A Case for Crowd Sourcing in Stem Cell Research

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PERSPECTIVES

A Case for Crowd Sourcing in Stem Cell Research

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SUMMARY

Thousands of patients and placebo-treated controls have been included in many clinical trials of stem cell therapy over the last decade or so, but often the study groups have been small. Their scientific value may therefore be limited and their ethical justification questionable. Would "crowd sourcing" for data sharing be a means of increasing the collective value of clinical trials? Here, we make a case for open access of all data emerging from stem cell studies (trials but also observational studies) independent of whether they are investigator-initiated or commercially driven. STEM CELLS TRANSLATIONAL MEDICINE *2014;3:1–3*

INTRODUCTION

Regenerative therapy based on stem cells holds the promise to transform medicine, and there has been huge pressure from patients and clinicians to use stem cell products clinically and translate basic research rapidly into therapies. This has led to a rise in stem cell clinical trials for an increasing number of indications [1] and also to marketing of stem cell treatments outside normal regulatory procedures. The tension between hope and evidence was illustrated recently in the controversy surrounding the Italian Stamina Foundation: scientists criticized Stamina's mesenchymal stromal cell treatment as being unproven, yet the parliament decided that selected patients could be treated [2].

Randomized controlled trials (RCTs) provide the most reliable answer to the question of whether interventions are effective. However, for stem cell-based therapies, there are two important caveats to standard RCTs. Firstly, it is unclear whether observations from RCTs carried out on selected patients can be extrapolated to routine clinical care [3]. Secondly, RCTs are not designed to pick up signals that affect safety, because they are often based on small numbers of patients with short follow-up. This means that the contribution to scientific progress may be limited, and as a consequence, ethical justification for conducting these small studies might be questionable. In addition, many phase 1 or phase 2 studies lack a (randomly selected) control group, further limiting valid risk assessment.

There is urgent need to optimize ways to study the effects and safety of stem cell therapies [4], for example, by making use of data obtained from *all* treated patients. In this commentary, we challenge the current framework for clinical development of cell therapy in favor of a system that is based on data sharing.

MECHANISMS, RISKS, AND BENEFITS

In any stem cell therapy, safety risks associated with malignant transformation, immune suppression, and inappropriate differentiation are a concern. However, intermediate endpoints, such as biomarkers, are often studied rather than (long-term) risks, and there are many examples in which intermediate endpoints showed no correlation with clinically relevant endpoints. Research on underlying mechanisms and signaling pathways will never exclude the possibility of negative effects of an intervention. Additionally, the majority of stem cell RCTs are not designed to assess long-term efficacy or safety (there are too few patients, and follow-up is too short), so that uncertainties on the risks remain. Safety assessment therefore often necessarily relies on observational data (i.e., data from nonrandomized studies), and there is growing evidence that such negative effects can be estimated reliably from observational studies [5].

Assessment of efficacy might also benefit from observational data, particularly because newer methods (such as instrumental variable analysis and inverse probability weighting) are being developed that could lead to valid inferences. However, there is a need for data based on an adequate nonrandomized control group. Ideally, clinicians would include those patients in a database as controls if they were considered eligible for stem cell therapy, even if these patients did not actually receive stem cell therapy.

TOWARD OPEN-SOURCE, COMMUNITY-BASED RESEARCH

Although large randomized phase III clinical trials for efficacy will not be feasible for many conditions for which stem cells might be a treatment option, the goal should still be to base evidence on as many patients as possible. One way to improve the evidence-base in stem cell treatment is to enable different researchers to participate and to include patients in a registered study with an online database in which protocols for cell therapy are deposited and can be searched. Such a website should include the complete protocol, including all eligibility criteria, treatment details, follow-up

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requirements, and so on. Clinicians would then be able to search the website to see whether a patient fits into one of these stem cell protocols. Importantly, the results of patients that have completed the protocol should be accessible.

Within the FP7 program of the European Union (EU), multiple consortia have been funded to create harmonization of stem cell isolation and expansion protocols [6, 7]. If these aspects of a clinical trial can be standardized, clinicians might consider adding a patient to the study and treating and monitoring that patient based on the specific protocol and specific clinical release criteria of the stem cell products used previously. In line with this, control patients could be added to the database and also monitored according to protocol. Comparability of cell products used might be an issue, but this can be guaranteed by the combination of process standardizations and product specifications. Auditing of process and product deviations may ensure data quality. Several clinical cell therapy trials have been set up within the FP7 grant program from the European Union, aiming to create exactly these conditions, but it remains that the hallmark of comparability is the possibility of judging comparability. This means transparency and optimal registration.

An open-source approach such as described here would serve two purposes. Firstly, it would show all protocols currently under study because all researchers would be encouraged (or required) to add patients to protocols. Secondly, the approach would ensure that researchers and treating physicians are continuously updated on the results of all protocols under study. The potential for using the data for pooled analysis should be a strong incentive to provide data at the level of the individual patient. This would optimize the information available for adequate treatment decisions and also for decisions regarding future randomized studies. There is one more advantage here: as mentioned earlier, data on safety are of major importance in stem cell therapy. Because different conditions can be treated with the same protocol, a well-indexed register offers the possibility to define a safety profile of a protocol irrespective of condition being treated.

The proposed framework will not replace the incentive to perform RCTs (it can even be thought of as a web-based and open RCT approach in which doctors would be encouraged to include a patient in a current RCT). It would, however, definitely help to fill the important gaps that RCTs leave in stem cell research: firstly, because the registries would aim to include *all* treated patients, not just a relatively healthy subgroup as is often the case now. Secondly, and importantly, it would add to data on long-term safety, because RCTs are often not designed to detect these. Thirdly, it would help assess effectiveness of stem cell therapy for rare conditions for which few patients were available for inclusion.

The open-source approach to studies in stem cell therapy would have one other very important advantage if registration at the level of individual patients became compulsory: for each patient registered before the start of therapy, there would be an obligation to provide the results at the end, irrespective of the outcome. This would circumvent the problem of publication bias (studies with no effect are less likely to be published), which might be a problem, especially for small studies. The recent decision from the European Parliament that obliges researchers to publish their trial results, notwithstanding the positive signal, is unlikely to solve the problem of publication bias completely. Researchers might be inclined to design a study not as a trial (in which case the obligation for registration and publication would be absent) but as a description of a patient series treated for compassionate need. Such inconsistencies have very recently been shown to influence effect estimates of published stem cell trials in cardiology [8]. Also, registration has not thus far prevented publication bias [9].

A Realistic View?

We propose an open-source approach to clinical development of stem cell therapies. Such an approach has already been successful in other fields. For example, the reports of experiments trying to reproduce the stimulus-triggered acquisition of pluripotency (STAP) study, which claimed reprogramming of somatic mouse cells, resulted in reappraisal of these results [10]. Other examples using crowd-sourced science are the search for drug targets for tuberculosis [11] and the proof of a mathematical theory [12].

It might be important to explore the possibility of placing such a stem cell database within the framework of existing databases. One such option is the European Society for Blood and Bone Marrow Transplantation (EBMT) database. The EBMT framework is a nonprofit organization and is devoted to studies (trials but also nonrandomized studies) in bone marrow transplantation but also stem cell transplantation. Moreover, data confidentiality is guaranteed and in agreement with national laws of participating countries.

It is important to note however, that the implementation of open-source approaches is not straightforward and requires a true paradigm shift. One important hurdle could be the current regulatory framework. Stem cell products are considered advanced medicinal therapeutic products in the EU and are therefore subject to a regulatory framework that is oriented toward commercial market authorization. Consequently, stem cell products either have the status of an investigational drug or can be applied clinically as a hospital exemption or a registered product. The status of investigational drug or hospital exemption would be congruent with the concept of open-source clinical development. However, when a stem cell product receives market authorization, its development for investigational purposes and uses as a hospital exemption would be restricted. It would therefore be essential to develop such open-source clinical development together with the regulatory authorities. At the same time, it is important to acknowledge that the involvement of (biotech) companies is essential for implementation in medical practice. We argue, however, that sharing data to assess efficacy and safety helps companies to design pivotal registration trials and does not preclude the development of intellectual property. Another hurdle within the scientific community could be that this approach challenges authorships and investigator-associated research funding. At the same time, the scientific community has shown on multiple occasions that it can act collaboratively on big projects.

The ideas of patient registration and data sharing should be facilitated maximally up to the obligation to register. Such a process can be supported by journals (making publication conditional on registration) and funding agencies and governments (requiring stem cell treatment to be funded or financed only within the register framework).

Conclusion

Open-source clinical development might enhance transparency of results from stem cell research, improve data on safety outcomes, and minimize overestimation of effects caused by publication bias, which will advance progress in stem cell therapy and provide opportunities for generalizing therapies. The price to be paid is a necessary change in mind-set: from possessing data to sharing it.

Author Contributions

O.M.D., C.L.M., and T.J.R.: conception and design, manuscript writing.

Disclosure of Potential Conflicts of Interest

C.L.M. has an uncompensated consultancy with Pluriomics BV.

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