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Perspective

Clarifying Stem-Cell Therapy's Benefits and Risks

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The current excitement over the potential for stem-cell therapy to improve patient outcomes or even cure diseases is understandable. We at the Food and Drug Administration (FDA) share

this excitement. However, to ensure that this emerging field fulfills its promise to patients, we must first understand its risks and benefits and develop therapeutic approaches based on sound science. Without a commitment to the principles of adequate evidence generation that have led to so much medical progress, we may never see stem-cell therapy reach its full potential.

The safety and efficacy of the use of stem cells derived from peripheral blood or bone marrow for hematopoietic reconstitution are well established. Increasingly, however, hematopoietic stem cells and stem cells derived from sources such as adipose tissue are being used to treat multiple orthopedic, neurologic, and other diseases. Of-

ten, these cells (whether derived from autologous or allogeneic sources) are being used in practice on the basis of minimal clinical evidence of safety or efficacy, sometimes with the claim that they constitute revolutionary treatments for various conditions.

Despite the absence of compelling evidence from adequate, well-controlled clinical trials, some practitioners assert that stem cells have a unique capacity to restore health because they can sense their environment and differentiate in a manner that repairs any defect. A separate argument is that conducting controlled trials and meeting regulatory standards for such promising therapies is too complex for all except large industrial sponsors and that therefore broad

use in clinical practice should be allowed and encouraged while evidence regarding efficacy is gathered. Proponents of both arguments generally assert that stem-cell therapies are quite safe, particularly when the cells are derived from an autologous source.

Outside the setting of hematopoietic reconstitution and a few other well-established indications, the assertion that stem cells are intrinsically able to sense the environment into which they are introduced and address whatever functions require replacement or repair — whether injured knee cartilage or a neurologic deficit — is not based on scientific evidence. Published data derived primarily from small, uncontrolled trials plus a few well-controlled, randomized trials have not reliably demonstrated the effectiveness of stem-cell treatments even in some of the most systematically studied conditions, such as heart failure and graft-versus-host disease.^{1,2}

This lack of evidence is worrisome. The literature is replete with instances of therapeutic interventions pursued on the basis of expert opinion and patient acceptance that ultimately proved ineffective or harmful when studied in well-controlled trials comparing them with the standard of care. One of the most unfortunate therapeutic misadventures in contemporary times was the widespread use of autologous stem-cell transplantation to treat metastatic breast cancer, a practice ultimately shown to be ineffective, costly, and risky.

Claims that therapies are safe and effective must be based on evidence. Standards of evidence help keep unsafe or ineffective therapies out of routine use, while permitting adoption of therapies with a favorable risk-benefit balance. Before the 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act were passed, thousands of ineffective and dangerous therapies were routinely used despite their merely anecdotal support. After the amendments' passage, the FDA adopted a standard of evidence for efficacy based on phased product development culminating in evaluation in randomized, controlled trials. Congress has since added flexibility to the FDA's approach, and guidance based on subsequent legislation details approaches that can expedite product development or provide support for development programs.

The safety of stem-cell therapies for indications other than hematopoietic reconstitution also cannot be taken for granted. In one recent case, a patient was treated with multiple injections of allogeneic stem cells from different sources that were intended to

reduce neurologic deficits stemming from a middle cerebral artery stroke.³ The injections were associated with the development of a glioproliferative lesion, which led to paraplegia and ultimately required radiotherapy.

Although autologous stem cells may typically raise fewer safety concerns than allogeneic stem cells, their use may be associated with significant adverse events. Autologous hematopoietic stem cells injected into the kidneys of a patient with renal failure resulting from systemic lupus erythematosus were associated with the development of tumors (angiomyeloproliferative lesions) that eventually led to nephrectomy.⁴ In another instance, autologous stem cells derived from adipose tissue and injected intravitreally into the eyes of people with macular degeneration were associated with worsening vision in three people, two of whom became legally blind.⁵

And stem-cell therapies have been associated with other adverse effects as well. Furthermore, such adverse effects are probably more common than is appreciated, because there is no reporting requirement when these therapies are administered outside clinical investigations. The occurrence of adverse events highlights the need to conduct controlled clinical studies to determine whether these and allogeneic cellular therapies are safe and effective for their intended uses. Without such studies, we will not be able ascertain whether the clinical benefits of such therapies outweigh any potential harms.

Mammalian cells comprise tens of thousands of different proteins, lipids, carbohydrates, and other molecules, all interacting in

an extraordinarily complex manner. This complexity makes it challenging, if not impossible, to predict cellular behavior a priori when these cells are introduced into a new environment, and empirical data are therefore necessary to document safety. There is no scientific reason to believe that demonstration of efficacy for stem-cell products should be any different from that for other biologic products. For treatments that truly provide an impressive benefit to patients, the FDA does not require larger studies than are needed to prove that benefits outweigh risks, and when benefits are dramatic, trials for regulatory approval can be modestly sized. For example, a statistically significant 100% improvement in an outcome measure ($\alpha=0.05$, $\beta=0.1$) could be detected with a randomized trial involving as few as 42 participants.

We believe that the assertion that existing standards for regulatory approval are too rigorous for stem-cell therapies results largely from a lack of familiarity with the available pathways for developing cellular therapy products and from the lack of a systematic, facilitated approach to assembling the clinical data necessary to support the licensure of stem-cell therapies produced by individual practitioners at different sites. For serious and life-threatening diseases in which there is unmet medical need, expedited pathways are readily available. The field of oncology in particular has successfully relied on these pathways to develop creative approaches that generate the evidence that patients and physicians need to have confidence in marketed drugs and biologics. For applications in non-

life-threatening situations such as accelerating healing after orthopedic surgery, modestly sized trials could most likely demonstrate a favorable benefit-risk profile, given the relatively large numbers of patients who undergo such surgeries. Such trials would allow truly effective cell preparations and delivery methods to move forward along developmental pathways.

The FDA is committed to facilitating the development and ultimate licensure of safe, effective stem-cell therapies. We can do so by engaging frequently with developers to optimize the efficiency of their programs; ensuring that they make full use of programs designed to expedite advancement and approval of new products (e.g., breakthrough therapy designation,

accelerated approval); and establishing innovative approaches to evidence generation that allow smaller sponsors or researchers to develop needed data collaboratively.

We believe that addressing the unique challenges of stem-cell clinical research provides an important pathway for ensuring that safe, effective stem-cell therapies are readily available to patients in need and for building the scientific foundation for further advances. The FDA is committed to working with investigators and sponsors who are developing the evidence needed to ensure that innovation in this field delivers on its promise for patient care.

Disclosure forms provided by the authors are available at NEJM.org.

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