

Soo-Youn Lee , M.D., Ph.D.<sup>1,2</sup><sup>1</sup>Department of Laboratory Medicine and Genetics, <sup>2</sup>Department of Clinical Pharmacology and Therapeutics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

## Therapeutic Drug Monitoring of Biologic Agents in the Era of Precision Medicine

Life-long treatment of chronic disease conditions is an important issue in aging populations worldwide. Thanks to research on disease mechanisms and the development of the pharmaceutical agents, treatment modalities have become more diverse. Targeted therapy, rather than just symptomatic control, is now possible to treat the underlying causes of diseases. As a representative example, the introduction of anti-tumor necrosis factor therapy in the field of chronic immune-mediated inflammatory diseases, such as inflammatory bowel disease and rheumatoid arthritis, was ground-breaking.

There is a growing interest in biologic agents (native proteins, cytokines, growth factors, and antibodies) and biosimilars, which have become more widely available [1]. However, there are many challenges that need to be overcome before the use of these new agents becomes commonplace. There are considerable intra- and inter-individual variabilities in drug response. None of the therapeutic agents have been successful in all patients. Some patients do not exhibit a therapeutic response from the beginning (primary non-response), while the others experience diminishing effectiveness during treatment (loss of response or secondary non-response) [2]. Even in a single patient, the drug response is not fixed but changes continuously during the course of treatment. Various problems with medications can lead to poor patient compliance, discontinuation of medication, worsening of the disease, and poor prognosis. In addition, biological agents are very expensive and can lead to huge economic damage if the treatment fails, although the cost has decreased with the in-

creasing availability of biosimilars.

There are many environmental factors and inherent or genetic factors that affect the drug response [3], and the responsiveness changes continuously over the treatment period. Thus, selection of the initial treatment option, monitoring of therapeutic response, and dosage adjustment or switching treatment to suit individual patients are all in a constant and iterative flux throughout the entire treatment period. Although genomic testing has been in the spotlight during the era of precision medicine, it can never replace therapeutic drug monitoring (TDM). TDM is clinically useful in many ways and provides valuable information (inter- and intra-individual variabilities, pharmacokinetic and pharmacodynamic characteristics, drug interactions, and patient compliance, etc.).

TDM in biologic therapy refers to the evaluation of trough drug concentration and anti-drug antibody to help optimize the dosage regimen or select the right agents. Previous studies have shown positive correlations between drug concentrations and good clinical or laboratory outcomes, whereas low or undetectable drug concentrations can lead to immunogenicity and treatment failure [4, 5]. Loss of response is currently the major problem encountered in anti-tumor necrosis factor therapy. Although the underlying mechanisms are not understood completely, anti-drug antibodies are related to immunogenicity, which can be a common cause of secondary loss of response. Clinical trials on TDM of biologics are underway and a clinical decision-making algorithms based on the drug concentration and anti-drug

### © Korean Society for Laboratory Medicine

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

antibody status have been suggested by expert groups [2, 6]. Current antibody-based testing methods for measuring drug concentrations or anti-drug antibodies, such as radioimmunoassay and ELISA, are not standardized, which leads to discrepant results and limited comparison of results from different laboratories. Recently, mass spectrometry-based methods for simultaneous quantification of some therapeutic monoclonal antibodies have been introduced [7, 8].

In the review article by Benucci, *et al.* [9] in this issue of *Annals of Laboratory Medicine*, the authors have focused on laboratory monitoring in biologics treatment. This is a very timely review and shows an important approach to achieving our goals in the era of precision medicine. The authors begin with a general introduction to biologic therapies, review existing clinical studies related to drug concentrations, anti-drug antibodies, and treatment responses, and highlight the role of clinical laboratories in safe and effective management.

Drug testing and anti-drug antibody measurement can be performed when a patient has primary or secondary loss of response. In this reactive setting, the purpose of TDM is to assess possible causes of problems that already happened. However, according to recent study data, it is more desirable to apply proactive TDM from the induction phase, considering the inflammatory burden and development of immunogenicity [5]. Further studies are required to establish the clinical impact and cost-effectiveness of TDM and to develop practical guidelines for an optimal TDM process to enhance patient management in real clinical settings.

## Author Contributions

SY Lee has accepted the responsibility for the entire content of this manuscript and approved submission.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this paper were reported.

## Research Funding

None declared.

## REFERENCES

1. Yanai H and Hanauer SB. Assessing response and loss of response to biological therapies in IBD. *Am J Gastroenterol* 2011;106:685-98.
2. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. *Gastroenterology* 2017;153:835-57.
3. Choi R, Jeong BH, Koh WJ, Lee SY. Recommendations for optimizing tuberculosis treatment: therapeutic drug monitoring, pharmacogenetics, and nutritional status considerations. *Ann Lab Med* 2017;37:97-107.
4. Papamichael K, Cheifetz AS, Melmed GY, Irving PM, Vande Casteele N, Kozuch PL, et al. Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2019;17:1655-68.
5. Papamichael K, Vogelzang EH, Lambert J, Wolbink G, Cheifetz AS. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. *Expert Rev Clin Immunol* 2019;15:837-48.
6. Ooi CJ, Hilmi I, Banerjee R, Chuah SW, Ng SC, Wei SC, et al. Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. *Intest Res* 2019;17:285-310.
7. Jourdil JF, Nemoz B, Gautier-Veyret E, Romero C, Stanke-Labesque F. Simultaneous quantification of adalimumab and infliximab in human plasma by liquid chromatography-tandem mass spectrometry. *Ther Drug Monit* 2018;40:417-24.
8. Willeman T, Jourdil JF, Gautier-Veyret E, Bonaz B, Stanke-Labesque F. A multiplex liquid chromatography tandem mass spectrometry method for the quantification of seven therapeutic monoclonal antibodies: application for adalimumab therapeutic drug monitoring in patients with Crohn's disease. *Anal Chim Acta* 2019;1067:63-70.
9. Benucci M, Grossi V, Manfredi M, Damiani A, Infantino M, Moscato P, et al. Laboratory monitoring of biological therapies in rheumatology: the role of immunogenicity. *Ann Lab Med* 2020;40:101-13.

**Corresponding author: Soo-Youn Lee, M.D., Ph.D.**

 <https://orcid.org/0000-0001-7595-4042>

Department of Laboratory Medicine and Genetics, Department of Clinical Pharmacology and Therapeutics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea

Tel: +82-2-3410-1834, Fax: +82-2-3410-2719, E-mail: suddenbz@skku.edu