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A New National Framework for Clinical Trials and Evaluation of Innovative Medical Care Technologies Using Living Cell Transplantation in Japan

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Abstract

Following the global initiative to develop medical innovative technologies such as living cell transplantation, the Japanese promotion plan, "Five-year Clinical Trial Vitalization Plan 2012" was launched in 2012. Subsequently, "Clinical Trials Core Hospitals" or medical care institutions that performed research and development of innovative technologies were identified, which were regularly evaluated by the "Evaluation System for Investigational Medical Care." In addition, the regulatory guidelines for pharmaceuticals and medical devices have been reexamined and the revised Pharmaceutical Affairs Law (PAL), which was renamed as the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act), and the Act on the safety of regenerative medicine were developed in 2013 and is scheduled for implementation in November 2014. Based on these changes in the national framework for innovative medical care in Japan, this article aims to explain and evaluate the possibility for this framework to be utilized as the universal case model for stem cell and living cell transplantation.

Keywords: Regenerative medicine; Living cell transplantation; Regulation; Evaluation system

Introduction

Efforts in developing innovative medical care such as living cell transplantation techniques, also known as regenerative medicine, has recently increased in the past several years. The global interest in developing innovative medical technologies has thus prompted the Japanese government to establish the "Five-year Medical Innovation Strategy" in 2012 [1], which was subsequently followed by the conception of the "Health and Medical Strategy" in 2013 [2] as one of the centers of economic policy. The regulatory guidelines for pharmaceuticals and medical devices have been reexamined and the revised Pharmaceutical Affairs Law (PAL), which was renamed as the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act) [3], and the Act on the Safety of Regenerative Medicine [4] were developed in November 2013 and is scheduled for implementation in November 2014 [5]. Based on this new legal framework, Japan will have the potential to become the prime venue for international medical researchers and industries. This article aims to explain and examine the possibility for this framework to be utilized as the universal case model for stem cell and living cell transplantation efforts.

Present Status of Clinical Researches and Trials in Japan and the Five-Year Clinical Trials Vitalization Plan 2012

The Medical Service Law, Medical Practitioners Law, and the Ethical Guidelines for Clinical Studies are responsible in allowing clinical researches and trials to be conducted in Japan [6-8]. In addition, PAL [9] stipulates that clinical trials should be performed in accordance with the guidelines for Good Clinical Practice (GCP) [10], which was established by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. This system thus leads investigators in non-commercial clinical studies to consider that their research does not need to be based on GCP guidelines. The Ethical Guidelines for Clinical Studies has been developed on the basis of the Declaration of Helsinki [11] and defines the protective measures for safety, rights, and the compensation of patients according to the GCP guidelines. However, the quality control and assurance, as well as the reliability of the results of clinical trials have not been clearly defined. Based on the differences between GCP guidelines and the Ethical Guidelines, the results of non-commercial clinical trials, particularly those performed in academia; generally do not contribute to the marketing strategies of a novel treatment. Therefore, this results in failure to further develop and utilize innovative medical care technologies involving regenerative medicine and living cell transplantation after the completion of the non-commercial clinical trials. The inability to provide supporting evidence on the efficacy and safety of a novel medical technology further impedes product development. To decrease the gap between the GCP guidelines and the Ethical Guidelines, a reexamination of clinical research guidelines has been performed. These assessments have indicated that monitoring and auditing should be conducted to determine the efficacy or safety of pharmaceuticals and medical devices.

In parallel with these regulatory changes to clinical trials, the government of Japan has improved the conditions of clinical trials by implementing a promotion policy and budget in the medical innovation scheme. Subsequently, the Ministry of Health, Labour and Welfare (MHLW) formulated the Five-Year Clinical Trial Vitalization Plan 2012 in March, 2012 [12]. The goal of this plan was to increase the accessibility of new pharmaceuticals and medical devices and to assist in the search for the best treatments using a combination of

marketed pharmaceuticals and medical devices. MHLW thus launched the project, "Clinical Trial Core Hospital," which supports investigator-initiated high quality trials. Fifteen hospitals that were selected by MHLW as "Clinical Trials Core Hospitals" were granted priority to perform clinical studies. In addition, support was provided to each "Clinical Trials Core Hospital" to improve its quality of education, which may subsequently influence the quality and success of clinical trials and increase the employment rates. Furthermore, this project promoted the centralization of research and increased the national budget allowing high-quality trials that required smaller research funds to be performed. In June 2014, the revised medical service law was enacted and the "Clinical Trials Core Hospital" project was launched to identify eligible institutions [13]. It is planned to select up to 15 institutes as "Clinical Trials Core Hospital" in 2015, which have been granted by MHLW, and the criteria of eligibility is now under consideration.

In parallel with the creation of "Clinical Trials Core Hospital," the Japanese government established a new funding agency that would centralize medical research grant funding from the three ministries, namely, MHLW, Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Economy, Trade and Industry. The medical research core was called the "Japanese Organization for Medical Research and Development," and its corresponding act was approved in "Diet" in May 2014. This is considered the Japanese "National Institutes of Health (NIH)," which unifies research grants from around the country.

Improving the evaluation system for investigational medical care

In Japan, it has become a national rule that sufficient medical treatment, as part of the social security system, must be protected under the public health insurance system, so that people can receive suitable medical treatment regardless of taxation capacity. However, there has been an increase in the medical needs of patients, which is probably the consequence of recent advances in medical treatment schemes. Based on these needs, MHLW has established an evaluation system that combines public health insurance with innovative therapy and has been named as the "Evaluation System for Investigational Medical Care" [14]. The system is mandated to evaluate techniques that utilize unapproved or off-label pharmaceuticals and medical devices in select hospitals such as the "Clinical Trials Core Hospitals." These hospitals have been approved by the system to perform innovative and investigational medical care in combination with the health insurance, thus accelerating the collection of data that is essential in order to be covered by national insurance. This is the Japanese style of "Hospital Exemption" that has been implemented in EU, and the system has been improved in October, 2012. The results of the evaluation can also be used as reference when reviewing new or off-label products submitted for marketing approval. With this improvement, investigational medical care has been divided into two categories. Category A is allowed to perform trials only if the institution is deemed eligible. However, it can only use a limited amount of pharmaceuticals, medical devices, or clinical reagents. Category B is allowed to employ non-limited (unapproved or off-label) materials that have been determined to be safe and effective based on the GCP guidelines. Furthermore, the total insurance coverage for this special investigational medical care, such as regenerative medicine or personalized medicine, is also examined with a focus on its social validity and effectiveness. Several technologies in regenerative medicine or personalized medicine using an individual's own living cells may be too difficult to review in terms of marketing approval because the specifications of the final products vary with each case. In this evaluation system, investigational medical care is reviewed as a total technology, not as separate products. Therefore, the system does not focus on the specifications of the products but evaluates the entire technique, starting from the collection stage to the transplantation phase. Thus, the evaluation system is regarded as a more suitable system for regenerative medicine or personalized medicine.

Regenerative medical care using living cell transplantation and the new legal framework in Japan

Based on the need to develop innovative medical care, the field of regenerative medicine using living cell transplantation has been the global focus of research. Using living cells, regenerative medicine aims to regain the function of organs that have been damaged by illness or injury. This area of medicine thus increases the possibility of finding a treatment for diseases that have long been considered incurable.

Because regenerative medicine utilizes living cells, this innovative technology increases the risk for bacterial or viral infection and tumorigenicity. It is therefore imperative that sufficient safety measures are established. In the emergency economic policy measures (January 11, 2013; Japanese Cabinet decision), a reexamination of the special quick reviewing system for regenerative medicine was initiated. Based on the policy, the Regenerative Medicine Promoting (RMP) Act was established, which defines the duty of the government and citizens in Japan to utilize regenerative medicine, and a scheme for receiving regenerative medicine more quickly and safely was enacted by "Diet" on April 26, 2013 [15]. The RMP Act aims to comprehensively promote the use of regenerative medicine by ensuring that it is safe and does not present any ethical issues. On the basis of this act, the government has submitted the two acts relating to regenerative medicine [16]; one is the Act on Safety of Regenerative Medicine [4], and the other is the PMD Act [3]. In the Act on Safety of Regenerative Medicine, hospitals that wish to perform regenerative medical care using living cells should be reviewed by a certified special review board member and notify MHLW of the provision. On the other hand, hospitals can request a certified industry to manufacture specific cellular components that would be used in regenerative medical care. The regenerative medical care is divided into three categories on the basis of the risk of the technologies.

The PMD Act defines the category of regenerative medical products and conditional/time-limited authorization system. To perform an adaptive post-authorized clinical trial for determining the efficacy of a technology, the investigator is allowed to conduct an exploratory study. If the results clearly show efficacy and safety, the product is given conditional/time-limited authorization for use, which then facilitates in determining more suitable conditions for regenerative medical products. Regenerative medical products possess heterogeneous characteristics and are manufactured for a limited number of patients, particularly those who have developed incurable diseases. Based on this background, a major randomized and blinded pre-marketing clinical trial may not be feasible especially in orphan diseases, and prior authorization based on the epidemiological concept for effectiveness and public demand is considered. On the other hand, the products with conditional/time-limited authorization will have a duty to collect all patients' data and submit it to national patient's registry, which is planned to be established by MHLW. This is one type of adaptive licensing that has been utilized to improve product

accessibility to patients [17]. The limitation of this framework is that the concreate condition of approval is now under consideration and I think conditional/time-limited approval may be limited for the products for the intractable disease or orphan diseases.

Discussion

To eliminate medical disparities and to ensure "safe medical treatment," a secure system from which the Japanese society could receive the medical treatment with excellent hospitality from any facility is necessary [18]. On the other hand, the healthcare system of Japan is incapable of "specialization and centralization," thus becoming a weak point by which many resources invested in the field are later determined to be cost-ineffective. This present state of health care in Japan has become less attractive for researchers who want to conduct innovative product development. On the other hand, international researchers and sponsors who are interested in highly innovative fields such as regenerative medicine are constantly searching for optimal places to perform their research, as well as develop and market their novel technology. The Japanese government has embarked in transforming the medical institution by marketing these facilities as attractive venues for researchers and sponsors. The "Japan Agency for Medical Research and Development" and the "Clinical Trials Core Hospital" were established to promote research and development of medical innovative technologies. In the field of regenerative medicine using living cell transplantation, each "Clinical Trials Core Hospital" is assessed by a certified special review board and supported by national grants, with the vision of later becoming a world-renowned center for regenerative medicine. Within three years, some cellular- and tissue-based products will be submitted for marketing authorization based of the results of research cooperation between a sponsor and "Clinical Trials Core Hospital." The sponsor who aims at marketing regenerative medical products will be able to cost-effectively progress in technology or product development. These changes are envisioned to create an attractive place in Japan where researchers and developers could conduct investigations and research and development activities in regenerative medicine. In addition, "Clinical Trials Core Hospital" is planned to be granted and supervised by "Japan Agency for Medical Research and Development", which controlled the plan-do-check-act cycle of the development in "Clinical Trials Core Hospitals" and supported the collaboration with industries.

In addition to promoting innovative medical care and regenerative medicine, a new regulatory framework has been recently established. This framework is represented by three complementary acts, namely, the RMP Act, Act on the Safety of Regenerative Medicine, and the PMD Act. The Act on the Safety of Regenerative Medicine regulates the use of living cell transplantation techniques and supports a medical practitioner's research by permitting him or her to entrust the cell processing part of the research to an external industry. The PMD Act promotes the use of cellular- and tissue-based products by acting as the approving body that reviews the characteristics of these items. The RMP Act is responsible for investing in the field of regenerative medicine and in supporting the development of the field of regenerative medicine. This regulatory framework may facilitate in the development and the establishment of the safety of regenerative medicine and living cell transplantation techniques. This framework is also beneficial to patients because it increases their chance to receive a new treatment for an incurable disease, as well as the industry that develops the new cellular- and tissue-based products, or supports the medical practitioner to perform the living cell transplantation.

Through all plans, Japanese government aim to serve the new treatment for intractable disease's patients and increase the market scale of regenerative medicine to 10 billion dollars until 2020. It is our hope that the new regulatory framework is effectively applied and serves as the universal case model for the development of innovative medical care such as regenerative medicine using living cell transplantation.

References

1. (2012) Five-Years Medical Innovation Strategy.
2. (2013) Health and Medical Strategy [in Japanese].
3. (2013) Pharmaceuticals,Medical Devices, and Other Therapeutic Products Act [in Japanese].
4. (2013) Act on the Safety of Regenerative Medicine [in Japanese].
5. Hara A, Sato D, Sahara Y (2014) New Governmental Regulatory System for Stem Cell-Based Therapies in Japan. Therapeutic Innovation & Regulatory Science.
6. (2014) Medical Service Law [in Japanese].
7. (2014) Medical Practitioners Law [in Japanese].
8. Ministry of Health, Labour and Welfare (2003) Ethical Guidelines for Clinical Studies.
9. (2013) Pharmaceutical Affairs Law [in Japanese].
10. (1996) ICH Harmonised Tripartite Guideline Guideline for Good Clinical Practice E6 (R1).
11. World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310: 2191-2194.
12. (2012) 5-Year Clinical Trials Vitalization Plan 2012 [in Japanese].
13. (2014) Law on Establishment of the relevant Act to promote ensure overall care and medical care in the region.
14. (2012) Notificaiton of Evaluation System for Investigational Medical Care.
15. Cyranoski D (2013) Japan to offer fast-track approval path for stem cell therapies. Nat Med 19: 510.
16. (2013) Unknown territory Nature 494: 5.
17. Eichler HG, Oye K, Baird LG, Abadie E, Brown J, et al. (2012) Adaptive licensing: taking the next step in the evolution of drug approval. Clin Pharmacol Ther 91: 426-437.
18. Nomura H, Nakayama T (2005) The Japanese healthcare system. BMJ 331: 648-649.