Comment on: Low prevalence of resistance to azoles in Aspergillus fumigatus in a French cohort of patients treated for haematological malignancies

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Sir,

Azole resistance is an emerging clinical problem in patients with Aspergillus infections, primarily those caused by Aspergillus fumigatus. Alanio et al.1 describe the results of a study that investigated the prevalence of azole resistance in 118 clinical Aspergillus isolates obtained from a cohort of 89 patients with haematological malignancy. They found only one azole-resistant A. fumigatus isolate, which corresponded to a prevalence of 0.85%. Although the low prevalence of resistance may be reassuring, the circumstances surrounding the resistant isolate are a cause of great concern. The azole-resistant isolate was cultured from an azole-naive patient, which precludes resistance development through azole therapy. The only other possibility is that the patient acquired the resistant isolate from the environment, as A. fumigatus is a saprophytic mould and patient-to-patient transmission of aspergilli is highly unlikely. The probability of an environmental source for the azole-resistant isolate was further increased by the resistance mechanism that was found. As indicated by the authors, the position of the substitution in the CYP51A gene was similar to that found in Mycosphaerella graminicola, an important phytopathogenic mould that significantly affects wheat throughout Europe and is almost exclusively controlled with sterol 14α-demethylation inhibitors (DMIs). The similarity of the resistance mechanisms suggests that both moulds developed the mutation in response to exposure to the same compound. As both moulds share the same niche in the environment, this is the most feasible scenario.

In the Netherlands there is increasing evidence that a resistance mechanism involving two genomic changes, a substitution at codon 98 of the CYP51A gene and the insertion of a tandem repeat in the gene promoter (TR/L98H), has emerged through exposure to DMIs. Clinical isolates harbouring this resistance mechanism showed decreased susceptibility to the medical azoles itraconazole, posaconazole and voriconazole and were first found in 1998. Since then, an increasing prevalence over time has been observed, and such isolates now account for between 6% and 12.8% of clinical A. fumigatus isolates. Isolates containing the TR/L98H resistance mechanism were also cultured from environmental sources in the Netherlands, and were found to be cross-resistant to certain DMIs. Surveillance studies indicated that TR/L98H is now endemic in the Netherlands, and recently the same resistance mechanism was found in environmental A. fumigatus isolates in Denmark.2

It has been difficult to explain why azole resistance has emerged in the Netherlands, but apparently not in other European countries despite similar crop protection practices using the same DMIs. The significance of the observation of Alanio et al.1 is that their study suggests that the environmental route of resistance development is not restricted to the Netherlands, but has also taken place in another country and with the emergence of a new resistance mechanism. The recovery of A. fumigatus isolates harbouring G432S from the environment would confirm the environmental route of resistance development. The Dutch experience with TR/L98H shows that rapid spread and an increasing prevalence of resistant isolates can be expected if the acquisition of the resistance mechanism is not associated with a fitness cost. Patients with azole-resistant Aspergillus diseases commonly fail azole therapy and resistance significantly complicates their management.6 Furthermore, it can be anticipated that, unless effective measures are taken, the continued use of DMIs will result in the emergence of multiple resistance mechanisms in the countries that use these fungicides. A policy aimed at precluding the environmental route of resistance development requires more research into the relation between DMI use and resistance development to medical triazoles. The authors propose to perform surveillance studies, but these should not be limited to clinical Aspergillus isolates and should also include field isolates. Furthermore, surveillance studies should be performed in all countries with substantial DMI use and coordinated at the European level.

Transparency declarations

None to declare.

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Low prevalence of resistance to azoles in Aspergillus fumigatus in a French cohort of patients treated for haematological malignancies—authors’ response

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Sir,

We are grateful to Verweij et al.1 for the interest they took in our recent publication.2 We agree that the most probable scenario explaining the acquisition of itraconazole resistance in the unique isolate of Aspergillus fumigatus out of 118 with high itraconazole MICs in our prevalence study is the environmental pressure of azole drugs currently used in agriculture as reported for Mycosphaerella graminicola.3

Thus, we completely agree that environmental studies in relation to the use of sterol 14α-demethylation inhibitors are necessary to understand the spread of azole resistance in moulds, especially those with potential consequences for human or animal health. In the absence of these environmental studies, we cannot comment on the emergence or not in the Paris area of the multi-azole-resistant clone containing the TR/L98H mutation of CYP51a recovered from the environment and patients in the Netherlands4 and Denmark.5 Similarly, we cannot say that the mutation G432S we have reported is not undergoing clonal expansion or, in contrast, was selected in the environment in a time- and space-limited manner and does not present the fitness necessary for clonal expansion. To determine the proportion of azole-resistant isolates in specific niches, to identify their mechanisms of resistance and to follow their diffusion to prevent their expansion as soon as possible, European surveys of environmental moulds including A. fumigatus are needed, if possible with a consensual methodology.

Without anticipation of such environmental study results, our data underline nevertheless the low prevalence of A. fumigatus azole resistance among clinical isolates in the Paris area. If a 6% prevalence had been found, as reported in the Netherlands,6 one could have questioned voriconazole as first-line therapy for invasive aspergillosis. Therefore, up to now, this recommendation does not need alteration in our hospital. We are encouraging physicians and microbiologists caring for haematological patients to sample them in order to continue exploring azole resistance among clinical isolates of moulds, which will allow: first, diagnosis of invasive aspergillosis; and second, determination of A. fumigatus azole resistance prevalence in their hospital.

Transparency declarations
None to declare.

References