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PERSPECTIVES

Cell-Based Therapies: The Nonresponder

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SUMMARY

Cell-based therapies have come of age and several phase III trials are now being conducted. Cell-based therapies, especially involving mesenchymal stem cells (MSCs), have substantial nonresponder rates, as has been reported in some current clinical trials. This high rate is expected as the MSCs are neither tuned for each of the diseases that are being treated nor for the huge variance in the genetics and response characteristics of the individual patients being treated. Such nonresponders might be used as a control group, thus eliminating the need for placebo controls. STEM CELLS TRANSLATIONAL MEDICINE *2018;7:762–766*

SIGNIFICANCE STATEMENT

For every prescription or over-the-counter drug now approved and sold to patients, there is a significant rate of nonresponders. These drugs show high efficacy in responder populations, but there is a group of patients that do not respond for reasons not well understood. Cell-based therapies, like those using MSCs, also have a substantial nonresponder group which can be as high as 60% of the patients. This is, in part, due to two issues: the fact that the medicinal cell preparation is not optimized for the disease state being treated and because the responsiveness of patients to these cells has not been ascertained. The "tuning" of cells for therapeutic use represents the next technical challenge for cell-based therapies. In the interim, this expected nonresponder group could be used instead of placebos to represent the base or floor of the clinical response.

INTRODUCTION

What do we now know about the process of bringing cell-based therapies into our health care system? Cell-based therapies started with blood transfusions exactly 200 years ago and bone marrow transplants 62 years ago [1, 2]. The regulatory agencies at the local, national, and worldwide level, more or less, took a "hands-off" approach as most of these procedures are life-versus-death issues and most are obligatory transfusions. This hands-off approach still requires stringent safety procedures for handling cells, storing them, and reactivating them. So, although it is hands off, there has been considerable oversight regarding the how, where, and when of the procedure, with most efficacy studies derived from academic practitioners reporting short- and long-term outcomes [3, 4]. The health care industry itself has come a long way with regard to cell-based therapies and has pioneered new products and procedures in both the life-versus-death and quality of life sectors. The recent approvals of mesenchymal stem cell (MSC) for graft-versus-host disease [5, 6] and CAR-T therapies for cancers are evidence of how far we have come [7]. I will focus on MSC therapies, where I have some considerable experience, because I see some important milestones; I will propose here some potential changes in logics for the progression of regulatory rules for these MSC-based therapies. I will focus on the non–life-versus-death aspects of MSC therapies although I will use the data from the graft-versus-host clinical trials to justify my suggested changes. It is important to stress that non–life-versus-death conditions have long-term consequences, which must be more thoughtfully considered by both regulatory and third-party payer agencies.

HISTORICAL

We and others developed MSC-based therapies in the late 1980s and early 1990s based on several false assumptions [8, 9]. First, human MSCs (hMSCs) were successfully isolated and culture-expanded from bone marrow with parallel successes from rodents and other animals [10–12]. Two facts were established early: first, that the MSCs were culture dish adherent and that they could be induced in culture into several mesenchymal lineages, thus warranting my suggested use of the name "stem cell" [13]. With this as a basis, we established a company, Osiris Therapeutics, Inc. (Columbia, MD) as a bio-orthopedic company for the tissue engineering of autologous skeletal tissue focusing on cartilage and bone from MSCs; again, based on the assumption that they were stem cells. Indeed, hMSCs are stem cells in culture, but not in vivo.

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The second false assumption was that the multipotential capacity of the marrow MSCs in culture would be reflective of the activities that would be observed naturally in vivo [14]. Furthermore, it was incorrectly assumed that the MSCs were derived from the "stroma" of marrow [15]. When MSCs were isolated from other tissues, it was likewise falsely assumed that the MSCs were derived from the stroma (connective tissue) associated with the starting tissue. Again, for emphasis, the additional false assumption was made that there were in situ multipotent progenitors situated in the surrounding connective tissue of all mesenchymal tissues to provide progeny that would naturally replace expiring cells as all terminally differentiated cells have lifetimes and are routinely replaced in the circulation and all vital tissues and organs.

Based on the above false assumptions, the dogma of the day was that the MSCs were vital to the bone marrow stroma and that for bone marrow transplantations, the addition of exogenously provided MSCs would strengthen the marrow scaffold to enhance the engraftment of the hematopoietic progenitors and to speedup recovery of the hematopoietic system, thus de-risking the patient from infections or graft-versus-host disease. The first-in-man trials of exogenously expanded autologous MSCs added to bone marrow transplantations was started by us and it was proved to be highly successful [8]. This led others [16] in adults and especially at Osiris to provide data that allogeneic MSCs could be used quite spectacularly in children who were on death's door with graft-versus-host disease [17]. We now know that the mechanism for these very positive results had nothing to do with the marrow stroma and were attributable to the intense paracrine properties of the MSCs with especially potent immunomodulating components. With this clinical experience, it was soon established that MSCs had strong immunomodulatory and trophic activities that had medicinal effects [18]. This challenged the multipotentiality logic and suggested that the MSCs had a strong paracrine activity but not stem cell activity in vivo.

There was an explosion of interest in adult-derived MSCs when President Bush banned the use of federal funds for the study of embryonic stem cells in 2001; we worked with ADULT stem cells, which allow an exponential increase in interest and experimental activity using MSCs. This resulted in the publication of reports that MSCs could be isolated and culture expanded from almost every tissue of the body including menstrual flow specimens [19]. By 2008, it was clearly documented that MSCs were derived from perivascular mesenchymal cells, pericytes, and resident on every blood vessel in the body including the capillaries and sinusoid of marrow [20]. In fact, we now know that marrow contains a heterogeneous mixture of MSCs [21], perhaps 4–7 or more different subsets, and that with each subculture or passage, there is a selection process clearly dependent on the composition of the culture medium and the genetics of the donor MSCs [22].

Today

Given the misconceptions of the past and the fact that MSCs are not stem cells, as the originator of the name MSC in 1991 [13], I renamed MSCs as *medicine signaling cells* to focus on their broad range of clinical activities and how they were being used in clinical trials [23]. If one puts "mesenchymal stem cells" into the search engine on the website clinicaltrials.gov, more than 850 clinical trials are listed with more than 365 that are active worldwide. These trials cover a huge spectrum of clinical symptoms from MS and ALS to sepsis, all or most predicted on animal models and many of which use hMSCs from marrow, fat, and umbilical cord as the most popular sources of the curative MSCs. I focus on the corporate website press reports and published papers of clinical trials for the information I use to propose new logics for clinical trials. That said, it is impossible to estimate the number of patients that have received MSCs for different therapies because a large sector of use has not been reported (from domestic or offshore clinics). Estimates of the number of patients provided MSCs range from 10,000 to over 70,000 with no reported MSC-related serious adverse events warranting shutting down any trials [24, 25].

The Nonresponder

In carefully reviewing the publically available clinical data, I was struck by the high percentage of nonresponders in MSC clinical trials not involving the hematopoietic system. For example, Mesoblast, Inc. (which purchased all of Osiris' cell-therapy portfolio, October 2013) clinical trial on low back pain shows at least 50% of the patients did not respond to the injection of MSCs as early as 1–3 months into the trial [26]. Of the initial responders, most had sustained pain relief for 3 years. In these placebo-controlled trials, the placebos had some limited reported positive effects, but in a statistically lower frequency, duration, and intensity. Mesoblast is now conducting a multicenter phase III trial for low back pain based on their previous data. I have not contacted Mesoblast and only use them as an example. My use of this example reflects my esteem for the company and is not meant to suggest that their current approach is wrong or not valid.

The question can be raised as to the exact definition of a nonresponder, which, in itself, is both a quantitative and duration issue. The question arises because some placebo controls exhibit a response, and thus a responder must not only show a large quantitative clinical change, but it must also be sustained. For example, in clinical trial injection of hyaluronan (HA) into osteoarthritic joints, the placebo controls were patients receiving injections of 2 ml saline. Some saline-injected patients experienced substantial pain relief for 6 months. The problem with this data set is that the nonresponders were not identified in either the placebo or treated group [27]. As pointed out by Lohmander et al. [28], the data look different if you identify the responder group. The key issue here is that if patients exhibit a "little" pain relief, are they a responder or nonresponder? My view is that these borderline cases can be negotiated between the company/investigator and the regulatory agency when the trial details are established before the trial starts. Lastly, the issue of back pain stabilization must also be considered: is some pain stabilization a response or nonresponse? Again, if the company wants to claim pain "relief" then stabilization is not an improvement; if stabilization of pain is going to be part of the company's claim, then this must be articulated upfront before the trial begins; although, I would argue that pain stabilization is not a benefit that can be sustained for long term given the natural progression of these conditions.

I would propose that Mesoblast does not need the placebos in their phase III trial and that they can identify the nonresponders by a surrogate analysis as early as at the 3-month time point. I would propose that the nonresponders should be followed for long term to ensure that the MSC procedure is *safe* even for nonresponders, but that the efficacy calculation be based on the number of initial responders and the percentage that maintain the positive outcomes for a fixed duration, say one year (although I would ask that they also be followed for 5–8 years after approval to ensure safety). To receive FDA approval based on the outcomes of the responders at 1 year, the physician who administers the approved product must make known to the patient that the product has, at least, a 50% nonresponder rate.

The above proposal of eliminating the placebo control is based on the data available from phases I and II studies where the cell product is deemed safe and the placebo response rate has been documented to be substantially below the clinically effective rate of the treated group. The onus is on the company to ensure that each practitioner is properly trained in the use of its product so that the site/practitioner variability is minimized. This site/practitioner variability can be accurately accessed in the outcome data from each site; indeed, it would be best to access variability and efficacy at the 3-month nonresponder designation. If all the treated patients are nonresponders, then the batch of product or the practitioner would be the issue.

Because I have low back pain, I, for sure, do not want to be the placebo and why should I be the experimental cohort that proves that the product works in someone else. I am not alone in this view and this "attitude" is why some trials take a very long time to enroll their cohorts into the study. If the product MSCs are safe and the procedure can be standardized, then why the placebo? There are lots of reasons, but I would argue that the long-term benefit can only be accessed from the responding cohort.

Tuning

Why there is such a high nonresponder rate of using cell-based therapy? There are several reasons for the wide variation in response: first, the actual diagnosis can be flawed by the inability to provide a clear cause for the problem and the penetrance can be conditioned by the patient's ability to describe the issue and quantitate the severity of the pain or other problems. For example, low back pain is completely subjective and relates to the pain tolerance of the patient, the length of time the issue has made itself known, and other intangibles. Certainly, this is a quality of life issue that can be managed with gabapentin or other pain medications, but this can cause long-term psychologic and physical problems. "Fix it" is what both the patient and practitioner want.

Second, the same production runs of MSCs have been used for acute myocardial infarcts, low back pain, graft-versus-host disease, and diabetes. Thus, the MSCs are not specifically optimized (tuned) for the disease being treated. One would hope of choosing an MSC donor whose cells provide an optimal response to the disease microenvironment or by pretreating the donor cells to initiate a more powerful response for the disease being treated that the number of nonresponders would be diminished or minimal [29].

Third, predetermining that a patient, because of their genetics or medical history, is likely to be a nonresponder could likewise decrease that rate of nonresponders [29]. Although this issue is more challenging, it is the least studied. No current efforts to identify nonresponders exists yet the rewards are high in cost savings and speed through clinical trials. For example, I would propose as a first step if an immune issue is the target of MSC therapy, draw a sample of the patient's blood, and do a simple MLR with a standardized sample of MSCs or with the MSCs being used in the trial. In this case, the question is "what are the response characteristics of the patient's circulating immune-sensitive cells?" I also wonder if an osteoarthritic knee responses with an observed diminution of pain after an injection of 2 ml of saline, whether this is a first-order test to identify a responder?

The Formal Proposal

I propose that for cell-based therapies, MSCs in particular, do not set up phases I, II, or III trials as if they are drugs. MSCs are not drugs; they are cells that are home to body sites of damage, disease, or inflammation and then are activated by the microenvironment of the docking site. Many diseases or illnesses have multiple anatomic sites: stroke involves brain and spleen whereas heart attack involves heart muscle, vasculature, and the lymph system (it may be that the lung is also compromised; MSCs have been shown to improve lung function in AMI patients). In a product like MSCs from a single company like Mesoblast, the establishment of safety should be rather straightforward. If in a clinical trial, the effective dose is known especially for single or multiple injections into the back or knee, the timely medical follow-up and/or surrogate assay can be used to identify the nonresponders at 1–3 months. The efficacy of the responders should be the basis for approving the MSCs by the regulators. This would allow a relatively few people to enter the trial, certainly not as many are used in drug trials. Once these cell-based products are approved, the practitioners must properly consent the patient by telling them that X% could be nonresponders. For sure, with expedited approval, the company must follow the patients for 5–8 years and report the yearly outcomes in a publicly accessible website on a practitioner basis. The companies should be able to afford to do this as, hopefully, these approved products should be paid for by third-party payers. This proposal will shorten the approval process while ensuring that long-term outcomes become accessible to the lay public. The key issue here is to ask for a major change in third-party payers' modus operandi where they withhold reimbursement approval until the clinical data are "compelling." This is the capitalistic system at its worst. For emphasis, if only 40% of patients receive benefit that many not be compelling. Access of all the strata of our society to the newest medical miracles must be the moral bottom line of our health care system and this access is controlled by payments from third-party payers.

High nonresponder rates and physicians who properly consent patients do open-up obvious medical-legal issues: if the doctor knows that it is not going to work 50% of the time, why did the physician even attempt to use it on my client? (you can hear the lawyers now). The important issue is that if the procedure works even 30%–40% of the time, some third-party payers

might refuse to cover the costs of such a low success rate. I would argue that if it works, pay for it; if it does not work in all of the patients, provide incentives to improve its efficacy, but do not deny its use. Some HIV vaccines only have a 30%–40% protective effect yet their use has huge medical and economic benefit in long term. Likewise, pain relief from OA can have both direct and societal benefits that are comparable to protecting against a terrible communicable disease like HIV.

Implicit in this proposal is the additional legal and moral obligation of third-party payers to financially support the approval by paying for the procedure in an expedited fashion. Not only is the approval process currently slow, but also the lag time for third-party payers is criminally long and tortuous for the unsophisticated lay public. The wealthy can have MSC therapy whenever they want, the middle-class access is limited, and the poor have no access. Approval should mean that the payment code comes quickly (in Japan, approval comes with a price and a code). I fully understand the practical difficulty with the third-party payer refusals and slowness in recognizing new technologies and, indeed, the fact that the nonresponder issue raised here would make payments even slower; that said, a variety of changes in our health care system would be required if nonresponders could be separately recognized.

Key to approval is that the product is safe, that it shows some efficacy, and that the product is or can be optimized. The long-term follow-up and practitioner site-specific outcomes are easily made publically accessible either through a registry or through a manufacture's outcome website will allow a level of transparency that does not currently exist. These proposals do not intrude on the patient–physician relationship yet provides a level of transparency now provided by the bone marrow transplant registry.

FDA

It is very important to understand that this thesis is not anti-FDA. Quite the opposite, I believe that the FDA is essential for a variety of ethical and logical reasons. Indeed, the FDA understands the nonresponders issues. For example, in very high dose IL-2 exposure, less than 15% of the patients responded, but that response was quite remarkable and leads, eventually, to licensure. The FDA stresses very careful study design with endpoints that can be statistically reproduced and are statistically relevant in even small patient number trials. The issue of responders and nonresponders will sort out if the study design properly balances the variables. The use of crossover schemes is currently favored by the FDA, where placebo-treated patients can be given the therapeutics after their initial response has been quantitated (hopefully no or very little response). Again, I would argue that enrollment suffers from these crossover designs because none of us wants to be the placebo if we qualify for the trial. If we can use the nonresponders as pseudo-placebos, I believe that efficacy measurements can be more accurately obtained from the initial responders especially for long-term follow-ups.

Lastly, the FDA views life-versus-death trials more creatively than quality of life trials. My view is that all trials, including non-life-threatening maladies such as mild-osteoarthritis (OA), are of the same human value as life-versus-death trials. For a patient with OA, we now know the sequela of what will progress and the statistical factors that can shorten their lives. If such patients suffer with their pain for long periods, we could expect a shorter life span and indeed overdoses of opioids and serious depression, which itself will shorten their lives. Clearly, we (the MSC researcher, doctors, and industry) and the FDA are learning together as we go forward. I would strongly argue that my painful knees and low back pain are as important as someone else's leukemia although the latter requires more immediate and aggressive medical interface.

Conclusion

The objective of the above proposal is to set forth new logics for cell-based therapies. The "drug-logic" does not work and is inhibiting for allowing some curative therapies to make their way into practice. Again, some cell-based therapies can be curative as opposed to palliative. If the few remaining islet cells in vivo can be made to divide to increase their number by exposure to MSCs, a revitalized pancreas will form. Treating that patient with insulin will never regenerate the pancreas; MSCs have the potential to be curative as compared with insulin, which is palliative. Eventually, properly tuned MSCs may eliminate the nonresponder pool and more effectively provide rapid outcomes. Until that time, the nonresponders may be possibly used to eliminate or minimize the placebo pool. Clearly, it will take time and the creative talents of researchers and health care providers to optimize the MSC-based therapies, to have them properly approved, and to maintain the very high and necessary standards for new medical products and procedures.

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Disclosure of Potential Conflicts of Interest

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