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Does the Act on the Safety of Regenerative Medicine in Japan ensure "safety"?: Implications of low adverse event reporting

Tsunakuni Ikka,[1,2,*] Taichi Hatta,[3,*] Yoko Saito,[2] and Misao Fujita[4,5]
[1]Division of Bioethics & Healthcare Law, Institute for Cancer Control, National Cancer Center Japan, Chuo-ku, Tokyo 104-0045, Japan
[2]Division of Bioethics, Center for Research Administration and Support, National Cancer Center Japan, Chuo-ku, Tokyo 104-0045, Japan
[3]Graduate School of Public Health, Shizuoka Graduate University of Public Health, Aoi-ku, Shizuoka 420–0881, Japan
[4]Uehiro Research Division for iPS Cell Ethics, Center for iPS Cell Research and Application (CiRA), Kyoto University, Sakyo-ku, Kyoto 606–8507, Japan
[5]Institute for the Advanced Study of Human Biology (WPI-ASHBi), KUIAS, Kyoto University, Sakyo-ku, Kyoto 606–8501, Japan
*Correspondence: tikka@ncc.go.jp (T.I.), thatta@s-sph.ac.jp (T.H.)
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Public document analysis reveals that the adverse events reported for therapeutic administration under the Act on the Safety of Regenerative Medicine (ASRM) in Japan are substantially fewer than those under the Pharmaceuticals and Medical Devices Act. This study highlights the flawed reporting mechanisms and unmet legislative intentions of the ASRM.

The Act on the Safety of Regenerative Medicine (ASRM) was established to ensure that physicians follow procedures prescribed by law for the safe implementation of regenerative medicine (RM). We reported the lack of important concepts to regulate the process of translating research into treatment under the ASRM (Fujita et al., 2022); the serious issues with the validity of therapeutic plans implemented under the ASRM; and the independence, integrity, and quality of Certified Committees for RM (CCRMs) (Ikka et al., 2023). Here, we focus on the number of adverse event (AE) reports as an indicator of the safe implementation of RM and discuss serious doubts regarding the ASRM's guarantees of RM safety.

ARE ADVERSE EVENTS IN RM UNDER THE ASRM REPORTED?

The ASRM requires RM providers to report AEs suspected to be caused by the provision of RM to a CCRM and the Ministry of Health, Labour and Welfare (MHLW) in Japan. Seven types of AEs are mandated to be reported to both parties: (1) death, (2) cases that may lead to death, (3) cases that require hospitalization or prolonged hospitalization at a medical institution for treatment, (4) disability, (5) cases that may lead to disability, (6) serious cases, and (7) congenital disease or abnormality in later generations. In addition, cases of diseases or infections other than these seven need to be reported only to a CCRM. Thus, there is a difference in the number of AEs identified by the MHLW and the CCRMs.

The MHLW publishes the annual number of AEs (MHLW, 2022), the number of patients receiving RM, and the number of annually administered cells (MHLW, 2020, 2021). In addition, CCRMs must disclose their meeting minutes (including deliberations on reported AEs) since April 2019. Using these published data (method details are provided in supplemental information), we determined the number of administered cells and AE reports in fiscal year (FY) 2019 and 2020 (Table S1).

The number of cells administered for "therapy" was substantially greater than that for "research," although fewer AEs were reported for "therapy." This finding may be interpreted as unsurprising, as the safety of RM in research has not yet been established, whereas the safety of RM in therapeutical settings has been determined. Whether this interpretation is correct needs to be investigated.

COMPARISON WITH AE REPORTS FOR TREATMENTS UNDER THE PMD ACT

To address the above question, we investigated the number of treatments (synonymous with the number of cells administered under the ASRM) and the number of AEs reported as "RM treatment" under another legal system in Japan. The Pharmaceutical and Medical Devices Agency (PMDA) verifies the safety and efficacy of an RM product and approves its manufacture and marketing under the Act on Securing Quality, Efficacy, and Safety of Products, including the Pharmaceuticals and Medical Devices Act (PMD Act). A product distributor must report the occurrence of AEs suspected to be caused by side effects or defects in RM products to the PMDA if an AE occurs after the use of the product by physicians to treat a patient. The following six types of AEs are to be reported: (1) death, (2) disability, (3) cases that may lead to death or disability, (4) cases that require hospitalization or extended hospitalization at a medical institution for treatment, (5) serious cases according to the aforementioned criteria, and (6) congenital disease or abnormalities in later generations. In addition, these six potential AEs owing to defects in RM products are also subject to reporting.

Summaries of all AE reports for RM products have been published since November 25, 2014, when the PMD Act came into effect (PMDA, 2023). We estimated the accurate

number of treatments for three RM products (Jace, Jacc, and Temcell HS) on the basis of National Database (NDB) open data (MHLW, 2023), as these were the only products for which the number of annual uses was reported (Table S2). These published data were used (research method details are provided in supplemental information) to determine the number of treatments and AE reports using RM products in FYs 2019 and 2020 (Table S1).

One AE was reported for every three to four treatments using RM products under the PMD Act. By contrast, a single-digit AE report was received for every 100,000 administrations of RM therapy under the ASRM. This difference in reporting is unexpected, considering that the central content of reportable AEs in both legal systems shares common elements and assuming that the safety of the RM product approved by the PMDA following clinical trials is better established than the safety of therapy solely reviewed by a CCRM. Although one might expect AEs under the PMD Act to be more numerous because of the severity of target diseases of three products and the invasiveness involved in their use, many diseases targeted by RM under the ASRM are also serious, including cancer (Fujita et al., 2022), and the procedures for RM are not markedly less invasive than the three products, including procedures such as intravenous injection and implantation.

SIGNIFICANCE OF AE REPORTING FOR MEDICINE

The difference in the number of AE reports in the two systems suggests that AEs are inappropriately reported under the ASRM. Arita and Tobita also questioned the absence of AE reports in Japan for platelet-rich plasma (PRP) therapy, which accounts for approximately 66% of RM plans (the most common RM) in Japan, despite several reports of AEs overseas (Arita and Tobita, 2023).

Furthermore, a case reported in the press confirms our speculation (Kyodo News, 2023). A woman who underwent the cosmetic RM plan reported complications and AEs: "the whole face was swollen and misshapen," but the physician did not address her claim. She was eventually treated for recovery at another hospital. The plan included the use of PRP with basic fibroblast growth factor (bFGF), which is a dangerous method according to the practice guidelines of several societies (The Japanese Dermatological Association et al., 2022). However, as far as we have investigated, there is no indication in the meeting minutes that this AE case was reported to any CCRM.

We consider that RM providers are not the only cause of the small number of AE reports. CCRMs should scrutinize the lack of AE reports in the reviewed RM plans, but such close scrutiny cannot be expected from a CCRM that is a close stakeholder of therapy providers (Ikka et al., 2023). Similarly, the MHLW, acting as the administrator of the ASRM, should question the small number of AEs reported throughout Japan. Although the approval process for RM products under the PMD Act has received criticism (Cyranoski et al., 2023), there are three measures for safety—(1) limiting their use by medical institutions, (2) providing guidelines to promote the optimal use of each product, and (3) implementing a post-marketing adverse reaction relief system (Fujiwara et al., 2021)—and numerous AEs have been reported for RM products, ranging from serious to minor. The PMDA (PMDA, 2021), which reviews and approves RM products, states that "approval of a product is just the beginning, and appropriate management and measures after marketing (such as ensuring proper use of the product) are important." The differences in understanding the concept of "safety" between those involved in implementing the ASRM and the PMD Act are notable.

Verifying the results of RM implementation is crucial, as the primary objective of the ASRM is to ensure the safe implementation of RM. It is important to note that absolute safety cannot be guaranteed in medicine. The lack of awareness regarding the purpose and responsibilities of the ASRM on RM providers, CCRMs, and the MHLW is a critical issue that raises fundamental questions over the raison d'être of the law, as Lysaght and Sugii warned (Lysaght and Sugii, 2016). We agree with the recent recommendation by the International Society for Cell and Gene Therapy that the data collected through improved AE reporting systems that include patient reports will create effective regulation of unproven cell therapy (Ikonomou et al., 2023). Each country is encouraged to verify whether its national AE reporting systems are functioning as a prerequisite to implementing this suggestion. In particular, it would be desirable to amend the ASRM to incorporate this suggestion.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2023.10.012.

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AUTHOR CONTRIBUTIONS

Conceptualization, T.I.; methodology, T.I. and T.H.; investigation and validation, T.I., T.H., and Y.S.; writing – original draft, T.I.; writing – review & editing, all authors; supervision, M.F.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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