## Voriconazole as secondary antifungal prophylaxis in stem cell transplant recipients

A recently published editorial by Dr. Girmenia addressed the difficult issue of preventing invasive fungal disease in hematology patients.[1] The author concluded that several questions remained unanswered concerning the use of secondary antifungal prophylaxis in this setting. We agree with Dr. Girmenia that most previous reports on secondary antifungal prophylaxis were retrospective, uncontrolled, and potentially biased toward reporting positive experiences,[2] which reduces our ability to come to clear-cut conclusions. An exception is our recently published prospective, non-comparative study of secondary antifungal prophylaxis with voriconazole in allogeneic hematopoietic stem cell transplant recipients.[3]

The relapse rate of previous invasive fungal disease during subsequent high-risk periods (i.e. following hematopoietic stem cell transplant or during prolonged neutropenia in general) appears to be extremely high.[2,4,5] The use of secondary antifungal prophylaxis in affected hematology patients may, therefore, be of considerable benefit, despite the shortage of prospective data supporting such a strategy. This is actually reflected in current international, European and Italian consensus guidelines which generally grade secondary antifungal prophylaxis for hematopoietic stem cell transplant recipients as "AII" (i.e. highly recommended, limited clinical evidence) or "AIII" (i.e. highly recommended, expert opinion).[6-8] Ultimately, a placebo-controlled trial would be required to confirm the efficacy of secondary antifungal prophylaxis in hematopoietic stem cell transplant recipients. However, such a study is improbable, given the likely reluctance of clinicians to withhold secondary antifungal prophylaxis from hematopoietic stem cell transplant candidates with a history of invasive fungal disease. The optimal antifungal agents in this setting, on the other hand, remain to be established. Of note, the causative pathogen of the prior invasive fungal disease and the individual response to specific antifungal therapy are major considerations when choosing the optimal agent for secondary antifungal prophylaxis.

A key issue for retrospective clinical trials is the actual definition of secondary antifungal prophylaxis. Dr. Girmenia mentions that the efficacy of secondary antifungal prophylaxis in patients with active invasive fungal disease or persistent radiological abnormalities has not yet been clarified. Strictly speaking, however, the term secondary prophylaxis is only applicable to a population with inactive or "apparently resolved" disease, as defined by Sipsas *et al.*[2] Retrospective studies of secondary antifungal prophylaxis were limited by the fact that they generally included patients with presumably inactive as well as those with active invasive fungal disease. Our study of secondary antifungal prophylaxis with voriconazole[2] avoided this issue by enrolling only patients with inactive/resolved invasive fungal disease, according to a list of minimum criteria in agreement with the proposed definitions by Sipsas *et al.* Our criteria may not have fully ensured a complete cure of the previous episode, but they did allow us to better distinguish between: a) the actual treatment phase of the previous episode; and b) the secondary antifungal prophylaxis phase aiming to avoid disease relapse. While the methodology for evaluating primary antifungal prophylaxis was developed years ago during the fluconazole era, our study represents the first attempt at prospectively assessing secondary antifungal prophylaxis. Although our methodology is certainly open to criticism, it should prove useful for future clinical trials of secondary antifungal prophylaxis in hematology patients.

Another key consideration is the aim of secondary antifungal prophylaxis. While primarily aiming to prevent the recurrence of a previous infection, an invasive fungal disease posttransplant may also be due to an entirely new infection. These two types can be difficult to differentiate; for example, if diagnosis of a previous probable *aspergillosis* was based on a positive galactomannan test, without species identification. Most invasive fungal disease risk factors during acute leukemia induction chemotherapy, including genetic predisposition, likely remain posttransplant.[9] Such patients are consequently at a considerably increased risk of a new invasive fungal disease, even though the previous invasive fungal disease may not relapse. Indeed, candidates for secondary antifungal prophylaxis are excellent subjects for illustrating the benefit of antifungal prophylaxis due to their high risk of developing a new or reactivated invasive fungal disease episode. In our study, the one-year cumulative incidence of invasive fungal disease was 6.7%±3.6% among 42 allogeneic hematopoietic stem cell transplant recipients.[2] This is close to the incidence observed with primary prophylaxis[10] and, therefore, strongly supports recent international guidelines recommending voriconazole prophylaxis in allogeneic hematopoietic stem cell transplant recipients with a previous history of invasive *aspergillosis*.[7] Since the invasive fungal disease incidence during secondary antifungal prophylaxis with voriconazole appears to be so low, it will be extremely difficult to conduct comparative trials in this setting. To detect potential differences between drugs, such trials would have to include hundreds of patients, which may be logistically impossible given the very low incidence of previous invasive fungal disease among hematopoietic stem cell transplant recipients observed in previous case series.[4,5] Hopefully, the increased use of effective primary prophylaxis will further reduce the number of patients referred to transplant with a past history of invasive fungal disease. For those patients who do fall into this category, secondary antifungal prophylaxis with voriconazole is likely to reduce the incidence of invasive fungal disease and transplant-related mortality.

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