Posaconazole prophylaxis in neutropenic patients with hematological malignancies: limits in clinical practice

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Received 14 December 2013; Revised 6 May 2014; Accepted 17 May 2014

Abstract

Posaconazole (PSZ) is being used for prophylaxis in hematological patients who are at high risk for invasive fungal disease (IFD), but absorption limitations have been reported. Our objective was to assess both the feasibility and the efficacy of PSZ prophylaxis in clinical practice. From March 2010 to September 2010, all patients admitted to our unit for chemotherapy for acute leukemia or hematopoietic stem cell transplantation received optimized PSZ prophylaxis 200 mg four times daily with cola soda. PSZ trough concentrations (Cmin) were monitored at days 5, 7, 14, and 21. The incidence of IFDs was determined and compared to that of a historical control group. Thirty-five consecutive patients were prospectively included. PSZ prophylaxis was interrupted for 29% of them at day 14 and 51% of them at day 21. The main limitations were impracticality of oral feeding (29%) and occurrence of suspected IFDs (23%). PSZ median Cmin were 0.47, 0.40, 0.24, 0.36 µg/mL at days 5, 7, 14, and 21, respectively. Eighty percent of patient results were lower than the target Cmin of 0.5 µg/mL on day 14, the higher-risk period associated with neutropenia. Four probable breakthrough IFDs (11%) were diagnosed in 2010; no clear association between PSZ Cmin and occurrence of infection was observed. The incidence of IFDs was unchanged (historical control group: 9.7%; P = 0.72).
Implementation of systematic PSZ prophylaxis did not significantly decrease the incidence of IFDs at our center. PSZ interruptions related to mucositis and too low $C_{min}$ were the main limitations to its use.

Key words: posaconazole prophylaxis, invasive fungal infection, hematopoietic stem cell transplantation, acute leukemia.

Introduction

Invasive fungal disease (IFD) is a major cause of morbidity and mortality among hematological patients. In allogeneic hematopoietic stem cell transplant (HSCT) patients and those with acute leukemia, prolonged periods of neutropenia and mucositis significantly increase the risk of IFD. Posaconazole (PSZ) is an extended-spectrum triazole agent, mainly used for the treatment of refractory IFD and for the prophylaxis of IFD in patients receiving chemotherapy for acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) and for HSCT recipients. The 3rd European Conference on Infections in Leukaemia Working Group recommended PSZ for leukemia patients for induction chemotherapy (grade AI), and both fluconazole (FCZ) and PSZ are recommended for allogeneic HSCT patients (grade AI) with the following phase-specific guidelines: FCZ prophylaxis is recommended in the initial phase, combined with a mould-directed diagnosis (preemptive approach) or a curative therapeutic approach; PSZ is the drug of choice for prophylaxis during acute or chronic graft-versus-host disease (GVHD) [1].

Due to its wide spectrum, including use in the treatment of aspergillosis, PSZ is increasingly used for hematology patients at high risk for IFD. Although there have been reports regarding the potential underexposure to PSZ and its poor oral absorption, only a few studies on prophylaxis with PSZ in clinical practice have been published [2–6]. Our aim in this study was to assess the feasibility, efficacy, and safety of PSZ prophylaxis in neutropenic patients with acute leukemia and allogeneic HSCT recipients.

Patients and methods

Patients

All consecutive patients admitted between March 2010 and September 2010 to Besançon University Hospital, France, for acute leukemia induction or consolidation chemotherapy and for allogeneic HSCT received PSZ prophylaxis. This treatment and monitoring were part of our approved local policy during this period for the prevention of opportunistic infections. We prospectively recorded feasibility, efficacy, safety, and pharmacokinetics data regarding the prophylactic use of oral PSZ as defined below. All patients gave their informed consent prior to data collection and analyses. Incidence of IFDs during the study was compared with that observed in our hospital during the similar period of the previous year, that is, March 2009 to September 2009, when fluconazole was the antifungal prophylaxis for IFD.

All patients received the usual hematological support care according to ongoing and standardized local Joint Accreditation Committee of the International Society for Cellular Therapy–Europe and the European Society for Blood and Marrow Transplantation procedures (http://www.jacie.org) [7]. This included transfusions, antibiotics, biological evaluations, and supportive care. All patients systematically received an oral proton pump inhibitor (PPI; esomeprazole) as prophylaxis for stress ulcers. The ad hoc institutional review board approved the study, which was carried out in accordance with the ethical standards described in the Helsinki Declaration of 1975, as revised in 1983.

For all patients, antiinfectious prophylaxis included bacterial and fungal oral decontamination with gentamicin and amphotericin B in order to limit the risk of bacterial intestinal translocation, and valaciclovir was used as a herpetic prophylaxis. Allogeneic HSCT recipients also received oral antibacterial prophylaxis against capsulated bacteria and inhaled pentamidine after discharge. Broad-spectrum antibacterial therapy was started when neutropenic fever occurred.

Posaconazole prophylaxis and therapeutic drug monitoring

PSZ was started orally on the first day of induction, consolidation chemotherapy, or conditioning regimen. Patients received 200 mg of PSZ in an oral suspension four times daily with meals and cola soda [8,9]. PSZ prophylaxis was stopped when the oral route became impracticable and prophylaxis was continued with intravenous (IV) fluconazole or caspofungin or when a fungal infection requiring active IV antimould therapy was suspected as defined below (see IFD assessment section). PSZ was never administered with a nasogastric tube. In all cases, PSZ was continued after
the induction chemotherapy cycle, even after hospital discharge, until the end of the consolidation chemotherapy cycle.

The clinical pharmacology laboratory routinely performed PSZ therapeutic drug monitoring [10]. Blood samples were taken just before the first drug intake in the morning. PSZ trough concentrations (C_{min}) were assessed on days 5, 7, 14, and 21 after the beginning of prophylaxis with a validated high-performance liquid chromatography and photodiode array detector as previously described by Chhun et al. [11]. The lower limit of quantification was 0.05 µg/ml.

**IFD assessment**

Each patient had a daily clinical examination. Presence of the *Aspergillus* galactomannan antigen was tested on sera sampled twice a week by using the double-sandwich enzyme-linked immunosorbent assay, platelia *Aspergillus* (Bio-Rad, Marnes-La-Coquette, France), with an optical density index cutoff ≥0.5. Oral swab, stool, and urine samples were systematically tested weekly for the presence of fungi. If a patient had any sign of suspected fungal infection, including persistent fever despite 48 h of broad-spectrum antibacterial therapy and/or positive galactomannan screening, computed tomography evaluations were performed and multiple samples (oral, urine, stool, blood, sputum) were rechecked for bacterial or fungal contamination.

In all cases of proven, probable, or possible fungal disease, defined according to the consensus criteria of the European Organization for the Research and Treatment of Cancer and the Mycoses Study Group [12], PSZ prophylaxis was stopped and patients received IV treatments with voriconazole or liposomal amphotericin B [1].

**Results**

**Patient characteristics**

Thirty-five consecutive patients received PSZ prophylaxis from March 2010 to September 2010, of which five received two cycles of PSZ prophylaxis during the study period: four received induction and then consolidation chemotherapies and one received consolidation chemotherapy followed by an allogeneic HSCT. We therefore analyzed 40 consecutive PSZ prophylaxis cycles of patients whose median age was 50 years (range 8–67), of who 13 received induction (n = 9) and consolidation (n = 4) chemotherapy for acute leukemia and 22 received an allogeneic HSCT. Patient characteristics are summarized in Table 1. All patients received PPI (esomeprazole) cotreatment. Of the 35 patients, 2 died during the study period, and 1 of these deaths was related to breakthrough invasive pulmonary aspergillosis (patient 3). From March 2009 to September 2009, 31 patients, hospitalized in the unit for the same indications, received prophylaxis with fluconazole and were used as a control group.

**Table 1. Patient demographic and clinical characteristics and indications for prophylactic antifungal therapy.**

<table>
<thead>
<tr>
<th>Demographic/clinical characteristics</th>
<th>Patient data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), median (range)</td>
<td>50 (8–67)</td>
</tr>
<tr>
<td>Weight (kg), median (range)</td>
<td>70 (25–115)</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>12/23</td>
</tr>
<tr>
<td>Underlying hematological malignancy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukemia*</td>
<td>17 (48.6)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Acute lymphoid leukemia*</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Refractory anemia with excess of blasts*</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia*</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Medullary aplasia</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Plasmablastic leukemia</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Indication for posaconazole prophylaxis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Induction then consolidation chemotherapy</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Consolidation chemotherapy then HSCT</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>HSCT</td>
<td>21 (60)</td>
</tr>
</tbody>
</table>

HSCT, hematopoietic stem cell transplantation,
*Patients receiving chemotherapy including anthracyclines.

**Antifungal treatments**

Among the 35 patients in the study group, 33 (94%) were treated with PSZ prophylaxis on day 7, 25 individuals (71%) on day 14, and 17 (49%) on day 21 during the first prophylactic cycle. PSZ was stopped because of mucositis, and the oral route of administration became impossible to use in 10 cases (29%). Therefore, prophylaxis was continued with IV fluconazole in seven cases and caspofungin for three patients. Parenteral nutrition was administered to 33 (94%) patients beginning on an average of 12 days after the onset of PSZ prophylaxis and for a median duration of 13.5 days (range 1–35). For eight patients (23%), PSZ prophylaxis was stopped because of suspected fungal infection, and an antifungal preemptive treatment was administered, that is, caspofungin to five patients, liposomal amphotericin B to two, and IV voriconazole to one. During the second cycle of prophylaxis, PSZ was discontinued for two patients, as one had IFD and the other developed facial palsy.
Table 2. Distribution of posaconazole trough concentration depending on cycle and duration of prophylaxis.

<table>
<thead>
<tr>
<th>Date of PSZ monitoring</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSZ C_{min} during cycle 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>35</td>
<td>33</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Median (µg/ml)</td>
<td>0.47</td>
<td>0.40</td>
<td>0.24</td>
<td>0.36</td>
</tr>
<tr>
<td>Range: minimum–maximum</td>
<td>0.10–2.36</td>
<td>0.17–1.83</td>
<td>0.10–1.15</td>
<td>0.12–1.26</td>
</tr>
<tr>
<td>PSZ C_{min} during cycle 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Median (µg/ml)</td>
<td>0.44</td>
<td>0.56</td>
<td>0.88</td>
<td>0.53</td>
</tr>
<tr>
<td>Range: minimum–maximum</td>
<td>0.29–1.15</td>
<td>0.29–2.03</td>
<td>0.25–1.21</td>
<td>0.40–1.24</td>
</tr>
</tbody>
</table>

C_{min}, trough concentration; PSZ, posaconazole.

Pharmacokinetics

The median C_{min} after the first prophylaxis cycle were 0.47, 0.40, 0.24, and 0.36 µg/ml on days 5, 7, 14, and 21, respectively. The trough concentration of PSZ was ≥0.5 µg/ml on day 5 for 16 patients (46%) and on day 7 for another 12 patients (36%). Among patients continuing PSZ prophylaxis, the C_{min} of 20 patients (80%) did not reach the target of 0.5 µg/ml on day 14 nor did those of 10 patients (59%) on day 21 (Table 2). Five received a second cycle of PSZ; plasmatic PSZ concentrations were higher than during the first cycle, but concentrations for two patients who stopped prophylaxis before day 21 still did not reach the minimal target concentration of 0.5 µg/ml.

Invasive fungal disease

Four cases (11.4%) of probable and one case (2.85%) of possible aspergillosis were diagnosed in the PSZ prophylaxis group (Table 3). The time between the start of PSZ prophylaxis for the ongoing chemotherapy cycle and diagnosis of probable or possible aspergillosis was 17.4 days on average. Two patients contracted aspergillosis during the consolidation cycle, even though they had received continuous PSZ prophylaxis since the beginning of the induction cycle. Another patient (patient 2) had major environmental mould exposure (hay harvesting) just before leukemia diagnosis and hospitalization. PSZ prophylaxis was stopped for the two other patients, one because of fever, despite broad-spectrum antibacterial therapy and positive galactomannan antigen in serum (patient 3; Table 3), and one because the oral route had become impossible (facial paralysis) to use. Invasive aspergillosis was treated with voriconazole (n = 3) and amphotericin B (n = 2). Of these five patients, the C_{min} of three did not reach the lower target of 0.5µg/ml during the entire prophylaxis treatment; the C_{min} of the two others were between 0.5 and 0.6 µg/ml when IFD was diagnosed. Nevertheless, no clear correlation was shown between PSZ plasmatic concentrations and risk of aspergillosis in our study.

In the retrospective control cohort of 2009, three IFDs were reported (9.7%): one case of probable aspergillosis and two of possible aspergillosis. The incidence of IFDs was similar for the two periods (P = 0.72).

Discussion

Recent guidelines and consensus statements support the requirement that prophylactic antifungal agents be used when treating leukemia patients who are receiving chemotherapy and allogeneic HSCT [1,13,14]. Thus, all the patients in our hematologic care unit received antifungal prophylaxis. For some years, a new generation of oral azoles, PSZ in particular, has shown activity against a wide spectrum of medically relevant fungi, including species of Candida, Aspergillus, Mucorales, and Fusarium [15,16]. Guidelines for the use of PSZ prophylaxis are based on randomized controlled trials that have shown that PSZ is more effective than fluconazole for prevention of IFD [17–19]. However, routine use of a prophylactic drug may yield efficacy results that are different from those of clinical trials and may reveal different pharmacokinetic characteristics [20]. Only a few studies have evaluated the efficacy of PSZ prophylaxis in clinical practice [5,21].

In our study, we highlighted unexpected limitations of implementation of systematic PSZ prophylaxis in a hematology transplant and intensive care unit. One point assessed in our study was the feasibility of PSZ prophylaxis in terms of patient compliance. We found that it was interrupted in 51% of patients in our study (n = 18). An observational study reported that PSZ prophylaxis was interrupted in 33% of cycles (25 of 76) in 40 patients with AML [3]. Mucositis is one of the main obstacles to the success of strategies based on oral delivery, especially for HSCT recipients. Indeed, 75% of patients who receive high doses of
Table 3. Characteristics of patients with *Aspergillus* breakthrough infection during posaconazole prophylaxis.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>EORTC classification</th>
<th>Sex/Age</th>
<th>Underlying disease</th>
<th>Chemotherapy cycle</th>
<th>Risk factor</th>
<th>First sign, date/type</th>
<th>Posaconazole trough concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Probable IPA</td>
<td>F/37</td>
<td>AML</td>
<td>Induction</td>
<td>Neutropenia</td>
<td>Day 23, GM +</td>
<td>0.11, 0.48, 0.52, 0.22, 0.29</td>
</tr>
<tr>
<td>2</td>
<td>Probable IPA</td>
<td>M/43</td>
<td>Acute lymphoid leukemia</td>
<td>Induction</td>
<td>Neutropenia, GC, high environmental exposure to mould spores</td>
<td>Day 20, GM +</td>
<td>0.14, 0.60, 0.21, 0.11</td>
</tr>
<tr>
<td>3</td>
<td>Probable IPA</td>
<td>F/59</td>
<td>Refractory anemia with excess of blasts</td>
<td>Consolidation</td>
<td>Neutropenia, high dose glucocorticoids (GC), cyclosporine, tacrolimus</td>
<td>Day 7, GM +</td>
<td>0.36, 0.29, 0.22, 0.14</td>
</tr>
<tr>
<td>4</td>
<td>Probable IPA</td>
<td>M/46</td>
<td>Myeloma</td>
<td>Hematopoietic stem cell transplant</td>
<td>Neutropenia, GC</td>
<td>Day 18, GM +</td>
<td>0.39, 0.48, 0.58, 0.18</td>
</tr>
<tr>
<td>5</td>
<td>Possible IPA</td>
<td>M/53</td>
<td>AML</td>
<td>Consolidation</td>
<td>Neutropenia, GC</td>
<td>Day 19, thorax computed tomography</td>
<td>0.29, 0.31, 0.25 ND</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; EORTC, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; GC, glucocorticoids; GM +, positive serum galactomannan; IPA = Invasive pulmonary aspergillosis; ND, not done (posaconazole was stopped).

Mucositis has been significantly associated with lower PSZ absorption and decreased $C_{\text{min}}$ concentrations in HSCT recipients as well as in patients with acute myeloid leukemia and myelodysplastic syndromes [23–25]. Less than 50% of our patients reached the recommended target threshold of 0.5 µg/ml during PSZ prophylaxis. This was particularly clear on day 14 when the PSZ $C_{\text{min}}$ > 0.5 µg/ml was obtained for only 20% of patients, whereas this was the highest risk period for profound neutropenia. These results are similar to those obtained by Bryant et al. with 90% of 21 patients with $C_{\text{min}}$ not reaching the target threshold of 0.7 µg/ml and 76% not attaining 0.5 µg/ml [2]. Pharmacokinetic studies of PSZ showed that a steady state was achieved in 7–10 days [9]. However, in our study, on day 5, PSZ $C_{\text{min}}$ were ≥0.5 µg/ml for 46% of patients ($n = 16$) and on day 7 this was true for 36% ($n = 12$). Contrary to recent studies, increasing the dose (200 mg four times a day instead of 200 mg three times a day) did not help our patients reach target concentrations [26]. Absorption is saturated above a daily dose of 800 mg, thus, increasing the dose served no purpose [27]. In an assessment of different dosing strategies in patients with gastrointestinal dysfunction (400 mg two times a day, 400 mg three times a day vs. 200 mg three times a day), a subset of patients with low steady-state PSZ concentrations (“poor absorbers”) was observed; for these patients, a change in dosing regimens was not associated with improved absorption [21].

Several other strategies have been designed to maximize PSZ absorption, such as administration in divided doses with meals and acidic beverages. Administration with an acidic beverage was associated with an increase in PSZ $C_{\text{max}}$ and in areas under the concentration-time curve over 24 h (AUC) by 92% and 70%, respectively, compared with the results obtained with administration of PSZ alone [9]. PSZ coadministration in a “bundle” consisting of 500 mg ascorbic acid, carbonated soda or acidic fruit juice, and food/snack yielded optimized PSZ concentrations (median $C_{\text{min}} = 1.8$ µg/ml; $n = 5$) [28]. Although we used a similar bundle to improve PSZ absorption, $C_{\text{min}}$ were suboptimal. This is probably related to the concomitant use of PPIs at our center. Indeed, the coadministration of PSZ with esomeprazole decreased the mean PSZ $C_{\text{max}}$ and AUC by 33% and 21%, respectively, compared with the administration of PSZ alone, despite the associated use of an acidic carbonated beverage [9]. The deleterious effect of PPIs on PSZ concentrations has been confirmed in several studies [25,26,29,30]. The linear accumulation of PSZ improved in patients without PPI coadministration compared with that in patients receiving PPIs [26].
The deleterious impact of other variables on PSZ absorption should be considered, especially occurrence of diarrhea, which was not investigated in our study. It has been found that PCZ C\text{min} were below the 0.7-µg/ml threshold in only 18% of patients without diarrhea compared with 49% of those with diarrhea [5]. Similar associations between diarrhea and decreased PSZ concentrations have been reported elsewhere [20,24,29].

An exposure–response relationship has been suggested by several pharmacokinetic analyses [31–33], but the relationship between PSZ exposure in plasma and clinical efficacy has not been confirmed [34]. However, C\text{min} > 0.5–0.7 µg/ml has been recommended by several authors for prophylactic antifungal efficacy (reviewed in [34]). A recent multicentric study reported that median PSZ C\text{min} were significantly lower for those who developed breakthrough fungal disease than for those who did not (median 0.29 ng/ml vs. 0.49 ng/mL respectively; P < 0.01) and that the PSZ concentration was a significant predictor of breakthrough fungal disease (P < 0.05) [29]. Although no clear correlation between PSZ concentration levels and risk of aspergillosis could be demonstrated in our limited study, all patients with breakthrough aspergillosis presented with C\text{min} <0.6 µg/ml at the time of infection diagnosis.

We have reported a high rate of probable invasive aspergillosis (11.4%) despite PSZ prophylaxis, and this incidence was similar to that of the previous year, when we administered fluconazole prophylaxis (3/31 vs. 5/35; P = 0.72). This incidence is much higher than the 2% incidence of proven or probable IFD and the 1% incidence of invasive aspergillosis reported by Cornely in his randomized controlled trial [17]. However, it is similar to the incidence reported elsewhere in neutropenic patients receiving PSZ prophylaxis (14.8%) [2] and similar to the results found in a multicentric Australian study on PSZ therapeutic drug monitoring (17%) [29]. In addition, in an evaluation with standard long-term PSZ prophylaxis in adult allogeneic SCT recipients, there were eight cases of breakthrough IFD for patients on PSZ (7.5%) within 6 months after SCT [6]. In another study of patients with PSZ prophylaxis in the early phase of allogeneic HSCT, no breakthrough IFD was diagnosed; however, this study excluded the primary phase of conditioning before HSCT or AML induction chemotherapy [35]. Digestive GVHD can also significantly affect PSZ concentrations and decrease the clinical efficacy of this prophylaxis in HSCT recipients [5].

In our hospital, corridors and the hematology unit have been scanned weekly for environmental fungal contamination (surface and air) for the past 10 years [36]. No significant abnormal fungal contamination was observed during the two periods (the PSZ study and the retrospective period), leaving us with no specific explanation for our high incidence of IFD. We add, however, that the regional distribution of aspergillosis varies in France, and the highest average annual incidence rate of aspergillosis is in the east, where our center is located [37]. Of the five patients who suffered from invasive aspergillosis, only one was exposed to a major environmental risk because of his farming job. Two patients with aspergillosis had plasma PSZ concentrations that were potentially adequate for effective prophylaxis (≥0.5 µg/ml). In these cases, perhaps both the diagnosis of aspergillosis and the implementation of preemptive/curative treatment were delayed because clinicians knew that an a priori effective prophylaxis had been given to their patients. In our study, unlike the results obtained by Winston et al., PSZ prophylaxis was not associated with an increasing rate of Candida infections [6].

To conclude, the implementation of a systematic prophylaxis with PSZ did not result in a significant decrease in the incidence of IFD. Our experience highlights the frequent rate of interruptions of prophylactic treatment due to mucositis. The interruptions, the low patient PSZ concentrations especially on day 14, concomitant with profound neutropenia, limited the clinical effectiveness of PSZ prophylaxis in the routine management of our leukemia and HSCT patients. The new tablet form for PSZ could improve bioavailability and do away with the food requirement for PSZ oral suspension administration [38,39]. Also, a new IV solution of PSZ is being developed, and with it, a mould-active prophylaxis could be administered to patients who are unable to take or absorb oral medication [40].

Acknowledgments

We are grateful to Lois Rose for her editorial assistance.

Declaration of interest

During the last five years, F. G. has received speakers’ fees from MSD and Schering-Plough. All other authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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