VIEWPOINT

Identifying the Risks of Unproven Regenerative Medicine Therapies

Peter W. Marks, MD, PhD
US Food and Drug Administration, Silver Spring, Maryland.

Stephen Hahn, MD
US Food and Drug Administration, Silver Spring, Maryland.

In the middle of the coronavirus disease 2019 (COVID-19) public health response, many priorities are currently competing for the attention of the US Food and Drug Administration (FDA). Some of these are directly related to the pandemic, but others have been challenging issues for years. Over the past several years, hundreds of clinics across the US have been offering unproven regenerative medicine therapies to patients for the treatment of conditions ranging from aging to arthritis to autism.[1,2] Some of these same clinics are now offering similar unproven products for the treatment of complications of COVID-19 and are making claims that are simply not supported by compelling clinical data. Overall, the safety and efficacy of regenerative medicine products outside a narrow range of indications have yet to be demonstrated.[3]

The products administered by clinics under the broad rubric of regenerative medicine include those derived from individuals' own bone marrow or fat, those derived from birthing tissues such as placenta or cord blood obtained from a donor unrelated to the recipient, as well as products that are secreted or derived from unrelated donor cells. Despite assertions by some individuals to the contrary, these products, whether autologous or allogeneic, are not inherently safe and may be associated with serious adverse consequences. This is particularly true for those products that are not manufactured consistent with current good manufacturing practice. Lapses in good manufacturing practice are likely responsible for numerous serious bacterial infections requiring hospitalization. Such lapses may also be responsible for noninfectious complications due to substances introduced during the manufacturing process, as potentially was the case for 3 individuals who developed blindness following treatment with unproven and unapproved stem cell products.[4] The increasing number of adverse events being reported following the widespread use of unapproved regenerative medicine therapies at hundreds of clinics across the country make it necessary for the FDA to act to prevent harm to individuals receiving them.[1]

> It is time for unproven and unapproved regenerative medicine products to be identified and recognized for what they frequently are: uncontrolled experimental procedures at a cost to patients, both financially and physically.

Unapproved regenerative medicine therapies are concerning precisely because they have not been treated as what they are: investigational therapeutics for which evidence for safety and efficacy is not available. Many of these products do not meet the criteria of the FDA's regulations to obviate the need for premarket authorization because they require significant manufacturing or are used in a different way in the recipient than in the donor, so they require study under an Investigational New Drug application and premarket approval. Companies involved in selling products that violate the regulations do so under the erroneous assertion that they are exempt from these FDA provisions. Because these unproven regenerative medicine therapies are being administered without regard to the FDA's regulatory oversight, it is impossible to know with certainty the number of individuals who have experienced serious adverse events following their administration.

To protect the public from unproven regenerative medicine therapies that have caused harm or have the potential to cause significant harm, the FDA has taken a variety of compliance and enforcement actions over the past several years, ranging from letters to manufacturers telling them that they are in violation of federal statutes and FDA regulations to seizing products that were considered dangerous to public health. However, the agency needs the engagement of both clinicians and patients to help to ensure that instead of remaining unintentionally or intentionally hidden, potentially harmful unapproved regenerative medicine therapies are identified and removed from the market. Medical professionals, such as primary care physicians and advanced practice nurses, are often in the best position to help patients identify whether a regenerative medicine therapy is appropriate for them to pursue, including whether a proposed therapy is being administered under the appropriate regulatory oversight.[5]

To summarize, in addition to consulting with their primary health care clinician, prior to considering cellular therapies, patients should ask if the therapy is approved by the FDA. If it is not, they should ensure that an active Investigational New Drug application is on file with the FDA, and they should expect to review and sign an informed consent (**Box**). Patients and their families also should not expect to be charged for investigational products they receive. An exception is cost recovery, whereby the sponsor provides evidence from a clinical trial to the FDA that a product may provide clinical benefit and the sponsor is then permitted to charge for manufacturing of the product but may not make a profit.

Corresponding Author: Peter W. Marks, MD, PhD, Center for Biologics Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, WO71-7232, Silver Spring, MD 20993 (peter.marks@fda.hhs.gov).

Box. Appropriate Practices for the Investigation of Unproven Regenerative Medicine Therapies

- Active Investigational New Drug (IND) application for the specific product in development is on file with the Food and Drug Administration
- Requirement for the provision of written informed consent in an institutional review board–approved clinical trial under an IND
- No charge is requested from the patient for the unapproved product or for participation in the clinical trial[a]
- Reporting of potential adverse events is encouraged and clear mechanisms are provided on how to do so
- A summary of results is reported back to those enrolled in the clinical trial

[a] Under circumstances in which there is some evidence of clinical benefit, the Food and Drug Administration permits sponsors to obtain cost recovery for direct costs associated with providing an investigational product under an IND. However, the amount charged cannot exceed the actual cost to make the product, as documented by a certified public accountant.

Patients participating in clinical research should also expect to receive information regarding the results of the trial in which they have taken part. If questions remain, clinicians should consider contacting the FDA directly with their questions or concerns.[6]

Perhaps most important, individuals who have chosen to pursue cellular therapies should be encouraged to report adverse events for products or treatments that they may have received, even if they have paid for them. They should also be encouraged to allow family, friends, or clinicians to report such events. Patients and their clinicians should use the MedWatch form FDA 3500 (Voluntary Reporting for Use by Health Professionals, Consumers, and Patients) or the more patient-friendly form FDA 3500B to report adverse events that they perceive may be related to the administration of a cellular product.[7] If a patient, family member, or their clinician is unsure of the nature of the cellular product that the patient has received, simply noting "stem cell therapy" as the administered product is sufficient. The FDA will investigate the nature of the product as part of its evaluation of the event. Only through the reporting of such events will it be possible for the FDA to gain a better understanding of the potential spectrum of adverse events associated with these therapies. Having these data could help future patients make more informed decisions and identify products for which FDA intervention is rapidly required because they are causing patient harm.

It is time for unproven and unapproved regenerative medicine products to be identified and recognized for what they frequently are: uncontrolled experimental procedures at a cost to patients, both financially and physically. Patients and their caregivers should feel empowered to report adverse events to help make sure that purveyors of unproved products are identified, and the FDA can take appropriate action to bring them into compliance and thereby help protect more patients from harm. This goes to the core of the mission to which the FDA is committed: promoting and protecting the public health.

ARTICLE INFORMATION

Published Online: June 17, 2020. doi:10.1001/jama.2020.9375

Conflict of Interest Disclosures: Dr Hahn is Commissioner of Food and Drugs, US Food and Drug Administration (FDA). Prior to his appointment to the FDA, he was Chief Medical Executive at MD Anderson Cancer Center. Dr Marks does not have any conflicts of interest to disclose.

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