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International Journal of Antimicrobial Agents 61 (2023) 106711

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Therapeutic drug monitoring-guided treatment versus standard dosing of voriconazole for invasive aspergillosis in haematological patients: a multicentre, prospective, cluster randomised, crossover clinical trial☆

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ARTICLE INFO

Article history:
Received 24 May 2022
Accepted 3 January 2023

Editor: Dr Stephane Ranque

ABSTRACT

Objectives: Voriconazole therapeutic drug monitoring (TDM) is recommended based on retrospective data and limited prospective studies. This study aimed to investigate whether TDM-guided voriconazole treatment is superior to standard treatment for invasive aspergillosis.

☆ This work was presented at the 28th European Congress of Clinical Microbiology & Infectious Diseases (ECCMID), 23 April 2018, Madrid, Spain, in the session: Hot topics in antifungal use [O0799].

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https://doi.org/10.1016/j.ijantimicag.2023.106711

Keywords:
Voriconazole
Therapeutic drug monitoring
Haematological malignancy
Invasive fungal infection

Methods: A multicentre ($n = 10$), prospective, cluster randomised, crossover clinical trial was performed in haematological patients aged ≥18 years treated with voriconazole. All patients received standard voriconazole dose at the start of treatment. Blood/serum/plasma was periodically collected after treatment initiation of voriconazole and repeated during treatment in both groups. The TDM group had measured voriconazole concentrations reported back, with dose adjustments made as appropriate, while the non-TDM group had voriconazole concentrations measured only after study completion. The composite primary endpoint included response to treatment and voriconazole treatment discontinuation due to an adverse drug reaction related to voriconazole within 28 days after treatment initiation.
Results: In total, 189 patients were enrolled in the study. For the composite primary endpoint, 74 patients were included in the non-TDM group and 68 patients in the TDM group. Here, no significant difference was found between both groups ($P = 0.678$). However, more trough concentrations were found within the generally accepted range of 1–6 mg/L for the TDM group (74.0%) compared with the non-TDM group (64.0%) ($P < 0.001$).
Conclusions: In this trial, TDM-guided dosing of voriconazole did not show improved treatment outcome compared with standard dosing. We believe that these findings should open up the discussion for an approach to voriconazole TDM that includes drug exposure, pathogen susceptibility and host defence.
Clinical trial registration: ClinicalTrials.gov registration no. NCT00893555.

1. Introduction

One of the most common mould infections is invasive aspergillosis (IA), which is a life-threatening complication frequently seen in patients with haematological malignancy or patients who received an allogeneic haematopoietic stem cell transplant [1]. In patients with IA, voriconazole or isavuconazole are recommended as primary treatment [2].

Despite using the licensed dosing strategy of voriconazole, large inter- and intra-individual differences have been observed in voriconazole serum concentrations showing little to no correlation between the voriconazole dose and measured serum trough concentration [3]. Factors influencing voriconazole serum concentrations include age [4], liver function [5], cytochrome P450 polymorphism [6], co-medication [7] and inflammation [8]. Since the serum concentration is associated with efficacy and safety, therapeutic drug monitoring (TDM) of voriconazole has been suggested to improve treatment outcomes and to avoid adverse effects, such as neurological toxicity including confusion and visual hallucinations [9]. In a recent meta-analysis, a therapeutic trough concentration ranging from 1.0–6.0 mg/L was proposed [10]. However, the optimal serum concentration may differ for an individual patient [11].

It is debated whether TDM-guided voriconazole treatment for adult patients with IA is superior to standard voriconazole treatment [9]. In a post-hoc analysis of phase II/III clinical trials, an exposure–response relationship was found for the efficacy and safety of voriconazole [12,13]. Here, the utility of TDM with dose adjustments was not determined. Retrospective studies may have been hampered by selection bias [3,14]. Other studies have shown that individualised treatment of voriconazole by using TDM is beneficial compared with the standard dosing regimen of voriconazole, but these studies have some limitations, including small sample size [14,15]. Only one single-centre randomised controlled trial demonstrated the additional value of TDM, where TDM of voriconazole reduced drug discontinuation due to adverse events and improved treatment response [16]. Based on the available evidence, US, European and British guidelines have recommended routine use of TDM for voriconazole [2,11,17]. However, multiple randomised trials showing the additional value of TDM for voriconazole are lacking. Therefore, the aim of this study was to determine whether TDM-guided dosing of voriconazole indeed improves treatment outcome and reduces toxicity in adult patients with IA compared with standard of care.

2. Methods

2.1. Ethics statement

This research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The trial protocol was approved by the institutional review board of the University Medical Centre Groningen for all Dutch participating centres (registration no. 2009.027) and by the Bundesinstitut für Arzneimittel und Medizinprodukte for the Oldenburg Clinic in Germany. Additionally, all Dutch centres had a local feasibility assessment. Written informed consent was obtained from all patients. This study was registered at ClinicalTrials.gov (NCT00893555).

2.2. Study design

A multicentre, prospective, cluster randomised, crossover clinical trial was performed. Patients were enrolled from April 2009 to September 2016 and were recruited from nine centres in the Netherlands and one centre in Germany (see Supplementary Table S1).

2.3. Participants

Patients aged ≥18 years with a haematological malignancy or an allogeneic stem cell transplant, diagnosed with IA that was treated with the recommended dose of voriconazole according to the summary of product characteristics [18], were eligible to enter the trial. Patients were excluded if they were hypersensitive or allergic to voriconazole or its excipients.

2.4. Randomisation

A cluster randomised, crossover design on hospital level was chosen to minimise logistical problems and to limit bias during the study. Allocation of each hospital to start with the intervention or control group was generated per computer at random. The number of patients to be included in both groups per hospital was predetermined. A wash-out period of 28 days was established between the two periods to avoid two strategies being operational at the same time (see Fig. 1). Patients were enrolled in this study by the principal investigator or their delegate at each participating centre.

Table 1
Baseline patient characteristics by treatment group.

Characteristic	TDM group (n = 83)	Non-TDM group (n = 87)	P-value
Age (years) [a]	60.0 (50.0–65.0)	56.0 (48.0–64.0)	0.269
Sex			
Male	55 (66.3)	50 (57.5)	0.271
Female	28 (33.7)	37 (42.5)	
Body mass index [a]	24.7 (22.2–27.7)	24.5 (22.3–26.5)	0.690
Race			
Caucasian	78 (94.0)	84 (96.6)	0.489
Other	5 (6.0)	3 (3.4)	
Primary diagnosis			
Newly diagnosed leukaemia	60 (72.3)	63 (72.4)	0.954
Relapsed leukaemia	10 (12.1)	12 (13.8)	
Lymphoma	7 (8.4)	6 (6.9)	
Multiple myeloma	5 (6.0)	4 (4.6)	
Other [b]	1 (1.2)	2 (2.3)	
Concomitant disease			
Diabetes, coronary heart disease or thromboembolic disease	22 (26.5)	20 (23.0)	0.722
Not applicable	61 (73.5)	67 (77.0)	
EORTC/MSG classification			
Possible	33 (39.8)	43 (49.4)	0.271
Probable	45 (54.2)	42 (48.3)	
Proven	5 (6.0)	2 (2.3)	
Route of administration			
Oral	49 (59.0)	50 (57.5)	0.877
Intravenous	34 (41.0)	37 (42.5)	
Initial voriconazole maintenance dose (mg/kg/day) [a]			
Oral	5.7 (4.7–7.2)	5.2 (4.6–5.9)	0.008
Intravenous	8.0 (7.7–8.3)	7.8 (6.6–8.0)	
Overall	7.2 (5.3–8.0)	5.9 (5.1–7.7)	
Recovery of neutropenia within 28 days			
Yes	49 (73.1)	49 (66.2)	0.360
No	18 (26.9)	25 (33.8)	
Unknown	–	2	
Number of voriconazole trough concentrations per patient	5 (3–11)	4 (2–7)	–
Duration of voriconazole treatment (days) [a]	49 (13–84)	40 (11–76)	–

TDM, therapeutic drug monitoring.
Data are presented as number of patients (percentage) unless otherwise specified.
[a] Median (interquartile range).
[b] Other primary diagnosis included folliculotropic mycosis fungoides, haemophagocytic syndrome and hypereosinophilic syndrome.

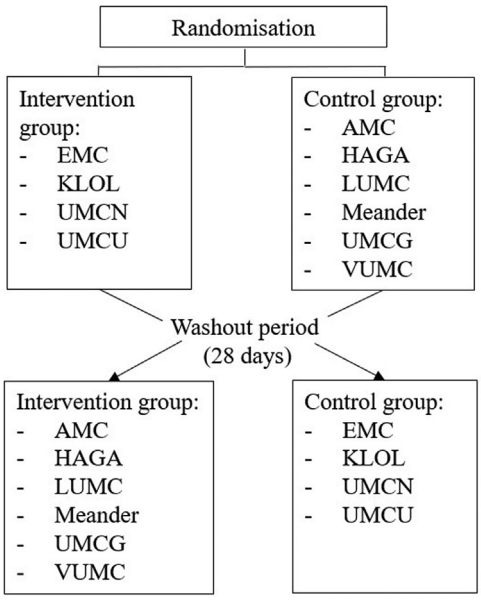

Fig. 1. Study design. Schematic overview of the cluster randomised, crossover design. AMC, Academic Medical Centre Amsterdam; EMC, Erasmus Medical Centre; HAGA, HAGA Hospital; KLOL, Oldenburg Hospital; LUMC, Leiden University Medical Centre; Meander, Meander Medical Centre; UMCG, University Medical Centre Groningen; UMCN, Radboud University Medical Centre; UMCU, University Medical Centre Utrecht; VUMC, VU Medical Centre.

2.5. Procedure

Patients were diagnosed with IA according to the 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group's criteria and were classified as having a possible, probable or proven invasive fungal infection [19].

At the start of treatment all patients received the standard voriconazole dose, which consisted of a loading dose of 6 mg/kg intravenously or 400 mg orally twice daily, followed by a maintenance dose of 4 mg/kg intravenously or 200 mg orally twice daily [18]. For both groups, a voriconazole trough sample was collected around Day 3 after treatment initiation and twice weekly from that day onward until the end of treatment or hospital discharge [11,17]. After discharge, surveillance samples were drawn during outpatient visits. For the TDM group, the voriconazole dose was adjusted if the trough concentration was $<$2 mg/L or $>$5 mg/L. A dosing algorithm was defined that could be used as a tool for dose adaptations in the TDM group (see Supplementary Table S2).

The turnaround time, i.e. the time elapsed between blood samples received by the laboratory up to measuring the voriconazole concentration and reporting the results back to the attending physician, was 8 h up to 72 h. The turnaround time mainly depended on the availability of an in-house analytical method for determination of the voriconazole concentration. If the voriconazole concentration needed to be determined by another laboratory, this typically resulted in prolongation of the turnaround time.

In the non-TDM group, patients received the standard voriconazole dose and samples were stored and measured afterwards to evaluate trough concentrations. The attending physician could decide to de-blind the voriconazole trough concentration for patients in the non-TDM group at any time if deemed clinically necessary. If the voriconazole concentration was de-blinded, the results were available for the attending physician after 8 h up to 72 h (again depending on the availability of an in-house analytical method). De-blinding of the voriconazole trough concentration was also considered to be an endpoint. Furthermore, treatment modifications (such as addition of or switch to another antifungal agent) could be made for both groups, also based on the clinical condition of the patient, whether or not supported by new microbiological findings or radiological progression.

2.6. Outcomes

The response to treatment was defined according to the 2008 EORTC/MSG criteria and was categorised as complete response, partial response, stable disease or failure (defined as progression of disease or death). Additionally, a complete or partial response was classified as successful treatment. Stable disease, progression of the disease or death of the patient was classified as failure of treatment [20]. To prevent investigator bias, an expert panel unaware of allocation of patients to either the TDM or non-TDM group determined the response to treatment.

The primary outcome was a composite endpoint including both response to treatment determined 28 days after treatment initiation and an adverse drug reaction (ADR) that resulted in voriconazole discontinuation within 28 days. For some critically ill or discharged patients, radiological examination was not possible at 28 days after treatment initiation. Therefore, response to treatment was assessed within two time windows (28 days ±5 days or ±10 days). Response to treatment and ADR resulting in voriconazole discontinuation were also assessed separately for both groups. If voriconazole treatment was discontinued due to an ADR, the likelihood was assessed using the Naranjo scale [21]. For the composite primary endpoint, a possible or higher Naranjo score (1 up to 13) was considered as an ADR caused by voriconazole and subsequent discontinuation was considered as failure of treatment.

Patients were followed for up to 12 weeks after treatment initiation. Secondary outcomes included the overall mortality 28 days and 84 days after start of voriconazole treatment and the percentage of voriconazole trough concentrations within the therapeutic range. Furthermore, the number of de-blinded patients in the control group was assessed.

2.7. Sample size calculation

Based on the occurrence of low and high voriconazole trough concentrations, it was estimated that TDM could reduce the failure of voriconazole treatment from 40% [22] to 20%. In the most unfavourable assumption, the intra-cluster correlation coefficient equals the intra-period correlation coefficient and varies between 0.002 and 0.02. We anticipated the participation of 12 centres. To obtain 80% power with an unreliability of 5% (two-sided), each cluster should include 16 patients to detect a clinically relevant improvement of 20% in the intervention group compared with the control group, resulting in a calculated sample size of 192 patients in total.

2.8. Statistical analysis

Descriptive statistics of the patient characteristics are reported by treatment group. For numerical data, the median with interquartile range were determined and the Wilcoxon rank-sum test was used to determine whether there was a difference between the groups. For categorical data (nominal, ordinal and binary), frequencies were determined and the χ^2 test was used to determine differences between treatment arms.

Categorical outcome variables were analysed with (binary or nominal) logistic regression, and survival times were analysed with Cox proportional hazard method. The effect size for treatment is reported as an odds ratio for logistic regression analysis and a hazard ratio for survival analysis. *P*-values are based on the Wald test statistic. Subgroup analyses are performed in the same way. Analyses were done with procedures GENMOD and PHREG of SAS Institute version 9.4. All analyses were performed as per-protocol analyses. A *P*-value of <0.05 was considered statistically significant.

Since enrolment of patients in the intervention and control period did not fully proceed according to schedule, an additional analysis was performed to determine the confounding factors at baseline that would affect the treatment indicator. A logistic regression analysis with a stepwise model selection approach was applied to find possible influencing confounders, using procedure HPGENSELECT of SAS Institute version 9.4. Bayesian information criterion (BIC) was used to determine the best possible treatment indicator model, similar to a propensity score. Confounders and their two-way interactions may enter the model when the overall *P*-value was <0.25 and they may leave the model when the *P*-value was >0.10. The confounders that were considered were: age; body mass index (BMI); race; sex; type of underlying disease; type of fungal infection; recovery of neutropenia within 28 days after start of voriconazole treatment (if applicable); medical history of diabetes, coronary heart disease or thromboembolic disease; route of administration; and voriconazole dose. Subsequently, outcome variables were analysed that were corrected for the variables that influenced the treatment indicator at the start of the trial.

3. Results

In total, 189 patients were enrolled. In the per-protocol analysis 170 patients were included, and 142 patients were evaluable for the primary outcome (see Fig. 2 for an overview and the reasons of exclusion).

All patients in the non-TDM group had pulmonary IA, while in the TDM group four patients had IA sinusitis. The most common host factor was neutropenia both for the non-TDM (89.7%) and TDM (79.5%) group, either or not in combination with another host factor. Use of mould-active azole prophylaxis (e.g. posaconazole or itraconazole) prior to the diagnosis of IA was comparable between both groups (6.9% for the non-TDM group vs. 3.6% for the TDM group). Other patient characteristics are presented in Table 1. Patients in the non-TDM group received a lower initial maintenance dose than patients in the TDM group (5.9 mg/kg/day and 7.2 mg/kg/day, respectively; $P = 0.008$).

Fig. 3 shows the initial and median voriconazole trough concentration per patient (Fig. 3A,B). The initial voriconazole trough concentration is the concentration without implementing TDM practices for the TDM group. The median initial trough concentration was similar in both groups (TDM group 3.8 mg/L and non-TDM group 3.9 mg/L; $P = 0.614$). The percentages of patients with an initial and median voriconazole trough concentration in the therapeutic range of 1–6 mg/L [10] are shown in Fig. 3C,D. Results for a more stringent therapeutic range of 2–5 mg/L are shown in Supplementary Fig. S1. The initial voriconazole concentration was within the therapeutic range of 1–6 mg/L for 80.6% of all included patients, and 3.9% of the patients had a trough concentration <1 mg/L.

Although randomisation of the trial occurred to protocol, enrolment of patients in each cluster differed (i.e. different number of included patients per treatment group per centre and between

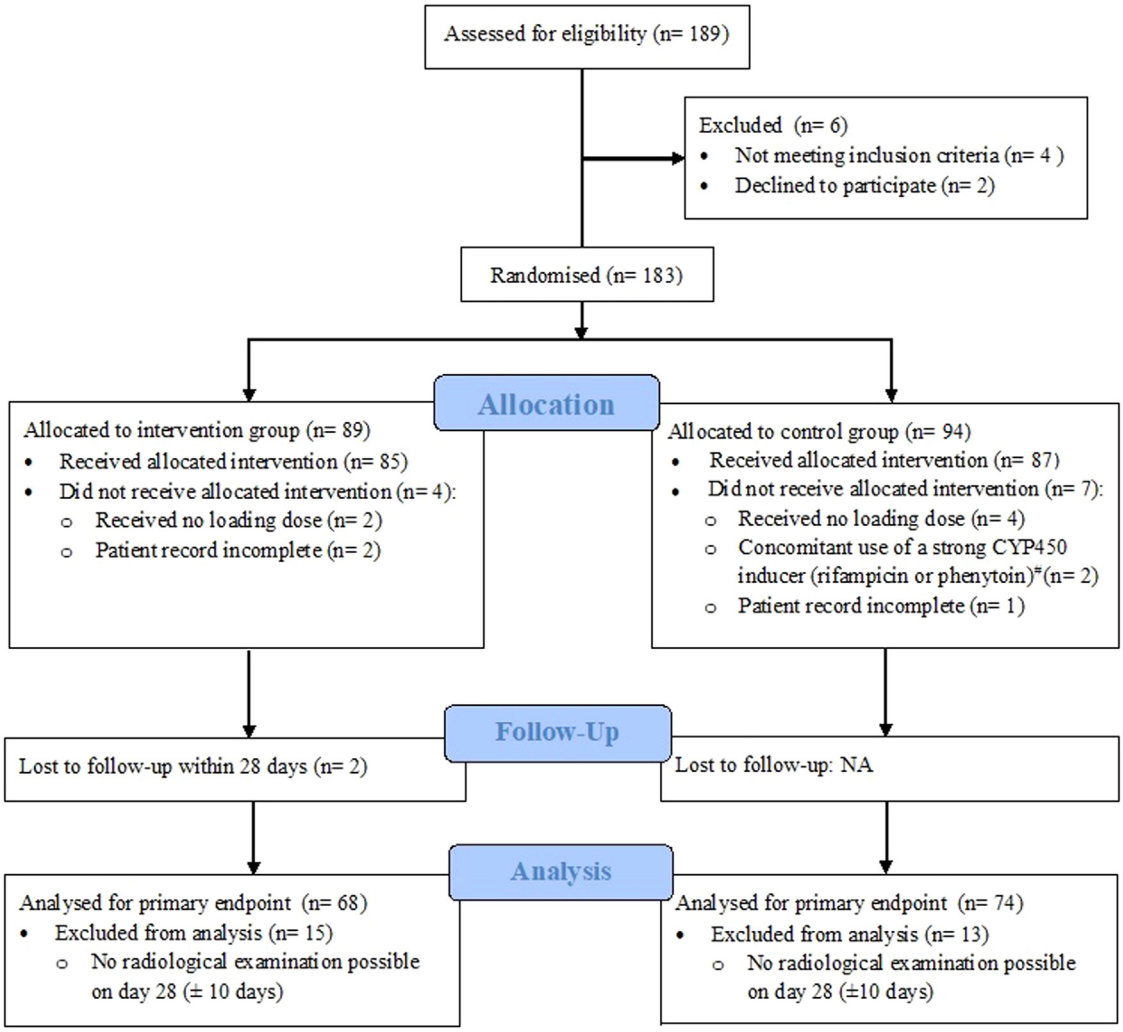

Fig. 2. Number of patients included. Number of patients included in the per-protocol analysis and number of evaluable patients for the combined primary endpoint. # Not dosed according to the summary of product characteristics of voriconazole [18].

centres, different inclusion period for a treatment group per centre and between centres). Therefore, we determined which confounding factors at baseline could influence the outcome parameters. Thus, in addition to the uncorrected analysis of the outcome variables, the analysis of the outcome variables was corrected for these confounders (see statistical analysis, Section 2.8).

During the entire treatment period with voriconazole, for 60 patients in the TDM group a dose adjustment was proposed and implemented (see Supplementary Table S3) for details. Significantly more trough concentrations were found within the therapeutic range (1–6 mg/L) for the TDM group compared with the non-TDM group (74.0% and 64.0%, respectively; uncorrected analysis $P < 0.001$, corrected for confounders $P = 0.006$).

The composite primary outcome was not significantly different between the TDM and non-TDM group (uncorrected analyses: 1.027, 95% CI 0.553–1.906, $P = 0.933$; response 28 ± 10 days: 1.138, 95% CI 0.618–2.094, $P = 0.678$; corrected analyses: 0.889, 95% CI 0.454–1.743, $P = 0.732$; response 28 ± 10 days: 1.149, 95% CI 0.594–2.223, $P = 0.681$).

For 60 patients in the non-TDM group and 53 patients in the TDM group response to treatment could be assessed (or 74 vs. 68 patients, respectively, using a time window of ±10 days instead of ±5 days), based on clinical, microbiological and radiological response. A failure rate of 45.0% was seen in the non-TDM group and 49.1% in the TDM group (or 39.2% vs. 45.6%, respectively, using a time window of ±10 days instead of ±5 days), which was not significantly different (see also Table 2). Mortality 28 days after treatment initiation and overall mortality up to 12 weeks were not significantly different between both groups (see Table 2; Fig. 4).

For 17 patients in the TDM group and 18 patients in the non-TDM group voriconazole treatment was discontinued because of an ADR (Fig. 5; $P = 0.658$). Increased hepatic enzymes were the main reason to discontinue voriconazole treatment (non-TDM group 55.6%, TDM group 64.7%).

De-blinding of voriconazole trough concentrations in the non-TDM group was requested for 17 patients within 4 weeks after treatment initiation because of their clinical condition ($n = 14$) or the occurrence of side effects ($n = 3$). This resulted in treatment modifications in nine patients. Six of the de-blinded patients had a complete or partial response, two patients had stable disease, and for two patients antifungal treatment had failed according to the 2008 EORTC/MSG criteria. For seven patients the response to treatment could not be determined since radiological imaging was not possible after 28 days (±5 days). If the response to treatment was determined after 28 ± 10 days, nine patients had a complete or partial response, two patients had stable disease, treatment failed for two patients, and for four patients the response could not be assessed. We performed an additional anal-

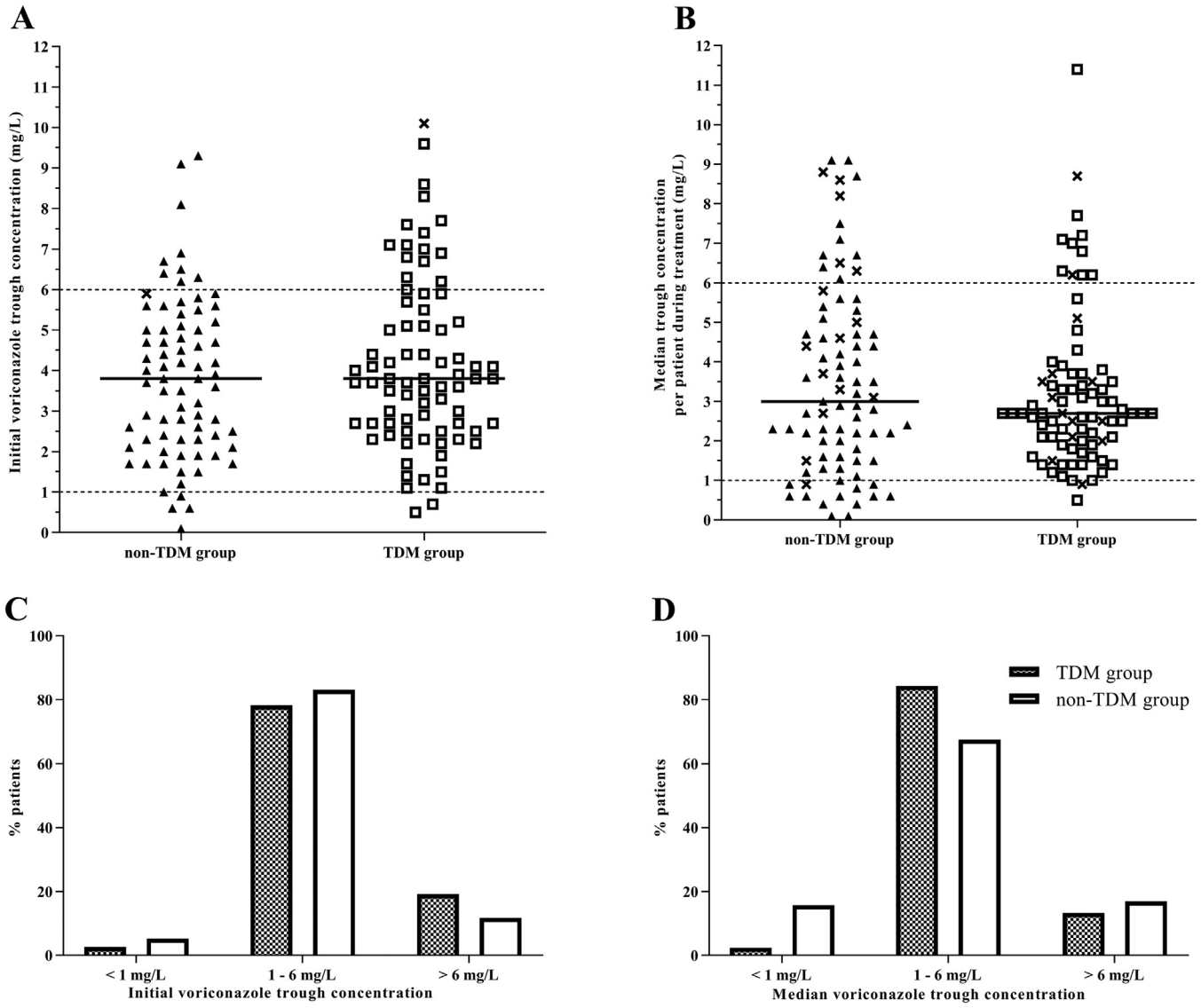

Fig. 3. (A,C) Initial and (B,D) median voriconazole trough concentration for the control (non-TDM) and intervention (TDM) group. (A) Initial voriconazole trough concentration, drawn approximately 3 days (up to 6 days) after treatment initiation for the control (non-TDM) and intervention (TDM) group. (C) Percentage of patients with an initial voriconazole trough concentration <1 mg/L, 1–6 mg/L and >6 mg/L, stratified by the TDM (bar with squares) and non-TDM (open bar) group. (B) Median voriconazole trough concentration per patient during treatment with voriconazole, stratified by non-TDM and TDM group. (D) Percentage of patients with a median voriconazole trough concentration <1 mg/L, 1–6 mg/L and >6 mg/L, stratified by the TDM (bar with squares) and non-TDM (open bar) group. The solid line in panel A and B represents the median voriconazole trough concentration, and the dotted lines the therapeutic range for voriconazole. An x in panel A and B indicates voriconazole discontinuation due to an adverse drug reaction. TDM, therapeutic drug monitoring.

Table 2
Primary (response to treatment 28 days after treatment initiation ±5 days and ±10 days) and secondary outcomes (occurrence of an event) in the control (non-TDM) group and intervention (TDM) group.

Outcome variable	TDM group (n = 83)	Non-TDM group (n = 87)	Uncorrected analysis		Corrected for confounders	
Response to treatment 28 ± 5 days	n = 53	n = 60	Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value
Success	27 (50.9)	33 (55.0)	0.850	0.666	0.797	0.595
Failure	26 (49.1)	27 (45.0)	(0.405–		(0.344–	
Not determined	30	27	1.782)		1.843)	
Response to treatment 28 ± 10 days	n = 68	n = 74				
Success	37 (54.4)	45 (60.8)	0.769	0.441	0.724	0.381
Failure	31 (45.6)	29 (39.2)	(0.395–		(0.351–	
Not determined	15	13	1.499)		1.492)	
Survival analysis						
Deaths within 28 days	10 (12.0)	9 (10.3)	1.187 (0.457–3.087)	0.725	1.336 (0.487–3.665)	0.574
Deaths up to 12 weeks	17 (20.5)	23 (26.4)	0.758 (0.405–1.420)	0.387	0.782 (0.397–1.541)	0.477
Lost to follow up	–	1				

CI, confidence interval; TDM, therapeutic drug monitoring.
Data are presented as number of patients (percentage).

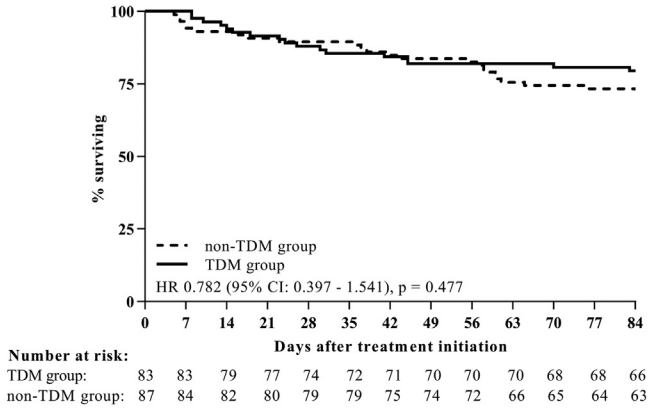

Fig. 4. 12-week survival after treatment initiation with voriconazole stratified by control (non-TDM) and intervention (TDM) group. No significance difference was observed in mortality between the non-TDM (dotted line) and TDM (solid line) group. Hazard ratio (HR) is shown for the statistical analysis corrected for confounding factors. TDM, therapeutic drug monitoring.

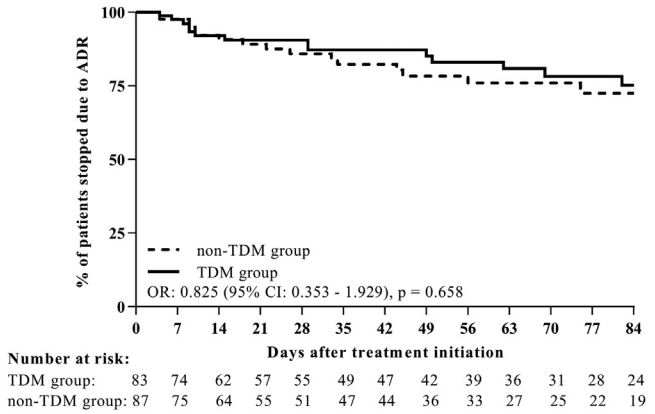

Fig. 5. Percentage of patients stopped due to an adverse drug reaction (ADR) stratified by control (non-TDM) and intervention (TDM) group. No significant difference was observed in the percentage of patients stopped due to an ADR between the non-TDM (dotted line) and TDM (solid line) group. Odds ratio (OR) is shown for the statistical analysis corrected for confounding factors. TDM, therapeutic drug monitoring.

ysis of patients in the control group for whom the voriconazole trough concentration was de-blinded, considering these as intervention patients. For the composite endpoint no significant difference was observed between both groups (see Supplementary Table S4).

Furthermore, we performed a post-hoc subgroup analysis for patients with a probable or proven fungal infection (n = 94), thereby excluding patients with a possible fungal infection. The combined endpoint including both response to treatment and ADRs could be determined for 79 patients. No significance difference was found between both groups (uncorrected analyses: 0.869, 95% CI 0.384–1.967, P = 0.736; response 28 ± 10 days: 0.933, 95% CI 0.414–2.101, P = 0.867; see also Supplementary Table S5).

4. Discussion

In this multicentre, prospective clinical trial, individualised voriconazole treatment (by routinely using TDM) did not result in improved outcome in adult patients with IA compared with the standard dosing regimen of voriconazole without performing TDM. For the composite primary endpoint, no significant difference was found between the intervention (TDM) and control (non-TDM) groups.

The cumulative data of observational, retrospective and small prospective studies and one single-centre randomised controlled trial [3,12,14–16] have resulted in a number of guidelines recommending routine use of TDM for voriconazole [17,23]. In these studies, voriconazole trough concentrations were included, although the 24-h area under the concentration–time curve (AUC) in relation to the minimum inhibitory concentration (AUC_{0-24h}/MIC) is proposed as the effective pharmacokinetic/pharmacodynamic parameter for voriconazole [24]. However, several studies have shown that the voriconazole trough concentration gives a good estimation of the AUC and trough concentrations can therefore be used [25,26]. Although our results showed significantly more trough concentrations within a therapeutic range of 1–6 mg/L for the TDM group, this difference of 10% did not translate into better treatment outcome.

In our study, 40–50% of patients had a possible IA. In patients with a possible infection, the likelihood of having an invasive aspergillus infection is lower compared with patients with a probable or proven infection. Therefore, the potential advantage of TDM in these patients may be limited to prevention or reduction of toxicity. A post-hoc subgroup analysis was performed for the primary endpoint in patients with a probable or proven fungal infection. In contrast to other studies, we found no significant difference in response to treatment in this subgroup analysis. However, failure rates were comparable with the results of a phase III study with strict inclusion and exclusion criteria, but without performing TDM [22]. Due to the small sample size of our subgroup analysis, the results should be interpreted with caution. In addition, this subgroup analysis mainly focused on efficacy and not on prevention or reduction of toxicity, since toxicity can occur regardless of the severity of the fungal infection. Furthermore, we mainly included patients treated with voriconazole as first-line treatment for IA. This could explain why our results differ from the results of the randomised controlled trial of Park et al. [16]. The study by Park et al. included more patients with a probable or proven infection [n = 81 patients (75%), of which 38 patients were in the TDM group and 43 patients in the non-TDM group] and approximately 30% (n = 35) of the included patients had already failed on other antifungal treatment [16]. We suggest that the beneficial effect of TDM for voriconazole found by Park et al. might be driven by the higher percentage of patients with proven and probable infections and the high percentage of patients who failed on previous antifungal treatment, where optimised exposure would result in better outcomes. Therefore, TDM of voriconazole remains valuable in patients who failed on previous antifungal treatment or in patients with a more severe invasive fungal disease.

Voriconazole treatment was discontinued because of an ADR in 20.5% of patients in the TDM group and 21.4% in the non-TDM group during treatment. Several studies have shown an association with high voriconazole trough concentrations (≥6 mg/L) and the occurrence of an ADR [9]. In our study only 15.0% and 11.6% of all measured voriconazole trough concentrations were <1 mg/L or ≥6 mg/L in the TDM group and 21.5% and 14.0% in the non-TDM group. Therefore, the opportunity to optimise treatment or prevent ADRs by using TDM was minimal in our study. Furthermore, the main ADRs of voriconazole are well understood and managed accordingly [18]. Although some of our patients experienced side effects during treatment with voriconazole, these were transient and did not result in discontinuation of treatment. In addition, only 3.9% of all patients had an initial trough concentration <1.0 mg/L and 7.7% had an initial trough concentration <1.5 mg/L. To compare, 11.0% of the patients in the randomised trial of Park et al. had a trough concentration <1.5 mg/L [16]. In studies where low voriconazole trough concentrations are associated with poor treatment outcome, minimal information is provided on voriconazole trough concentrations in the initial and most critical phase

of voriconazole treatment. It could therefore be argued whether TDM practices in our patient population could result in improved treatment outcome because only a small number of patients had a voriconazole trough concentration <1 mg/L or <1.5 mg/L during this phase.

This study has limitations. First, the sample size calculation of our study (with a power of 80%) was based on a failure rate of 40% [22] and a clinical improvement of 20% by performing TDM. Based on the estimated standard error of the response to treatment in our study (in the uncorrected logistic regression analysis) and the anticipated effect size (reduction from 40% to 20%), we obtained an asymptotic (two-sided) power value of 80.5%. Therefore, our study was powered to detect the anticipated event reduction. However, the benefit of TDM practices in our study population was not enough to achieve this reduction. This could be caused by the large proportion of patients with a possible fungal infection. Additionally, we cannot rule out a reduction in treatment failure less than 20% by using TDM. Furthermore, the enrolment rate of patients was different between clusters, potentially impacting the study results. However, the results from the additional analysis corrected for potential confounders were not different.

As TDM was already operational in most of the participating centres, we had to allow, for ethical reasons, that the attending physician could decide to de-blind the voriconazole trough concentration for patients in the non-TDM group, especially for those who experienced signs of toxicity or did not respond to treatment. Although the attending physician could decide to de-blind the voriconazole trough concentration for these patients, no significant difference was observed in the composite endpoint after a subgroup analysis where patients in the non-TDM group were considered as the TDM group if the voriconazole trough concentration was de-blinded. Therefore, the impact of de-blinding of patients in the non-TDM group on study outcome was limited.

Due to the real-life setting, we faced difficulties in determining the response to treatment despite this being extensively described in the study protocol [20]. Some patients did not have follow-up radiological examination after discharge from the hospital when clinical symptoms of the fungal infection were absent. For some patients, radiological examination was done with a chest X-ray instead of high-resolution computed tomography, which complicated assessment of radiological response to treatment.

The current study sheds new light on the applicability of TDM for voriconazole. In contrast to our study, clear exposure–response relationships are found in vitro as well as in animal studies [27,28]. Yet these signals appear to be absent in the human setting. This may be driven by the absence of information on drug susceptibility and the host defence. When considering our findings in this study, it can be strongly debated whether a beneficial effect of TDM will ever be found, considering the complex interplay between host, drug and bug. Nowadays, more complex mathematical analysis are becoming available that could help shed light on these relationships. Perhaps now the time is right, driven by the results of our study, to set the first step along this path and also the next step in individualised therapy.

To conclude, our study did not show a clinical improvement of ≥20% for the composite endpoint (including both response to treatment and discontinuation of voriconazole due to an ADR within 28 days after treatment initiation) by performing TDM for all haematological patients with IA. Optimised TDM using dosing software could potentially increase the success rate of TDM in improving target attainment compared with standard of care. Additionally, a more targeted approach including severity of IA, clinical condition of the patient and prior treatment may be more appropriate to select those patients who may benefit from TDM, but this should be confirmed in a follow-up study.

Competing interests

R.J. Bruggeman has received fees for consulting from Gilead, F2G and Amplyx and has received research grants and given lectures for Gilead, Pfizer, Merck and Astellas. All contracts were with Radboudumc and all payments were with Radboudumc. B.J. Biemond has received research support of Sanquin, Global Blood Therapeutics and Novartis. B.J.A. Rijnders reports grants from Gilead Sciences and personal fees from F2G, outside the submitted work. J.J. Swen reports personal fees from Roche, outside the submitted work. P.E. Verweij reports grants from MSD, Gilead Sciences, F2G and Pfizer and non-financial support from IMMY, outside the submitted work. J.W.C. Alffenaar reports other financial support from Pfizer, MSD and Gilead and grants from MSD, outside the submitted work. All other authors declare no competing interests.

Acknowledgements

The authors would like to acknowledge the other members of the ZonMw Study Group who provided critical review of the taxonomy, but are not responsible for the content of this article: Jan P. Arends; Imke Bartelink; David M. Burger; Yuma A. Bijleveld; Simon M.G.J. Daenen; Nielka P. van Erp; Jan den Hartigh; Mirte M. Malingré; Erik M. van Maarseveen †; Ron A.A. Mathôt; Tahar van der Straaten; Karin M. Vermeulen; Bob Wilffert †; Abraham J. Wilhelm; and Marjolijn J.P van Wanrooy. They also thank all investigators, trial teams and patients for their participation in the trial.

Funding

This work was supported by the Netherlands Organization for Health Research and Development [grant no. 170995005]. This funding source had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the paper for publication.

Ethical approval

This research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The trial protocol was approved by the institutional review board of the University Medical Centre Groningen for all Dutch participating centres (registration no. 2009.027) and by the Bundesinstitut für Arzneimittel und Medizinprodukte for the Oldenburg Clinic in Germany. Additionally, all Dutch centres had a local feasibility assessment. Written informed consent was obtained from all patients. This study was registered at ClinicalTrials.gov (NCT00893555).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106711.

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