In reply to comment on 'Therapeutic drug monitoring-guided treatment versus standard dosing of voriconazole for invasive aspergillosis in haematological patients

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Letter to the Editor

In reply to comment on 'Therapeutic drug monitoring-guided treatment versus standard dosing of voriconazole for invasive aspergillosis in haematological patients: a multicenter, prospective, cluster randomised, crossover clinical trial'

Editor: Dr Stephane Ranque

We conducted a multicentre, prospective, cluster randomised, crossover clinical trial in haematologic patients aged ≥18 years who were treated with voriconazole, and investigated whether therapeutic drug monitoring (TDM)-guided treatment was superior to standard treatment [1]. There was no significant difference for the composite endpoint, which included response to treatment and treatment discontinuation due to an adverse drug reaction. The results are surprising and unexpected and we therefore understand the comments by Elodie Gautier-Veyret, Anne Thiebaut-Bertrand and Françoise Stanke-Labesque, authors of the Letter. We have considered several possible reasons for these results.

Elodie Gautier-Veyret, Anne Thiebaut-Bertrand and Françoise Stanke-Labesque pointed out that the initial voriconazole trough concentration (C_{min}) and the initial proportion of C_{min} within the therapeutic range are high in our study; we agree with this. The initial voriconazole C_{min} in our study was 3.9 mg/L (IQR 2.3–5.5 mg/L) in the non-TDM group vs. 3.8 mg/L (IQR 2.7–5.5 mg/L) in the TDM group, and 3.9% of patients in the TDM group had an initial C_{min} <1 mg/L. Other studies, also cited by Elodie Gautier-Veyret, Anne Thiebaut-Bertrand and Françoise Stanke-Labesque, reported a lower voriconazole C_{min} and a lower proportion of voriconazole C_{min} within the therapeutic range compared with our observations. Elodie Gautier-Veyret, Anne Thiebaut-Bertrand and Françoise Stanke-Labesque speculate that there are multiple factors that could explain this, including genetic polymorphism, drug-drug interactions, liver dysfunction, and inflammatory status.

In our study, CYP2C19 genotyping was determined in only a small number of patients and therefore not included in the analysis. This decision was driven by the low likelihood (2–3%) of being a homozygous poor metaboliser of CYP2C19*2/*3 in a Caucasian population. Genetic polymorphism therefore does not seem to be a plausible explanation for the results of our study.

None of the patients included in our study used concomitant medication with a clinically relevant interaction; therefore, drug-drug interactions are unlikely to explain the high initial trough concentrations [2]. Furthermore, the results of liver function tests conducted in the study indicate that liver dysfunction was not a potential cause for the high initial voriconazole concentrations.

The high initial median voriconazole concentration in our study could be explained by reduced voriconazole metabolism in patients with inflammation, indicated by higher C-reactive protein (CRP) concentrations [3]. High CRP concentrations are likely in the first week after initiation of treatment for invasive aspergillosis in neutropenic leukaemia patients [4]. Unfortunately, CRP concentrations were not routinely measured in our study, and therefore were not included in the analysis. A potential downregulation of clearance could contribute to higher exposure and hence the higher proportion of initial voriconazole C_{min} within the therapeutic range [5].

As reported by Elodie Gautier-Veyret, Anne Thiebaut-Bertrand and Françoise Stanke-Labesque, the proportion of initial voriconazole C_{min} within the therapeutic range is high in our study compared with other studies. However, in the study of Blanco-Dorado, to which the authors of the Letter referred, 33.3% of the patients had a haematological malignancy and almost half the patients received voriconazole as empirical treatment. Therefore, the results of the Blanco-Dorado study cannot be extrapolated to the results of our study. Additionally, in the study by Patel et al., patients received voriconazole as prophylaxis, and in the study by Hamadeh et al., a different therapeutic range was used, which again makes it difficult to extrapolate the results to our study.

A failure rate of 45.0% and 49.1% (for a time window of ±5 days) was observed in our study in the non-TDM and TDM group respectively (or 39.2% vs. 45.6% using a time window of ±10 days). If clinical efficacy depends on voriconazole concentration, as Elodie Gautier-Veyret, Anne Thiebaut-Bertrand and Françoise Stanke-Labesque suggest, a higher success rate would be expected as voriconazole concentrations were in the range 1–6 mg/L. The results of our study indicate that factors other than exposure are also important for treatment response and highlight the need for individualised treatment. Host-specific immunological responses should be taken into account, together with drug concentration. In addition, biomarkers must be investigated to distinguish early responders from those likely to fail therapy.

Based on the results of our study, and the study by Park et al. [6], TDM could be beneficial in vulnerable populations, such as patients who failed on previous antifungal treatments. Furthermore, follow-up with TDM could have more additional value in patients with specific risk factors, such as persistent neutropenia, compared with patients who recover from neutropenia after one or two weeks.

Our study showed no clinical improvement of ≥20% for the composite endpoint; however, we do not conclude that TDM provides no clinical benefit in general. TDM should be considered as a diagnostic tool and not a goal. The results of our study open the discussion on value-based healthcare and the importance of determining which patients may benefit most from TDM.

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Declarations

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