
<td>&gt;12</td>
<td>Y</td>
<td>PR</td>
<td>[10]</td>
</tr>
<tr>
<td>Tabon et al.</td>
<td>2003</td>
<td>56</td>
<td>Intersitial nephritis, severe dilated cardiomyopathy</td>
<td>SOT, heart-kidney, hemodialysis</td>
<td>Rhizopus sp.</td>
<td>Mediastinum, pericardium</td>
<td>Y</td>
<td>800</td>
<td>4</td>
<td>N</td>
<td>CR</td>
<td>[36]</td>
</tr>
</tbody>
</table>

**Notes:**
- ALL, acute lymphatic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphatic leukaemia; CR, complete response; GvHD, graft vs. host disease; IDDM, insulin-dependent diabetes mellitus; ND, no data; NIDDM, non-insulin-dependent diabetes mellitus; PR, partial response; SCT, stem cell transplant; SD, stable disease; SOT, solid organ transplant; Y, yes; N, no; NA, not applicable.
- <sup>a</sup>Dual infection with an unidentified Basidiomycete.
- <sup>b</sup>Dual infection with Trichosporon ovoides.
- <sup>c</sup>Dual infection with Alternaria alternata.
samples over substantial periods of time [10]. The available antifungal treatments which are active against Zygomycetes include amphotericin B (AmB) in its various formulations and posaconazole. Of the polyene formulations, AmB lipid complex (ABLC) has been clinically evaluated for efficacy against zygomycosis in two series. In one, an emergency-use programme for salvage treatment described a complete and partial response rate of 71% [11]. In the other, using post-marketing data (n = 64) with a median daily dose of 4.8 mg/kg, cure or improvement occurred in 52% and stable disease in another 20% of patients [12]. Liposomal AmB (L-AmB) is frequently used, but prospective series of patients have rarely been published. However, a multivariate analysis characterized L-AmB treatment as the single prognostic factor correlating with recovery from infection [13].

**Use of Posaconazole Against Zygomycetes Infections**

Posaconazole has *in vitro* and *in vivo* activity against Zygomycetes. The properties of posaconazole have been thoroughly described elsewhere [14]. In general, posaconazole is considered a safe drug, even when given over long periods of time [15].

Two series have been published. The first (n = 24) reported on two non-randomized compassionate-use programmes evaluating salvage treatment with posaconazole oral suspension 200 mg administered four times per day or 400 mg administered twice per day. The infections were rhinocerebral in 46% of cases and the median treatment duration was 182 days. The overall rate for complete and partial response was 79% and was similar in both patients with refractory disease and those with intolerance to standard therapy. The survival rate was 79% and was associated with surgical debridement and improvement in underlying diseases. Posaconazole oral solution was generally well tolerated [16]. The second publication reported on a higher number of patients (n = 91) in a compassionate-use programme. Its data were retrospectively analyzed. All patients were treated with a dose of 800 mg/day administered in two or four doses. Eleven patients from the previous report were included. Of the patients, 76% had proven and 24% had probable invasive infection, and 89% were refractory towards previous treatment. The overall rate of complete or partial response was 60% at 12 weeks. An additional 21% of patients achieved stable disease [17].

More than 20 case reports of posaconazole salvage treatment have been published (Table I). Common to almost all is a complete response in severely ill patients. There may be some overlap with the two larger series described above [16,17] and some publication bias towards the reporting of cases with favourable outcomes is likely to have occurred. However, the published results are encouraging and warrant further evaluation of the role of posaconazole in treating zygomycosis.

**Proposal for a Combined Treatment Approach for Zygomycosis**

Currently, all the treatment options described should be considered for patients with zygomycosis. A recommended treatment plan is shown in Fig. I. Surgical debridement should be used to the extent feasible to reduce the fungal burden. Medical treatment should rely on ABLC at a daily dose of ≥5 mg/kg or L-AmB at a daily dose of ≥3 mg/kg. In cases of toxicity or treatment failure, switching to oral posaconazole, 200 mg four times per day, is an effective second-line option. Treatment with posaconazole also appears to facilitate the discharge of patients who achieve at least stable disease.

![FIG. I. Recommended treatment options for patients with zygomycosis.](image-url)
Conclusions

If impaired kidney function is overt or expected on grounds of long-term uncontrolled diabetes mellitus or substantially elevated HbA1c results, primary treatment of zygomycosis with posaconazole 200 mg four times per day is a reasonable option. Antifungal combinations have not been evaluated thoroughly enough to warrant their recommendation outside the clinical trial setting.

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Transparency Declaration

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References


