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Editorial

Monitoring of Diseases in Bio-Therapeutics

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INTRODUCTION

In the modern era of cancer treatment, with targeted agents superseding more traditional cytotoxic chemotherapeutics, it is becoming increasingly important to use stratified medicine approaches to ensure that patients receive the most appropriate drugs and treatment schedules. In this context, there is significant potential for the use of pharmacodynamic biomarkers to provide pharmacological information, which could be used in a therapeutic drug monitoring setting. This review focuses on discussing some of the challenges faced to date in translating preclinical pharmacodynamic biomarker approaches to a clinical setting.

Pharmacodynamic monitoring typically is the monitoring of biochemical markers. A pharmacodynamic marker preferably is specific for the pharmacological action of a drug, but most of the time nonspecific pharmacodynamic markers are used, such as C-reactive protein and the erythrocyte sedimentation rate. Biopharmaceuticals, especially monoclonal antibodies, have been increasingly used to treat several chronic inflammatory diseases. Due to the complexity of their pharmacokinetics and concentration-effect relationship, Therapeutic Drug Monitoring (TDM) has been used to optimize their dosing regimen. Up to date, several decisional algorithms have been developed to provide tools for monoclonal antibodies' therapeutic drug monitoring. However, these algorithms are unable to determine the individual optimal dosing scheme.

Although we may not yet be in a position to systematically implement therapeutic drug monitoring approaches based on pharmacodynamic information in a cancer patient setting, such approaches are likely to become more commonplace in the coming years. Based on ever-increasing levels of pharmacodynamic information being generated on newer anticancer drugs, facilitated by increasingly advanced and accessible experimental approaches available to researchers to collect these data, we can now look forward optimistically to significant advances being made in this area.

The aim of this article is to deal with population Pharmacokinetic (PK) and Pharmacokinetic-Pharmacodynamic (PK-PD) modeling. Allowing the quantification of the variability of the dose-concentration-response relationship, population pharmacokinetic-pharmacodynamic modeling may be a valuable tool to determine the optimal dosing scheme. Based on population modeling, Bayesian estimators may be developed to optimize dosing schemes for each patient using limited sampling strategies. These estimators may allow accurate dosing adjustment for each patient individually.

Clinical pharmacodynamic markers typically evaluate physical variables or symptoms. Although physician-reported outcomes have been studied for a longer time and often have been shown to correlate well with molecular pharmacodynamic markers and treatment outcomes, the introduction of mobile health or mHealth technologies caused a shift toward patient-reported outcomes, with the associated challenge to consistently reflect the inflammatory state, thereby preventing undertreatment or unnecessary overdosing of patients.

Recent advances in important areas including circulating biomarkers and pharmacokinetic/pharmacodynamic modeling approaches are discussed, and selected examples of anticancer drugs where there is existing evidence to potentially advance pharmacodynamic therapeutic drug monitoring approaches to deliver more effective treatment are discussed. Biological medications including monoclonal antibodies against tumour necrosis factor-α (TNF-α), such as infliximab and adalimumab, have revolutionised the treatment of children and young people with autoimmune conditions such as inflammatory bowel disease, Juvenile Idiopathic Arthritis (JIA) and childhood chronic inflammatory uveitis. Emerging evidence is increasingly supporting the use of Therapeutic Drug Monitoring (TDM) to help optimise biological efficacy, safety and cost-effectiveness.

The pharmacokinetics of biologics is complex and in contrast to traditional medications; predominantly due to their large molecular size and structural complexity, they do not undergo hepatic metabolisation and are instead broken down by intracellular lysosomal proteolytic degradation. Also, unlike traditional medications, they have immunogenic potential and the formation of Antidrug Antibodies (ADA) can significantly affect their pharmacokinetic profile. ADA directed against the

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corresponding biologic can trigger proteolytic elimination in the Reticulo Endothelial System (RES) leading to increased clearance of these molecules. Conversely, an immune complex that does not trigger an RES response may slow down biological elimination by acting as a depot for the protein.1

The development of molecular methods in recent decades has enabled the detection of non-cultivable microorganisms in different environments, including human and animal ecosystems, and has shifted the perception that most microorganisms are threatening, to a greater understanding of the importance of balanced microbial ecosystems in human and animal health. Consequently, new therapeutic approaches have emerged, aiming at re-establishing the necessary balance between the microbiome and its host in several pathologies.