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Review

Cultivation of sensitivity to reverse translational research through pharmacy education

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ABSTRACT

Reverse translational research begins with actual, real-life patient experiences in the clinic and works backward to uncover the mechanistic basis for these clinical observations. The goal of reverse translational research is to generate actionable hypotheses about disease mechanisms and drug response supporting validation of existing targets, identifying new targets and disease mechanisms/indications, and driving precision medicine strategies. A report from Science Council of Japan pointed out that reverse translational research is a promising way to promote the science and practice of clinical pharmacy. The revised model core curriculum for pharmacy education in Japan proposed 10 professional competencies for pharmacists. Research is included in 10 competencies. By conducting research in the undergraduate course, students will develop the ability to use knowledge and skills comprehensively and to solve problems through research processes. Fostering a pharmacist with a research mind is expected to contribute to advancement of reverse translational research through detection of clinical problems and accumulation of objective information.

Key words: reverse translational research, pharmacy education, core curriculum, clinical pharmacy

1. Introduction

Advances in medicine and pharmacy and the arrival of an aging society have greatly changed the manner of medical care. For instance, precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. This approach will allow physicians and pharmacists to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. Utilizing artificial intelligence and big data is a promising way for promoting precision medicine and developing new drugs. It is crucial that big data consist of accurate and precise individual records.

Changes in the disease structure from acute disease to chronic one have led to physicians and pharmacists follow up patients over a long period of time. The pharmacist must provide appropriate pharmaceutical care for the patient over the entire dosing period. Monitoring the patient carefully and noticing the differences from others is important for proper treatment of the patient and may lead to the discovery of new findings. Deep characterization of the patient is the origin of clinical question and the start point of the reverse translational research.

2. Reverse Translational Research

Translational research is often used interchangeably with translational medicine or translational science or bench to bedside. It aims to convert the findings from basic science into meaningful therapeutic options and to improve medical practice for patients. On the other hand, reverse translational research starts with deep characterization of the patient on the occasion of encountering an unknown clinical event. Next, the thorough investigation of the patient by basic science elucidates the mechanism, which in turn drives deeper understanding and better selection of targets. The goal of reverse translational research is to generate actionable hypotheses about disease mechanisms and drug response supporting validation of existing targets, identifying new targets and disease mechanisms/indications, and driving precision medicine strategies (Wagner, 2018). In the reverse translation paradigm, research becomes a seamless, continuous, cyclical process, in which each new patient observation stimulates new testable hypotheses that help refine and direct the next iteration of benchtop therapeutics research, which, in turn, leads to the next clinical trial and the next human experience (Shakhnovich, 2018).

In September 2017, Science Council of Japan issued a report entitled "Promotion of clinical pharmacy research contributing to society". This report pointed out that reverse translational research is a promising way to promote the science and practice of clinical pharmacy (Fig. 1). Sugiyama (2017) reported some examples of reverse translational research and demonstrated the usefulness of conducting basic research with clinical events as a trigger and feeding back the result to the clinic.

We previously encountered a case in which an increase in the blood concentration of tacrolimus was observed after the administration of miconazole oral gel (Fig. 2). Miconazole is an imidazole antifungal agent and its oral gel is used to treat oral or esophageal candidiasis. Based on this case, we retrospectively investigated the blood concentration data of tacrolimus and cyclosporine in patients who concomitantly administered miconazole oral gel and showed that the trough blood concentration/dose ratios of tacrolimus and cyclosporine increased significantly with the administration of miconazole oral gel (Ishiwata et al., 2016). These results indicate that careful blood concentration monitoring of tacrolimus or cyclosporine is especially important in the combination therapy with miconazole oral gel.

Sunitinib is an oral multi-targeted tyrosine kinase inhibitor approved for the first-line treatment of metastatic renal cell carcinoma. The standard dosing schedule of sunitinib is 50 mg daily for 4 weeks, followed by 2 weeks without the drug. However, the sunitinib treatment is often associated with severe toxicity, necessitating dose reductions or discontinuation. The incidence of adverse events such as thrombocytopenia was previously reported to be greater in Asian patients from Asian sites than in non-Asian patients (Lee et al., 2014). The clinical question was why some patients suffer from severe thrombocytopenia and some others accomplish standard sunitinib therapy. Serum concentrations of sunitinib and its active metabolite N-desethyl-sunitinib were determined in six patients and were fit to the 1-compartment model with first-order absorption. Changes in platelet counts were fit assumed to be linearly inhibited by sunitinib and its metabolite. The pharmacokinetic-pharmacodynamic model successfully described the time course of sunitinib-induced thrombocytopenia (Fig. 3) and could predict changes in platelet counts after alterations to the dosage of sunitinib administered. The simulation results indicated that the total trough concentration of sunitinib to avoid severe thrombocytopenia should be less than 100 ng/mL, and also that the initial daily dose of sunitinib could be reduced to 37.5 mg or 25 mg in most Japanese patients (Nagata et al., 2015).

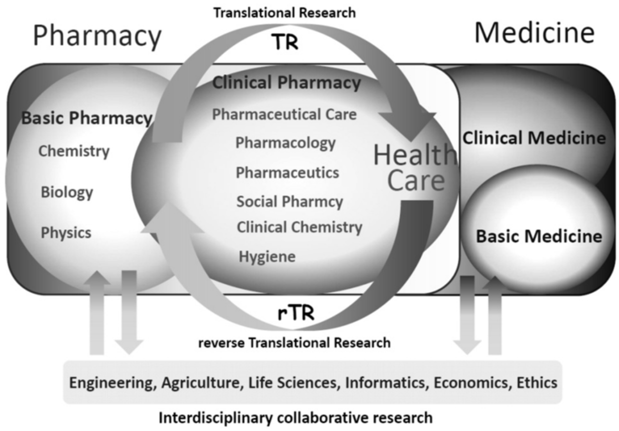

Fig. 1. Progress of clinical pharmacy research by interdisciplinary collaboration. (Science Council of Japan, Report; Promotion of clinical pharmacy research contributing to society. September 2017, cited with some modification)

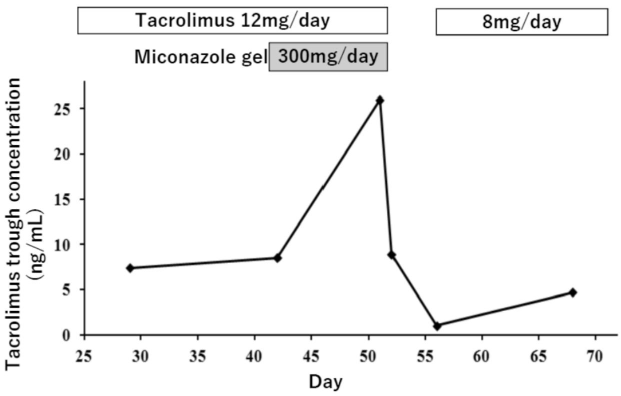

Fig. 2. Profile of the blood trough concentration of tacrolimus from days 25–70 in a patient concomitantly administered miconazole oral gel. (Ishiwata et al., 2016)

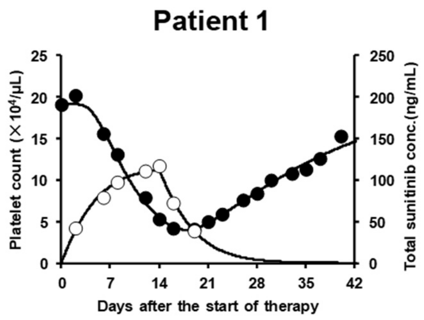

Fig. 3. Pharmacokinetic-Pharmacodynamic analysis of sunitinib-induced thrombocytopenia. Closed and open circles indicate platelet count and total sunitinib concentration (sunitinib + N-desethyl sunitinib), respectively. Solid lines denote computer-fitted curves individually. (Nagata et al., 2015)

3. Pharmacy Education in Japan

The model core curriculum for pharmacy education was originally compiled in 2002 and revised in 2013 by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT). The revised model core curriculum proposed 10 professional competencies for pharmacists; professionalism, patient-oriented attitude, communication skills, interprofessional team-care, basic sciences, medication therapy management, community health and medical care, research, lifelong learning, and education and training (Table 1). The pharmacy student should acquire these 10 competencies upon graduation from the 6-year course. It should be

Table 1. Professional competencies for pharmacists.

1. Professionalism: Fulfill the legal, ethical, and professional responsibilities of pharmacists.
2. Patient-oriented attitude: Respect the rights of individuals and promote the health and welfare of patients and consumers.
3. Communication skills: Communicate effectively with patients, consumers, and other healthcare professionals to provide necessary information.
4. Interprofessional team-care: Collaborate with healthcare teams in hospitals and regional communities.
5. Basic sciences: Understand the effects of medicines and chemicals on living bodies and the environments.
6. Medication therapy management: Contribute to the optimal use of medicines through pharmaceutical care.
7. Community health and medical care: Contribute to public health and pharmaceutical hygiene and enhance community healthcare and home care.
8. Research: Engage in research on drug development and the appropriate use of medicines to improve the healthcare environment.
9. Lifelong learning: Continue lifelong professional development in response to the advances in healthcare.
10. Education and training: Contribute to the development of the next generation of professional pharmacists.

The Pharmaceutical Society of Japan, Model core curriculum for pharmacy education-2015 version.

Table 2. Pharmacy education for reverse translational research.

What to teach?
- Patient oriented attitude
- Curiosity (research mind)
- Bird's eye view
- Respect for diversity

How to teach?
- Research experience
- Problem-based learning
- Small group discussion
- Inter-professional education

emphasized that research is included in these 10 competencies. The general instructional objective of research is to acquire the ability to undertake research and identify and solve problems to contribute to advances and improvements in the pharmaceutical and healthcare sciences. By conducting research in the undergraduate course, students will develop the ability to use knowledge and skills comprehensively and to solve problems through research processes.

Several factors indispensable for cultivating the sense of reverse translational research are shown in Table 2. Patient oriented attitude is essential to pharmacists. Curiosity and bird's eye viewpoints lead to ability to find problems. Attitudes that respect diversity create new perspectives and problem solving methods. As an educational method to acquire such attitudes, it would be most effective to let students experience their own research. Problem based learning and small group discussion may be useful for developing logical thinking and objective observation ability. Inter-professional education will be effective for cultivating respect for diversity and clinical communication skills.

Fostering a pharmacist with a research mind is expected to contribute to advancement of reverse translational research through detection of clinical problems and accumulation of objective information.

References

Ishiwata Y, Nagata M, Arai T, Makiishi M, Yoshikawa M, Takahashi H, et al. Effects of miconazole oral gel on blood concentrations of tacrolimus and cyclosporine: A retrospective observational study. Ther Drug Monit 2016; 38: 717-721.

Lee SH, Bang YJ, Mainwaring P, Ng C, Chang JW, Kwong P, et al. Sunitinib in metastatic renal cell carcinoma: An ethnic Asian subpopulation analysis for safety and efficacy. Asia Pac J Clin Oncol 2014; 10: 237-245.

Nagata M, Ishiwata Y, Takahashi Y, Takahashi H, Saito K, Fujii Y, et al. Pharmacokinetic-pharmacodynamic analysis of sunitinib-induced thrombocytopenia in Japanese patients with renal cell carcinoma. Biol Pharm Bull 2015; 38: 402-410.

Science Council of Japan, Report; Promotion of clinical pharmacy research contributing to society. September 2017 (Accessed 12/20/2018, at http://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-23-h170929-6.pdf)

Shakhnovich V. It's time to reverse our thinking: The reverse translation research paradigm. Clin Transl Sci 2018; 11: 98-99.

Sugiyama Y. Importance of reverse translational research (rTR). Yakugaku Zasshi 2017; 137: 673-679.

The Pharmaceutical Society of Japan, MODEL CORE CURRICULUM FOR PHARMACY EDUCATION -2015 version-, March 2018 (Accessed 12/20/2018, at https://www.pharm.or.jp/kyoiku/pdf/corecurri_eng180426.pdf)

Wagner JA. Patient-centered reverse translation. Clin Pharmacol Ther 2018; 103: 168-170.