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Individualized Medication of Voriconazole: A Practice Guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society

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Background: Voriconazole (VRZ) is a second-generation triazole antifungal agent with broad-spectrum activity. It is available in both intravenous and oral formulations, and is primarily indicated for treating invasive aspergillosis. The most commonly used dose for adults is 4 mg/kg or 200 mg twice daily. VRZ presents nonlinear pharmacokinetics in adults, whereas drug–drug interactions and cytochrome P450 2C19 (CYP2C19) polymorphism are of great concern for VRZ. Because the liquid chromatography method has been widely used for measuring VRZ blood concentration, and target VRZ blood concentration has been recommended in some guidelines regarding efficacy and safety, therapeutic drug monitoring is considered as a useful tool for VRZ-individualized medication. Also, the CYP2C19 genotype test is available for guiding relevant drugs use in some health care facilities. Our objective was to develop an evidence-based practice guideline for VRZ-individualized medication.

Methods: We followed the latest guideline definition from the Institute of Medicine and referred to the World Health Organization handbook for guideline development. The guideline was initially registered in the International Practice Guidelines Registry Platform (IPGRP-2015CN001). The guideline is, in principle, targeted at all Chinese health care providers. The quality of evidence and strength of the recommendations were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.

Results: Twenty-six recommendations were formulated regarding therapeutic drug monitoring, special groups of patients, drug safety, off-indication use, and drug–drug interactions. Of them, 12 were strong recommendations. Most quality of evidence was low, very low, or expert opinions.

Conclusions: We developed an evidence-based practice guideline for VRZ-individualized medication, which provided comprehensive and practical recommendations for health care providers. The development of the guideline exposed several research gaps to improve VRZ use.

Key Words: guideline, voriconazole, individualized medication, GRADE

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INTRODUCTION

Voriconazole (VRZ) is a second-generation triazole antifungal agent with broad-spectrum activity that is recommended as the first-line treatment against invasive aspergillosis and infections due to *Candida krusei*.[1,2] VRZ is widely used for the treatment and prophylaxis of a variety of invasive fungal diseases (IFDs). It is proved that VRZ is more effective than amphotericin B in treating aspergillosis, whereas it is as effective as posaconazole in IFD prophylaxis and micafungin in empirical antifungal therapies.[3–5] VRZ is also able to cross the blood–brain barrier, so it is recommended for patients with central nervous system IFDs. VRZ is available in both intravenous and oral formulations. The most commonly used dose for adults is 4 mg/kg or 200 mg twice daily. According to package insert from manufacturer, dose should be adjusted

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accordingly based on weight, hepatic function, and response to therapy.[6] The most common adverse effects of VRZ include visual disturbance, neurologic/psychiatric disorders, hepatotoxicity, gastrointestinal effects, and skin disorders.[6]

Based on 2 Chinese large-scale multicenter observational studies, the overall incidence of proven or probable IFD was 7.7%, 4.94%, 4.76%, and 3.83% for patients with hematopoietic stem cell transplant, myelodysplastic syndrome, acute hyperleukocytic leukemia, and acute myeloid leukemia, respectively.[7,8] Nevertheless, diagnosis of IFD in China is complicated by varying definitions of IFD, and diagnostic techniques that sometimes fail to comply with recognized guidelines, which makes it difficult to compare outcomes between IFD studies. In particular, triazoles were the most commonly used antifungals for treatment of IFDs (89.1% for hematopoietic stem cell transplant patients and 86.9% for hematological malignancy patients receiving chemotherapy), among which VRZ was the most frequently prescribed antifungal. This is due to the fact that empirical antifungals comprised more than 80% of initial antifungal strategy in China.[7,8] To cover *aspergillus* and some specific candida infections, a broad-spectrum antifungal is preferred. Less severe adverse events, flexible dosage forms, and national insurance coverage issue make VRZ stand out in China.

VRZ has a wide interindividual and intraindividual variability. This drug presents nonlinear pharmacokinetics (PK) in adults, and its blood concentration increases disproportionally with dosage escalation.[9] Drug–drug interaction (DDI) is also of great concern for VRZ because it is extensively metabolized through cytochrome P450 (CYP450) enzymes, whereas VRZ itself is an inhibitor of them.[10–12] CYP3A4-based interactions account for the majority of VRZ DDIs. In addition, CYP2C19 polymorphism has an ambiguous impact on the efficacy and safety of VRZ.[13] According to a references synthetic analysis, CYP2C19 poor metabolizer (PM) prevalence is 14.7% in China, which is much higher than Europe Caucasians and Africa (2.1% and 3.7%, respectively).[14] The significantly high prevalence of CYP2C19 PM puts Chinese patients at a higher risk of VRZ overdose and toxicity.

Individualized medication is achieved by using more individual patient-specific data (ie, demographic data, PK data, and genetic information) to select an appropriate drug and design a specific dosing regimen (administration route, dosage, frequency, duration, etc.) to improve patients' pharmacotherapeutic outcomes. Therapeutic drug monitoring (TDM) and the gene test are 2 commonly used strategies for individualized medication, and have both been discussed for optimizing VRZ therapy for years.[10,11] With the present guideline, the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society, intends to provide evidence-based recommendations regarding individualized medication of VRZ to health care providers.

MATERIALS AND METHODS

Principle

We followed the latest guideline definition from the Institute of Medicine and referred to the World Health Organization handbook for guideline development.[15] The guideline was initially registered in the International Practice Guidelines Registry Platform (IPGRP-2015CN001).[16] The protocol of the guideline development was also developed ahead of guideline development.[17]

Scope of the Guideline

The guideline is expected to provide guidance on 6 domains of individualized medication of VRZ: TDM, special groups of patients, drug safety, off-indication use, DDI, and pharmacogenetics.

Target Audiences and End Users

The guideline is, in principle, targeted at all Chinese health care providers, including physicians, pharmacists, and nurses, who help manage patients receiving VRZ. However, tertiary hospitals are more likely to benefit from the guideline due to their higher possibility of caring for critically ill IFD patients and availability of more advanced medical services (ie, TDM). Because most of our included evidence is worldwide, the guideline is also expected to be helpful to health care providers in other countries. Recommendations that are specific for Chinese health care providers are highlighted. Patients with various conditions who are taking VRZ comprise the end users of the guideline.

Development of the Guideline

Organization of the Guideline Working Groups

Three groups were established to develop the guideline. The Guideline Steering Committee (GSC) was comprised 2 pharmacists, 1 hematologist, 1 pharmacologist, and 1 methodologist. Their responsibilities were: (1) to lead the guideline development process, (2) to approve the questions and outcomes that were included in the guideline, (3) to audit the declaration of interests from other members involved in guideline development and evaluate the potential conflicts of interest, (4) to approve the draft and final recommendations of the guideline, and (5) to approve the final version of the guideline. The Guideline Consensus Panel (GCP) was organized by the GSC regarding distribution of regions and specialties and comprised 8 pharmacists, 4 infectious diseases physicians, 3 hematologists, 1 critical care physician, 1 pulmonologist, 1 pharmacologist, 2 methodologists, and 1 pharmacoeconomist. Their responsibilities were: (1) to formulate the questions and outcomes that were included in the guideline, (2) to provide input throughout all stages of the guideline development process, and (3) to reach a consensus on the recommendations. The guideline development group (GDG) was organized by the GSC as well and comprised 15 pharmacists who were qualified to conduct guideline-related research. They were also responsible for drafting the guideline.

Formulation of the Concerning Guideline Questions and Outcomes

The GCP identified 18 questions and 10 outcomes that should be included in the guideline using a 3-round Delphi method. Of the 18 questions, 7 were considered key questions that must be answered in the guideline. The importance of

each outcome was scored on a scale of 1–9 as follows: 7–9 indicated critical outcomes, 4–6 indicated important outcomes, and 1–3 indicated less important outcomes. Four outcomes (infection-related mortality, treatment response, prophylaxis failure, and hepatotoxicity) were considered critical, whereas 6 outcomes (nephrotoxicity, nervous system/psychiatric disorders, visual disturbance, skin disorders, economic outcomes, and length of hospital stay) were considered important. Only data from Asian population were considered for safety outcomes, unless the data were only available from non-Asian population. In addition, pharmacokinetic outcomes were used as surrogates of efficacy and safety outcomes.[18]

Evidence Synthesis and Patients' Values/ Preferences Investigation

Regarding the 18 questions, the GDG systematically collected related evidence and completed 9 systematic reviews (3 were further updated). References were searched on Pubmed, Embase, Cochrane Library, clinicaltrials.gov, and 3 Chinese databases (CNKI, Wanfang, and Sinomed) until January 26, 2016, using the single search term "voriconazole." For some of the questions that could not be answered by a systematic review, evidence was also collected systematically through a process of searching and identifying references. In addition, the GDG conducted a cross-sectional study to investigate 119 patients from 9 Chinese hospitals who were taking VRZ on their values and preferences toward TDM of VRZ and the CYP2C19 gene test. The hospitals were selected by the GSC regarding regional distribution, and the patients were selected through convenience sampling. A 6-minute video was played for investigated patients regarding background information for the questionnaire (ie, explanation of medical terminology, potential benefits and harms of VRZ TDM and the CYP2C19 gene test, and costs).[19] All the research results were presented to the GCP while formulating recommendations.[18]

Recommendations' Consensus, External Review, and Guideline Approval

Through a 3-round Delphi and Grading of Recommendations Assessment, Development and Evaluation (GRADE) grid method, the GCP voted on draft recommendations regarding the benefits and harms balance, quality of evidence, patients' values and preferences, and costs. A strong recommendation required a $\geq$70% affirmative vote for strong plus conditional recommendation and a $\geq$50% exclusive for strong recommendation. The percentage for opposing a consensus recommendation should be $\leq$20%.[20] After approval of the draft recommendations by the GSC, they were published on the official web site of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society, and were further submitted to 12 front-line physicians and 8 pharmacists, as well as 1 patient, for external review. Those external reviewers were selected through convenience sampling. Their feedback was discussed by the GSC, and revisions of the draft recommendations were made. The final version of 26 recommendations was formulated and approved by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society.[21] An update of the guideline is expected to be available before 2022.

Quality of Evidence and Strength of the Recommendations

The quality of evidence and strength of the recommendations were assessed using the GRADE method.[22] The evidence and recommendation grading scheme are shown in Table 1. For evidence that failed to form a systematic review, its quality was determined to be very low. For recommendations without any evidence or with in vitro evidence available only, we used the letter "E" to indicate their quality of evidence. A strong recommendation (Arabic numeral "1") is one that can apply to most patients in most circumstances. A conditional recommendation (Arabic numeral "2") is one to which the desirable effects of adherence probably outweigh the undesirable effects, but we are not sufficiently confident about these trade-offs.

RESULTS

GRADE evidence profiles and summary of findings are shown in **Supplemental Digital Content 1** (http://links.lww.com/TDM/A265).

Domain 1: TDM

Question 1

What are the indications for TDM of VRZ?

Recommendation 1

The TDM of VRZ is recommended for patients with hepatic dysfunction, concomitant drugs that potentially influence VRZ PK, CYP450 2C19 mutations, poor clinical response or VRZ adverse events, or life-threatening fungal infections (1D-E, *strong recommendation*, *very low quality of evidence to expert opinion*).

Summary of the Evidence

Concomitant use of several drugs had a significant impact on VRZ PK.[23,24] The quality of evidence varied from high to very low. The CYP2C19 polymorphism was not associated with the rates of treatment response (low quality of evidence), hepatotoxicity (very low quality of evidence), or nervous system/psychiatric disorders (very low quality of evidence).[25]

Patients' Values and Preferences

Overall, 95 of 119 patients (80%) preferred VRZ TDM over no TDM for VRZ. The proportions of those preferring VRZ TDM were 78% (25/32), 80% (39/49), 90% (18/20), and 91% (10/11) for patients with hepatic dysfunction, concomitant drugs that potentially influence VRZ PK, previous VRZ adverse events, and admission to intensive care units, respectively.[19]

Rationale

For patients with hepatic dysfunction, CYP450 enzyme activity is decreased, thereby reducing VRZ clearance. The

TABLE 1. Level of Evidence and Strength of Recommendation Using the GRADE Approach

	Strong Recommendation (1)	Conditional Recommendation (2)
High (A)	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.	The best action may differ depending on circumstances or patients or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (B)	Recommendation can apply to most patients in most circumstances. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	Alternative approaches are likely to be better for some patients under some circumstances. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low (C)	Recommendation may change when higher-quality evidence becomes available. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (D)	Recommendation may change when higher-quality evidence becomes available. Any estimate of effect is very uncertain.	Other alternatives may be equally reasonable. Any estimate of effect is very uncertain.
Expert opinion or in vitro evidence (E)	No human study is available. Recommendations can apply to most patients in most circumstances theoretically. Recommendation may change when higher-quality evidence becomes available.	No human study is available. Other alternatives may be equally reasonable.

concomitant use of drugs that affect CYP450 enzyme activity may also alter VRZ clearance. Although a systematic review suggested that the CYP2C19 polymorphism had no significant effect on the clinical outcomes of patients, the quality of evidence was extremely low, and it was proven that the CYP2C19 polymorphism significantly affected the patients' blood trough concentration and healthy subjects' peak plasma concentration and area under the curve (AUC).[25,26] The probability of poor clinical response and some toxicities may be increased in patients with abnormal VRZ exposures. For patients with life-threatening fungal infections, their hemodynamics are usually unstable, possibly resulting in liver blood flow variation, thus affecting VRZ clearance. In addition, achieving the target VRZ blood concentration as soon as possible can optimize their prognosis. Such patient groups also showed strong preferences toward TDM. Therefore, we strongly recommend conducting VRZ TDM for these patients.

Recommendation 2

TDM of VRZ is suggested for all pediatric and Chinese adult patients who are not mentioned in Recommendation 1 (2B-D, *conditional recommendation*, *moderate to very low quality of evidence*).

Summary of the Evidence

With the systematic review being updated, patients aged 12 years or older and 2–12 years had similar rates of treatment response, hepatotoxicity, nervous system/psychiatric disorders, and visual disturbance (very low quality of evidence), whereas patients aged 2 years or younger and 2–12 years had a similar trough blood concentration and rate of attainment of target concentration (very low quality of evidence).[27] TDM also did not improve the rates of treatment response, hepatotoxicity, nervous system/psychiatric disorders, or visual disturbance in pediatric patients (very low quality of evidence).[28] Compared with non-TDM adult patients, TDM adult patients had a significantly higher rate of treatment response [risk ratio (RR) = 1.38, 95% CI = 1.00–1.90, moderate quality of evidence], whereas the rates of hepatotoxicity and nervous system/psychiatric disorders were not changed significantly (low quality of evidence).[28]

Patients' Values and Preferences

The proportion of patients preferring VRZ TDM over no TDM for VRZ was 75% (18/24) and 82% (77/95) for patients younger than 12 years and 12 years or older without special conditions, respectively.[19]

Rationale

The livers of pediatric patients are not mature, with a higher activity of CYP2C19 and a stronger ability to metabolize drugs. It was proven that the variability in the bioavailability of oral VRZ in pediatric patients was greater than that in adults.[29] To date, China, the United States, and Europe have not approved VRZ for neonates and children younger than 2 years, although the use of VRZ in this

population is not uncommon. Due to the lack of experience and significant intervariability, VRZ TDM should be indicated for pediatric patients. For the remaining adult patients using VRZ, although they are free from the risk factors listed above, VRZ TDM is also suggested due to the nonlinear pharmacokinetic profile of VRZ and significant interindividual and intraindividual variability. Theoretically, hepatotoxicity will be weakly observed due to TDM because a long time of consistent overexposure is usually required to develop the effect. In most cases, the patients' CYP2C19 genotype is unknown, with the prevalence of CYP2C19 PM being 14.7% in China.[14] Regarding the variance of CYP2C19 mutation prevalence between Asian and non-Asian population, we suggest that VRZ TDM be conducted for all Chinese adult patients.

Question 2

Which parameter should be monitored for VRZ, the peak or trough blood concentration?

Recommendation 3

The steady-state trough blood concentration of VRZ is recommended to be monitored (1B, *strong recommendation*, *moderate quality of evidence*).

Summary of the Evidence

The VRZ trough blood concentration was found to be significantly associated with the rates of treatment response and hepatotoxicity (moderate quality of evidence).[30] No evidence of a relationship between the VRZ peak blood concentration and clinical outcomes was identified.

Rationale

Compared with monitoring the VRZ peak blood concentration, monitoring the trough blood concentration of VRZ is more evidence-based and practical. Trough blood samples of VRZ should be obtained within half an hour before the next dose.

Question 3

When should the initial blood sample be obtained to perform TDM of VRZ?

Recommendation 4

When the loading dose of VRZ is given, an initial blood sample is suggested to be obtained no earlier than immediately before the fifth dose (on the third day of treatment) (2D, *conditional recommendation*, *very low quality of evidence*).

Summary of the Evidence

Two population PK studies showed that when the loading dose was given, the time to reach the steady state of the VRZ blood concentration was at the end of the second day and immediately before the fifth VRZ dose, respectively.[31,32]

Rationale

Based on the pharmacokinetic theory, levels similar to those at steady state would be achieved on day 2 if the loading dose is given on day 1. Regarding the evidence and variability among patients, obtaining the first blood sample on day 3 is appropriate. When a population PK model is available, an earlier timing of the initial monitoring is acceptable, making dosage adjustment more timely. If no loading dose is given, the time to reach the steady-state levels is influenced by multiple factors, including liver function, concomitant drugs, CYP2C19 polymorphism, etc. It was reported that under the circumstances of no loading dose, the steady-state levels were reached on day 4–7.[33–35] Based on the poor evidence and large individual variability, the GCP failed to reach a consensus on the timing of initial monitoring when the loading dose is not given.

Question 4

What is the target trough blood concentration of VRZ?

Recommendation 5

The trough blood concentration of VRZ is recommended to be maintained above 0.5 $mg \cdot L^{-1}$ (1B, *strong recommendation*, *moderate quality of evidence*).

Summary of the Evidence

Patients whose VRZ trough blood concentration was $\leq$0.5 $mg \cdot L^{-1}$ exhibited a lower rate of treatment response (RR = 0.49, 95% CI: 0.29–0.81, moderate quality of evidence).[30]

Rationale

With the systematic review being updated, we determined that although 0.5 and 1 $mg \cdot L^{-1}$ are both valuable VRZ trough blood concentration cutoffs with respect to treatment response, the quality of evidence varied (moderate for 0.5 $mg \cdot L^{-1}$ but very low for 1 $mg \cdot L^{-1}$).[30,36] Patients whose VRZ trough blood concentration was $\leq$1.5 $mg \cdot L^{-1}$ exhibited similar efficacy outcomes (treatment response, infection-related mortality, and prophylaxis failure) compared with patients whose VRZ trough blood concentration was $>$1.5 $mg \cdot L^{-1}$.[30] Therefore, we recommend 0.5 $mg \cdot L^{-1}$ as the lower limit of the VRZ trough blood concentration.

Recommendation 6

The trough blood concentration of VRZ is recommended to be maintained below 5 $mg \cdot L^{-1}$ for Chinese population (1B, *strong recommendation*, *moderate quality of evidence*).

Summary of the Evidence

Asian patients whose VRZ trough blood concentration was $<$5 $mg \cdot L^{-1}$ exhibited a lower rate of hepatotoxicity (RR = 0.34, 95% CI: 0.13–0.87, moderate quality of evidence).[30]

Rationale

Based on a systematic review, a similar incidences of hepatotoxicity with VRZ trough concentration below or above cutoff levels of 3.0, 4.0, 5.5, and 6 $mg \cdot L^{-1}$ were observed. Subgroup analysis showed that Asian patients with lower VRZ trough concentration had a significantly lower incidence rate of hepatotoxicity compared with those with higher VRZ trough concentration at all cutoff levels, whereas for non-Asian patients, such results were not observed.

Sensitivity analysis showed that the difference of hepatotoxicity incidence rate between >3.0 and <3.0 $mg \cdot L^{-1}$ became insignificant when removing any 1 of 3 studies that was performed in predominantly Asian population.[30] Regarding a fluctuated VRZ trough blood concentration in the real world, a wider therapeutic window is more practical. Thus, under close monitoring of liver function, we recommend 5 $mg \cdot L^{-1}$ as the upper limit of the VRZ trough blood concentration. In addition, the association between the VRZ trough blood concentration and other safety outcomes (nervous system/psychiatric disorders and visual disturbance) remains uncertain.[30] Thus, close monitoring of the adverse events of VRZ is still required along with VRZ TDM.

Question 5

Under what conditions should TDM of VRZ be repeated?

Recommendation 7

TDM of VRZ is recommended to be repeated when adjusting the VRZ dosing regimen, patients show a poor clinical response or VRZ adverse events, or when initiating or holding concomitant drugs that potentially influence VRZ PK (1E, *strong recommendation*, *expert opinion*).

Rationale

After the dosage adjustment of VRZ, TDM should be repeated to ensure an optimal blood concentration. The probability of poor clinical response and some toxicities may be increased in patients with abnormal VRZ exposures, when TDM is recommended to be repeated immediately. The alteration of concomitant drugs that potentially influence VRZ PK results in a changing VRZ clearance, making the blood concentration unstable. In addition, the timing of repeated TDM is consistent with the initial sampling time under the circumstances of no VRZ loading dose, which is expected to be 4–7 days after adjusting the VRZ dosing regimen, or with initiating or holding concomitant drugs that potentially influence VRZ PK.[33–35]

Question 6

How should the VRZ dosing regimen be adjusted if necessary?

Recommendation 8

Population PK methods are suggested to be used to adjust the VRZ dosing regimen when a population PK model based on a native population is available (2E, *conditional recommendation*, *expert opinion*).

Recommendation 9

If the patients' steady-state trough blood concentration of VRZ is below 0.5 $mg \cdot L^{-1}$ or the clinical response is poor, maintenance dosage of VRZ is suggested to be increased by 50%, followed by dosage adjustment based on the blood concentration (2D, *conditional recommendation*, *very low quality of evidence*).

Recommendation 10

If the patients' steady-state trough blood concentration of VRZ is within 5–10 $mg \cdot L^{-1}$ without ≥grade 2 adverse events, maintenance dosage of VRZ is suggested to be decreased by 20%, followed by dosage adjustment based on the blood concentration (2D, *conditional recommendation*, *very low quality of evidence*).

Recommendation 11

If the patients' steady-state trough blood concentration of VRZ is above 10 $mg \cdot L^{-1}$ or has grade 2 adverse events, VRZ administration is suggested to be skipped once, with the maintenance dosage decreased by 50%, followed by dosage adjustment based on the blood concentration (2D, *conditional recommendation*, *very low quality of evidence*).

Summary of the Evidence

Six studies reported their strategies for empirically adjusting the VRZ dosing regimen during VRZ treatment without an available population PK model of VRZ. The indications of adjusting the VRZ dosing regimen included abnormal TDM results, poor clinical response, and occurrence of adverse events.[36–41]

Rationale

To date, the VRZ population PK model based on a Chinese population has been applied to calculate individual PK parameters and to subsequently adjust the VRZ dosage in certain hospitals. However, there are no studies comparing dosage adjustment based on the population PK method with empiric dosage adjustment. Although the relationship between VRZ blood trough concentrations and clinical outcomes has been clear, the treatment response and tolerance toward VRZ still vary among patients and cannot be fully explained by the blood concentrations. Fungal species resistance to antifungals may also be responsible for some VRZ treatment failure, although it has not been proved that susceptibility results are clearly associated with IFDs' treatment response. Therefore, the efficacy and safety of VRZ therapy are also indicated for adjusting the VRZ dosage beside VRZ blood concentrations. If VRZ trough blood concentration is at the upper or lower limit of the therapeutic range while efficacy or safety issues remain significant, switch from VRZ to other antifungals should be considered. In addition, trough blood concentrations mentioned in recommendations 9–11 should be obtained at steady state.

Domain 2: Special Groups of Patients

Question 7

How should VRZ be used in patients with severe hepatic dysfunction?

Recommendation 12

For patients with severe hepatic dysfunction, VRZ is not suggested as first-line treatment. After balancing the benefits and harms, VRZ can be used for these patients under rigorous TDM and hepatic function monitoring (2D, *conditional recommendation*, *very low quality of evidence*).

Summary of the Evidence

Two studies reported half-dosage VRZ use in patients with severe hepatic dysfunction. Among those patients, 14.3% (1/7) discontinued VRZ due to worsening hepatic function, 24.1% (7/29) suffered ≥grade 3 elevated liver enzymes, and 3.4% (1/29) suffered grade 4 hyperbilirubinemia.[42,43]

Rationale

With the various definitions of severe hepatic dysfunction, we followed the definition used by Child et al and Pugh et al in this guideline.[44,45] The VRZ package insert indicates that VRZ has not been studied in patients with severe hepatic cirrhosis (Child–Pugh class C) and should only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk.[6] Although we identified 2 studies concerning half-dosage VRZ use in patients with severe hepatic dysfunction, the overall quality was very low, and the safety profile was more problematic in this patient group, with a higher proportion of severe hepatic dysfunction than in other patients. The selection of VRZ for these patients should be cautious based on the balance of the benefits and harms, and rigorous TDM and hepatic function monitoring are required to ensure safety.

Question 8

Which administration route of VRZ is more appropriate for patients with severe hepatic dysfunction, i.v. or p.o.?

Rationale

No specific evidence was found for patients with severe hepatic dysfunction regarding administration route. For the other patient groups, the i.v. and p.o. of VRZ showed similar efficacy and safety, whereas the quality of evidence was very poor.[46] Because VRZ administration route is not intended to interact with hepatic function, no recommendation was developed for this question.

Question 9

How should VRZ be used in patients aged 2 years or younger?

Rationale

Patients aged 2 years or younger had a similar trough blood concentration and rate of attainment of the target concentration as patients aged 2–12 years.[27] However, limited evidence demonstrated the optimal dosage for these patients, and the dosage varied over a wide range.[47–49] Thus, no recommendation was developed for this question.

Domain 3: Drug Safety

Question 10

What measures should be taken to rescue VRZ overdose?

Recommendation 13

Temporarily holding VRZ, TDM, and supportive treatment with evident adverse events are recommended to rescue VRZ overdose (1D, *strong recommendation*, *very low quality of evidence*).

Summary of the Evidence

Two case reports illustrated their measures to rescue VRZ overdose (>3 times regular dosage). After temporarily holding VRZ, TDM, and supportive treatment with evident adverse events, the patients recovered in a few days.[50,51]

Rationale

VRZ can be cleared by hemodialysis, although the clearance is limited.[6] Hydration is not an effective means to clear VRZ because VRZ is mainly metabolized in the liver. In addition, no known antidote is available for VRZ. Therefore, the approaches to rescuing VRZ overdose are limited to temporarily holding drug, TDM, and supportive treatment with evident adverse events.

Question 11

What measures should be taken to address common adverse events of VRZ?

Recommendation 14

The recommended indications to withdraw VRZ are as follows: alanine aminotransferase, aspartate transaminase, alkaline phosphatase, or gamma-glutamyl transferase level 5 times above the upper limits; total bilirubin (T-Bil) level 3 times above the upper limits; severe neurologic, psychiatric, or eyesight symptoms with limiting self-care activities of daily living (ADLs); skin rash covering >10% body surface area, with limiting instrumental use or self-care ADL or with oral medications indicated (1E, *strong recommendation*, *expert opinion*).

Recommendation 15

The recommended indications to decrease the VRZ dosage are as follows: alanine aminotransferase or aspartate transaminase levels 3 times above the upper limits; alkaline phosphatase or gamma-glutamyl transferase levels 2.5 times above the upper limits; T-Bil levels 1.5 times above the upper limits; moderate neurologic, psychiatric, or eyesight symptoms with limiting instrumental use ADL (2E, *conditional recommendation*, *expert opinion*).

Rationale

Common adverse events of VRZ include hepatotoxicity, nervous system/psychiatric disorders, visual disturbance, and skin disorders.[6] Based on the Common Terminology Criteria for Adverse Events v4.0, we recommend grade 3 adverse events as indications to withdraw VRZ and suggest grade 2 adverse events as indications to reduce the VRZ dosage for hepatotoxicity, nervous system/psychiatric disorders, and visual disturbance.[52] Typically, apart from hepatotoxicity, the relationship between the VRZ blood concentration and other adverse events remains unclear.[30] Thus, we are unsure whether decreasing the VRZ dosage can relieve adverse events other than hepatotoxicity. If adverse events remain significant despite the dosage adjustment, withdrawing VRZ should be considered. It would be helpful to suggest patients,

especially who live in areas with high sunlight exposure, to avoid sunlight exposure as much as possible when taking VRZ to reduce the risk of skin disorders.

Question 12

What is the compatibility of VRZ?

Recommendation 16

Intravenous VRZ is recommended to be administered alone and is incompatible with any other drugs (1E, *strong recommendation*, *in vitro evidence*).

Recommendation 17

VRZ is NOT recommended to share the same Y-site tube with the drugs below: conventional amphotericin B, cefepime, cyclosporine, dantrolene, busulfan, diazepam, liposomal daunorubicin, idarubicin, mitoxantrone, moxifloxacin, nitroprusside, pantoprazole, phenytoin, thiopental, and tigecycline. Flushing the infusion line is required if VRZ is used consecutively with these drugs (1E, *strong recommendation*, *in vitro evidence*).

Rationale

With no other specific evidence being identified, we referred to recommendations concerning the compatibility of VRZ from Micromedex IV Compatibility.[53]

Domain 4: Off-Indication Use

Question 13

What sites of fungal infections can be treated by VRZ other than those of respiratory, central nervous system, and blood stream infections?

Recommendation 18

On the condition of pathogens being sensitive to VRZ, VRZ is suggested to treat the following infections: fungal keratitis, fungal endophthalmitis, bone and joint fungal infections, fungal peritonitis, and fungal endocarditis (2D, *conditional recommendation*, *very low quality of evidence*).

Summary of the Evidence

Two case series and one case report illustrated the use of VRZ combined with other antifungal agents in treating fungal keratitis. The treatment response rates were 82.4% (14/17) and 70% (7/10), respectively, in the 2 case series, and the patients (2/2) were cured in the case report. Two case series and 4 case reports illustrated the use of VRZ combined with other antifungal agents against fungal endophthalmitis. The treatment response rates were both 100% (3/3 and 3/3, respectively) in the 2 case series, and the patients (5/5 in total) in the case report were all improved. Three case series and 10 case reports illustrated the use of VRZ alone or combined with other antifungal agents against bone/joint fungal infections. The treatment response rates were 83.3% (10/12), 55% (11/20), and 100% (5/5), respectively, in the 3 case series; patients in 9 of the 10 case reports were cured (9/9 in total), whereas the remaining patient was improved. One case report illustrated the use of VRZ alone against fungal peritonitis, in which the patient was cured. One case report illustrated the use of VRZ combined with other antifungal agents against fungal endocarditis, in which the patient was cured.[54]

Rationale

The management strategy of fungal infections in rare sites is unclear. VRZ exhibits extensive distribution into tissues; thus, it is expected to be effective against fungal infections in rare sites. However, the reports of management are limited to case series and individual cases, most of which were treated with combined antifungal agents. For VRZ use for the 5 indications suggested in the guideline, the efficacy should be carefully monitored, and alternative or additional therapy (eg, surgery and other antifungal agents) should be considered as well.

Domain 5: DDI

Question 14

What measures should be taken to manage the concomitant use of VRZ and drugs that potentially influence VRZ PK?

Question 15

What initial dosage of VRZ should be taken when using drugs that potentially influence VRZ PK concomitantly?

Recommendation 19

Due to their significant impacts on VRZ, the following drugs are not recommended to be used concomitantly with VRZ: efavirenz (400 mg every day), ritonavir (400 mg Q12H), rifampin, phenobarbital, and St. John's wort (1A–D, *strong recommendation*, *high to very low quality of evidence*).

Recommendation 20

Due to their significant impacts on VRZ, the following drugs are not suggested to be used concomitantly with VRZ: secobarbital and amobarbital (2E, *conditional recommendation*, *expert opinion*).

Recommendation 21

The VRZ dosage is recommended to be increased to 400 mg Q12H when used concomitantly with the following drugs: efavirenz (300 mg every day) and phenytoin (1D, *strong recommendation*, *very low quality of evidence*).

Recommendation 22

The VRZ dosage is suggested to be increased when used concomitantly with the following drugs: rifabutin, carbamazepine, and nevirapine. For rifabutin, the VRZ dosage is suggested to be increased to 350 mg Q12H (2D-E, *conditional recommendation*, *very low quality of evidence to expert opinion*).

Recommendation 23

The efficacy and safety of VRZ are recommended to be closely monitored when used concomitantly with the following drugs: glucocorticoids and cimetidine (1D, *strong recommendation*, *very low quality of evidence*).

Recommendation 24

The efficacy and safety of VRZ are suggested to be closely monitored when used concomitantly with the following drugs: omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, norethindrone/ethinyl estradiol, ritonavir (100 mg Q12H), indinavir, atazanavir, saquinavir, rilpivirine, etravirine, *Ginkgo biloba*, erythromycin, azithromycin, and clarithromycin (2B–E, *conditional recommendation*, *moderate quality of evidence to expert opinion*).

Rationale

Summary of the evidence is shown in Refs. 23 and 24 **Supplemental Digital Content 1**, http://links.lww.com/TDM/A265. The concomitant use of CYP450 inducers or inhibitors, especially drugs inducing or inhibiting CYP3A4 or CYP2C19, is very likely to influence VRZ PK and clinical outcomes. However, a limited number of DDIs were confirmed by human studies. Depending on the severity of the influence on VRZ, we classified CYP inducers or inhibitors into 3 categories, among which only 7 drugs were not recommended or suggested to be used with VRZ concomitantly. Close TDM of VRZ is highly recommended when using concomitant drugs that potentially influence VRZ PK because for majority of VRZ DDIs, no specific dosing adjustment of VRZ is recommended. Also, DDIs can be avoided by selecting alternative drugs that have fewer DDIs.

Question 16

Which drugs are potentially influenced by VRZ?

Recommendation 25

VRZ has a significant pharmacokinetic impact on the following drugs, whose efficacy and safety are recommended to be closely monitored when used concomitantly with VRZ: oxycodone, methadone, fentanyl, alfentanyl, midazolam, etravirine, efavirenz, cyclosporine, tacrolimus, sirolimus, everolimus, vincristine, simvastatin, norethindrone, ethinyl estradiol, nifedipine, diclofenac, etoricoxib, meloxicam, warfarin, and glimepiride (1A–D, *strong recommendation*, *high to very low quality of evidence*).

Recommendation 26

VRZ has a significant pharmacokinetic impact on the following drugs, whose efficacy and safety are suggested to be closely monitored when used concomitantly with VRZ: tilidine, buprenorphine, venlafaxine, zolpidem, diazepam, estazolam, alprazolam, triazolam, rilpivirine, nevirapine, indinavir, saquinavir, ritonavir, atazanavir, lovastatin, atorvastatin, ergot alkaloid, ibuprofen, tolbutamide, glipizide, gliclazide, glibenclamide, gliquidone, acenocoumarol, cisapride, quinidine, terfenadine, and digoxin (2B-E, *conditional recommendation*, *moderate quality of evidence to expert opinion*).

Rationale

Summary of the evidence is shown[55,56] in **Supplemental Digital Content 1**, http://links.lww.com/TDM/A265. Because VRZ has an inhibitory effect on CYP450 enzymes, the exposure of many drugs is likely to be increased when concomitantly used with VRZ. Additive QT prolongation and transporter interaction are also responsible for some VRZ DDIs. However, a limited number of DDIs were confirmed in human studies. These 2 recommendations aim at listing drugs that may be potentially affected by VRZ. The strengths of the recommendations are based on the available evidence and consequences of excessive exposure.

Domain 6: Pharmacogenetics

Question 17

Should the CYP2C19 gene test be performed before using VRZ?

Question 18

What initial dosage of VRZ should be taken for patients with CYP2C19 mutations?

Rationale

According to a references synthetic analysis, CYP2C19 PM prevalence is 14.7% in China, which is much higher than Europe Caucasians and Africa (2.1% and 3.7%, respectively).[14] Compared with CYP2C19 extensive metabolizers (EMs), both PMs and heterogenetic EMs have a higher VRZ blood trough concentration, peak concentration, and AUC, whereas ultrarapid metabolizers have a lower VRZ blood peak concentration and AUC, based on 2 systematic reviews performed on patients and health volunteers, respectively.[25,26] Nevertheless, the benefits of the CYP2C19 gene test before initiating VRZ have not been confirmed regarding its efficacy, safety, and economy.[57,58] The dosage adjustment for patients with CYP2C19 mutants is inconsistent.[59–61] In addition, less than half of the investigated patients were willing to take the CYP2C19 gene test.[19] With respect to debating evidence from systematic reviews and patients' poor preferences, no recommendations were given for VRZ pharmacogenetics.

DISCUSSION

Based on our findings, well-designed and high-quality research on individualized medication of VRZ is lacking, which has led to 18.1% low and 58.3% very low quality evidence.[20] Despite the poor quality evidence, we still formulated 12 strong recommendations, of which 3 were supported by expert opinions. The strengths of recommendations were based on balance of benefits and harms, patients' values and preferences, and economic evaluation, apart from quality of evidence.

To the best of our knowledge, this is the first practice guideline focusing on individualized medication of VRZ. Compared with the existing national and international guidelines on VRZ TDM, our guideline has key strengths and distinctness.[62,63] First, we suggest that all Chinese patients using VRZ are indicated for TDM, whereas for a small group of patients, VRZ TDM is strongly recommended. Patients with CYP2C19 mutations or hepatic dysfunction were evaluated for the first time in our guideline. The recommendations of TDM on all Chinese VRZ users result from direct evidence confirming its benefits, patients' strong value and preference

toward TDM, as well as positive PK standing. Second, with the loading dose being administered, we suggest an earlier initial sampling time than in other guidelines, making the dosage adjustment timelier and consequently improving the efficacy and safety. This recommendation is based on the PK theory of loading dose and availability of the population PK model that can be used in clinical practice. Third, we recommend a lower target trough blood concentration of VRZ based on the latest systematic review with respect to stronger evidence of benefit on >0.5 mg·L^{-1} compared with 1 mg·L^{-1}, and higher risk of hepatotoxicity for Asian people. Fourth, we clarify the indications of repeated TDM and strategies for empirical VRZ dosage adjustment, which come from present VRZ TDM studies. Fifth, our recommendations regarding concomitant drugs are more specific, with stratified DDI risk and management on drugs that can potentially influence VRZ metabolism. Sixth, the scope of our guideline is much larger than the existing guidelines on VRZ TDM, including special group of patients, drug safety, and off-indication use other than TDM and DDI. Seventh, we emphasize data from Asian populations regarding safety outcomes, making the guideline more suitable for Asians. Asian people not only have a higher prevalence of CYP2C19 PM but also are more sensitive to VRZ-induced hepatotoxicity. Eighth, we adhered to the guideline definition of the Institute of Medicine and referred to the World Health Organization handbook for guideline development to develop this guideline. The design of the protocol and registration process before guideline development not only provided a systematic and practical method for developing the guideline step by step, but also ensured the transparency of the guideline development process and helped to avoid bias and development of similar guidelines. We also used a comprehensive searching method to identify the largest number of relevant studies possible, and considered patients' value and preference concomitantly with clinical and economic evidence. The GRADE system was more properly used than in the previous guideline.[63] In addition, the GRADE Grid method and Delphi vote were used to formulate the recommendations, making the process more transparent and efficient. The recommendations were externally reviewed by front-line physicians, pharmacists, and patients as well to receive feedback from target audiences and end users.

The development of the guideline exposed several research gaps to improve the use of VRZ. These changes could include the relationship among the CYP2C19 genotype, blood trough concentration, and clinical outcomes, especially nervous system/psychiatric disorders, visual disturbance, and skin disorders. The real-world study with a large sample size might be an effective way to address this point. There is also a need for research investigating VRZ use in patients with severe hepatic dysfunction. For commonly used CYP450 inhibitors such as proton pump inhibitors, more studies are also required to demonstrate their DDIs with VRZ. Due to the complex properties of VRZ PK, patients are very likely to benefit from dosage adjustment based on the native population PK model. Economic studies are needed to evaluate the benefits of TDM and the CYP2C19 gene test as well.

CONCLUSIONS

This is the first evidence-based practice guideline for individualized medication of VRZ adapted to Chinese population. The development of the guideline exposed several research gaps to improve the use of VRZ.

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