Regenerative Therapy 4 (2016) 103–104

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Commentary

Response to Nature's editorial regarding the Japanese legal system for regenerative medicines

Daisaku Sato [a, *], Yuji Arakawa [b], Soichiro Isobe [b]

[a] Pharmaceuticals and Medical Devices Agency, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo, 100-0013, Japan
[b] Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, 1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo, 100-8916, Japan

ARTICLE INFO

Article history:
Received 31 March 2016
Received in revised form
15 April 2016
Accepted 28 April 2016

Keywords:
Regenerative medicine
Marketing authorization
Legal system

ABSTRACT

Nature's editorial, dated 10 December 2015, made several criticisms of the new Japanese conditional and time-limited marketing authorization system for regenerative medical products. We believe these comments were based on a misunderstanding of the purpose of the regulations, which are patient-oriented, offering patients access to promising regenerative medicines in a timely manner at reasonable expense while also ensuring the efficacy and safety of the medicines. The new regulatory system represents an attempt by Japan to accommodate unmet medical needs, particularly for life-threatening diseases, and is in line with current global regulatory trends to enable early patient access to new therapies.

1. Main text

Nature's editorial of 10 December 2015 [1] suggested that the new Japanese conditional and time-limited marketing authorization system for regenerative medical products represents a subsidy of commercial clinical trials, and would result in proliferation of unsuccessful treatments. We appreciate Nature's interest, but think these comments are based on a misunderstanding of the purpose of the Japanese system, which is patient-oriented. A key aim of the conditional and time-limited marketing authorization system is to open up new treatment possibilities for patients who otherwise have very limited or no treatment options. In other words, clinical trials of new regenerative medicines can be regarded as limited treatment opportunities for limited patient subpopulations. We have conventionally conducted review processes for orphan drugs from such a point of view. The new legal regulatory system for regenerative medical products is based on the same philosophy, taking account of the fact that evaluation of such products is often difficult due to heterogeneity when live cells are used as raw materials. The resulting non-uniform character will make confirmation of their effectiveness and quality characterization relatively difficult, compared with pharmaceuticals and medical devices.

An example of a product covered by the new regulations is the cultured autologous myoblast product, HeartSheet. This product has been given conditional and time-limited marketing authorization for patients who have heart disease with severe left ventricular dysfunction (LVEF) due to ischemic heart disease. As required for a conditional and time-limited marketing authorization, HeartSheet demonstrated its likely efficacy through the exploratory study (phase II trial (n = 7), using efficacy endpoints: LVEF, etc.). It was additionally required a confirmation of product efficacy and further safety measures, including limiting medical institutions with capable facilities and experts for use. For full approval, following its conditional and time-limited approval within 5 years, the postmarketing study protocol has been designed to compare survival rates between patients with and without HeartSheet [2].

Patients who are eligible to receive this treatment must satisfy the criteria of the New York Heart Association (NYHA) III or IV, and show LVEF < 35% despite having received all available treatments, including invasive therapy such as valve replacement. For such patients, who have heart disease with severe dysfunction, are non-

Abbreviations: NYHA, the New York Heart Association; LVEF, left ventricular ejection fraction; ICH, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; FDA, The US Food and Drug Administration.

Peer review under responsibility of the Japanese Society for Regenerative Medicine.

* Corresponding author. Tel.: +81 03 3506 9471; fax: +81 03 3506 9495.
E-mail address: sato-daisaku@pmda.go.jp (D. Sato).

http://dx.doi.org/10.1016/j.reth.2016.04.003

responsive to standard drug therapy, and have a poor prognosis [3], heart transplantation is the only definitive treatment option. However, there is an extreme shortage of donors for heart transplantation in Japan. Therefore, myoblast sheets provide a new treatment option, with likely clinical benefit for patients with severe dysfunction of the left ventricle caused by ischemic heart disease, who cannot receive a ventricular assist device or cardiac transplantation.

In this sense, the conditional and time-limited authorization of HeartSheet is purely patient-oriented, its aim being to make potentially promising treatment available in a timely manner to patients without other options, not to provide profit to biotechnology enterprises. It should be noted that a large part of the cost of such treatments is met by the Japanese health insurance system, not by patients themselves, as long as the treatment is considered reasonably likely to offer clinical benefit. It is provided under the "High-cost medical care benefit" scheme, which places a maximum limit on patients' monthly payment, depending on their income. For example, a patient who is under 70 years old, whose annual income is 30,000–62,600 USD (3.7–7.7 million JPY), and whose medical expenses are 122,000 USD (15 million yen)/month, would pay only 1900 USD (230,000 JPY)/month (1 USD = 123 JPY on 9 December 2015).

Japan is one of the founding members of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), and has a sophisticated product review system to ensure product safety and efficacy. As pointed out by Konomi et al. [4], to obtain conditional and time-limited approval, it is required that exploratory clinical trials predict a reasonable likelihood of clinical benefit (for example, by using a surrogate endpoint). This approach is consistent with the US Food and Drug Administration's (FDA's) accelerated approval scheme for serious or life-threatening illnesses (www.fda.gov). The accelerated approval allows for approval if the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity, but is subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit. Moreover, the European Agency (www.ema.europa.eu/ema/) is also putting forward an adaptive approach to conditional approval for early access, which is prospectively planned, and where uncertainty is reduced through collection of post-approval data on the medicine's use in patients [5]. It requires confirming the benefit-risk balance of a product, following a conditional approval based on early data (using surrogate endpoints) considered predictive of important clinical outcomes. The approval is granted in stages, beginning with a restricted patient population.

In conclusion, we would like to emphasize that the new Japanese conditional and time-limited marketing authorization system for regenerative medical products represents an attempt to deliver potentially beneficial treatments in a timely manner to patients who have few or no other options, while ensuring efficacy and safety. This approach is well aligned with current global regulatory trends to enable early patient access to new therapies, particularly for life-threatening diseases.

Conflict of interest

The authors have no conflict of interest to declare.

References

[1] Stem the tide. Nature 2015;528(7581):163–4.
[2] Konishi A, Sakushima K, Isobe S, Sato D. First approval of regenerative medical products under the PMD act in Japan. Cell Stem Cell 2016;18(4):434–5.
[3] Imamura T, Kinugawa K, Hatano M, Fujino T, Inaba T, Maki H, et al. Status 2 patients had poor prognosis without mechanical circulatory support. Circ J 2014;78(6):1396–404.
[4] Konomi K, Tobita M, Kimura K, Sato D. New Japanese initiatives on stem cell therapies. Cell Stem Cell 2015;16(4):350–2.
[5] Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. Clin Pharmacol Ther 2012;91(3):426–37.