Progress in clinical pharmacology in China: a randomized controlled study to advance genotype-guided precision medicine

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Progress in Clinical Pharmacology in China: A Randomized Controlled Study to Advance Genotype-Guided Precision Medicine

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Currently, genotype-guided dosing strategies are gaining increased attention in precision medicine. The approach involves tailoring medication doses based on an individual's genetic makeup to optimize treatment outcomes and minimize adverse effects. Genetic factors that modulate drug response typically include polymorphisms in drug metabolizing enzymes that affect drug exposure, and dose adjustments based on genotype affect treatment outcome by modulating or normalizing drug exposure. Pharmacogenomic implementation services that inform drug and dose selection have been rapidly adopted in the academic healthcare centers in the United States and Europe. The rapid expansion of testing services has been based on the availability of new genetic technologies and a wealth of information, particularly on genetic variants that influence drug response in European ancestral populations. The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a group of experts in pharmacogenomics which develops guidelines for the use of genetic information to optimize drug therapy.[1] To date, the CPIC has published 26 guidelines covering 25 genes and 153 drugs across many therapeutic areas (https://cpicpgx.org/guidelines/, accessed on November 18, 2023). The guidelines are designed to help clinicians understand how available genetic test results should be used to optimize drug therapy. However, despite the widespread adoption in academic medical centers, there remains a resistance to pharmacogenomic testing, which is multifactorial, but includes cost-effectiveness, requirements for expensive infrastructure, lack of provider education, and skepticism that there is any cost benefit to the besting.

To date, the effectiveness of genotype-guided dosing strategies is still being studied and is inconclusive for some drugs.[2] Randomized controlled trials (RCTs) are prospective studies serving as the gold standard in terms of measuring the effectiveness and safety of a new intervention or treatment.[3] However, conducting prospective RCTs to evaluate genotype guided dosing regimens faces challenges, especially when testing for rare variants that demand large sample sizes. Ethnic diversity further complicates trial design, making it difficult to adequately represent all groups. Limitations in clinical trial validity may arise when important variants specific to the studied population are not tested. Illustrating this issue, the European

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Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial favored genotype-guided warfarin dosing, predominantly with White participants,[4] whereas the Clarification of Optimal Anticoagulation through Genetics (COAG) trial showed no improvement overall and poorer outcomes in Black patients due to incomplete genotyping for African ancestry alleles, such as CYP2C9*8.[5] These issues are further complicated for RCTs designed to evaluate genotype-guided dosing in rare diseases, including pediatric acute lymphoblastic leukemia (ALL), in a specific ethnic group.

In this issue, the manuscript entitled "Individualized use of 6-mercaptopurine in Chinese children with ALL: A multicenter randomized controlled trial" by Zhou *et al*. presents a well-performed, albeit small, randomized study comparing the benefits of TPMT/NUDT15 gene-based dosing of mercaptopurine (6MP) to standard dosing without pharmacogenomics. The goal of the study is to assess the impact of a genetic-guided dosing approach,[6] considering well-established knowledge about the influence of TPMT[7] and NUDT15 variants[8] on mercaptopurine clinical safety and dosage tolerance. TPMT and NUDT15 are both involved in the disposition of 6-mercaptopurine and its metabolites. TPMT activity is co-dominant, controlled by a single gene (monogenic), and responsible for methylation and inactivation of mercaptopurines. Variant alleles in TPMT are linked to decreased enzyme activity, resulting in notable pharmacological effects of thiopurines. NUDT15 is involved in metabolism of thiopurines. Of note, the poor metabolizer phenotype associated with NUDT15 occurs in ~1 out of 50 individuals of East Asian heritage, surpassing the frequency of the TPMT poor metabolizer phenotype in Europeans.[9] Therefore, conducting NUDT15 genotyping in Asian populations holds specific clinical significance.

Zhou *et al*. provide compelling evidence affirming the safety benefits for the tested genotype-guided dosing through the conduct of an RCT. The findings corroborated that the genetic-guided dosing approach reduces adverse effects (e.g., incidences of myelosuppression and leukopenia) compared with standard dosing in Chinese pediatric patients, demonstrating the effectiveness of pre-emptive starting dose adjustments through such an approach. Moreover, the authors attempt to show that there is no difference in efficacy outcomes, although given that the sample size is small, these conclusions need validation. This research is considered unique in its focus on children of Asian ancestry, where there have been no prospective RCTs of such dosing strategies conducted in the past. Of note, it is anticipated that additional randomized studies will not be conducted after this one, given ethical considerations of enrolling pediatric patients with ALL to thiopurine treatment without incorporating pharmacogenomic testing.

A major goal of precision medicine is to provide the right doses of the right drugs to individual patients. Well-designed RCTs can provide a high level of evidence for use of genotype in guiding drug or dose selection. Zhou *et al*., in this RCT, provide a high level of evidence for genotype-driven dosing of mercaptopurine in patients with ALL, increasing demand on genotype-guided dosing evaluations.[10] Genotype-guided dosing is an emerging area in oncology, and tailoring chemotherapy doses based on genetic factors can reduce adverse effects.[11] The field is moving beyond single-gene considerations to polygenic risk scores, incorporating multiple genetic factors to predict drug response. Efforts are being made to integrate genotype-guided dosing into routine clinical practice,[12,13] and all studies in this area are valuable in terms of exploring means to assess the practicality and effectiveness of incorporating genetic information into electronic health records and decision-support systems. Regulatory agencies are increasingly recognizing the importance of pharmacogenomics in drug development and clinical practice, and future guidelines may provide clearer recommendations on when and how genotype-guided dosing should be applied.[12] Of note, when conducting an RCT becomes costly, operationally challenging, or unethical particularly when high-risk variants predict life-threatening adverse events, alternative approaches with innovation will come into play. The alternative approaches can include meta-analyses for gene-drug pairs based on smaller studies involving diverse racial and ethnic groups, and well-designed retrospective studies involving matched historical controls. All of these needs warrant quality works by clinical pharmacologists from the globe to publish high quality ethnic-specific research outcomes to advance this area.[14] These publications should be included in expert evaluations of the literature to make dosing recommendations based on genotype.[1,6] It should be noted that at the upcoming annual meeting of the ASCPT "New Horizons for Global Outreach," a debate

Figure 1 *Clinical Pharmacology & Therapeutics* February 2024 cover image.

hosted by *Clinical Pharmacology & Therapeutics* (*CPT*) will focus on "Is pharmacogenetic testing a vital tool for enhancing therapeutic management of patients worldwide?" This debate will cover both ethnic-specific issues in pharmacogenomic testing and issues related to level of evidence needed for such testing.

Beyond the study and implementation of genotype-specific dosing, we have witnessed a fast-growing clinical pharmacology community in China, marked by a surge in original research contributions in recent years. Notably, the recent work by Zhou *et al.*, highlighted in the issue, is a testament to the quality and significance of the top research emerging from China. As the premier journal in the field, *CPT* has underscored the importance of Diversity, Equity, and Inclusion in the study populations featured in its publications, encompassing diversity in disease, sex, gender, geographic location, and race and ethnicity. *CPT* aims to provide a platform for publication of research work conducted in minority groups, including but not limited to the evaluation and implementation of genotype guided dosing based on Chinese population, given its under-representation in genomics research articles. Therefore, the journal has recently appointed Liang Zhao as editorial board member with a specific remit to establish further links with the Chinese clinical pharmacology community (LinkedIn Contact: cpteditor@ascpt.org). As the journal's ambassador, he will encourage and facilitate submission of high-quality clinical pharmacology research with the ultimate goal of increasing exposure of the best work to a global audience (see Figure 1).

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The authors declared no competing interests for this work.

DISCLAIMER

The opinions expressed in this manuscript are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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