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Review Article

Ethical implications of regenerative medicine in orthopedics: an empirical study with surgeons and scientists in the field

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Abstract

BACKGROUND CONTEXT: Regenerative medicine (RM) interventions, such as (stem) cell transplantation, scaffolds, gene transfer, and tissue engineering, are likely to change the field of orthopedics considerably. These strategies will significantly differ from treatments in current orthopedic practice, as they treat the underlying cause of disease and intervene at a biological level, preferably in an earlier stage. Whereas most of the RM interventions for orthopedics are still in the preclinical phase of research, the number of clinical studies is expected to increase rapidly in the future. The debate about the challenging scientific and ethical issues of translating these innovative interventions into (early) clinical studies is developing. However, no empirical studies that have systematically described the attitudes, opinions, and experiences of experts in the field of orthopedic RM concerning these challenges exist.

PURPOSE: The aim of this study was to identify ethical issues that experts in the area of RM for musculoskeletal disorders consider to be relevant to address so as to properly translate RM interventions into (early) clinical studies.

STUDY DESIGN/SETTING: In-depth qualitative interviews were conducted with 36 experts in the field, mainly spine surgeons and musculoskeletal scientists from The Netherlands and the United Kingdom.

METHODS: A topic list of open questions, based on existing literature and pilot interviews, was used to guide the interviews. Data analysis was based on the constant comparative method, which means going back and forth from the data to develop codes, concepts, and themes.

RESULTS: Four ethical themes emerged from the interview data. First, the risks to study participants. Second, the appropriate selection of study participants. Third, setting relevant goal(s) for measuring outcome, varying from regenerating tissue to improving well-being of patients. Finally, the need for evidence-based medicine and scientific integrity, which is considered challenging in orthopedics.

DISCUSSION: The overall attitude toward the development of RM was positive, especially because current surgical treatments for spine disorders lack satisfactory effectiveness. However, efforts should be taken to adequately address the ethical and scientific issues in the translation of RM interventions into clinical research. This is required to prevent unnecessary risks to study participants, to prevent exposure of future patients to useless clinical applications, as well as to prevent this young field from developing a negative reputation. Not only will the orthopedic RM field benefit from ethically and scientifically sound clinical studies, but the rise of RM also provides an

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opportunity to stimulate evidence-based practice in orthopedics and address hype- and profit-driven practices in orthopedics.

Keywords: Empirical research; Regenerative medicine; Stem cells; Translation; Orthopedics; Musculoskeletal disorders

Introduction

Regenerative medicine (RM) is a new, interdisciplinary, innovative field of complex interventions focused on biologically repairing, replacing, or regenerating damaged or diseased tissues [1]. Potential orthopedic RM approaches involve, among others, (stem) cell transplantation, scaffolds, gene transfer, and tissue engineering [2]. These approaches could be used for treating degenerative disorders, such as intervertebral disc disease, or for improving surgical treatments, such as spinal fusion [2]. Most of the RM interventions for orthopedics are still in the preclinical phase, although some early clinical (including first-in-human) studies have commenced and several have been completed [3–9]. Today only one orthopedic RM treatment, specifically the treatment for focal knee cartilage defects, is approved for market use [10,11].

As the amount of (early) clinical studies in this field is expected to rapidly expand in the near future, it is time to proactively discuss the scientific and ethical issues involved in the translation of preclinical research into clinical studies. For innovative technologies, like RM, the traditional ethical benchmarks for conducting clinical research proposed by Emanuel et al. [12] require refinement. In particular, the decision of when translation into first-in-human studies is justified is challenging, because these complex novel approaches have never been applied in humans before. Additionally, the combination of the specific characteristics of RM with the characteristics of orthopedic patients implies that new challenges will arise [13]. Specific characteristics of RM include complexity, new aims (compared with drugs and devices), and early-stage effectiveness, whereas orthopedic patients are characterized by their relatively healthy status (in the sense of having a nonlethal disorder) and the strong influence of psychosocial factors.

Empirical ethics research provides factual information about the state of affairs in a specific practice and identifies the attitudes, opinions, and experiences of relevant actors. By combining experts' attitudes, opinions, and experiences with ethical theories and principles, a coherent view on the ethical issues in orthopedic RM research can be formed [14]. The aim of this study was to identify the ethical issues experts consider necessary to address before translating RM interventions into clinical research, and to combine the mentioned issues with our own ethical analysis.

Materials and methods

Design

Qualitative research aims to generate rich, in-depth understanding of attitudes, opinions, and experiences of individuals in a specific context or practice [15,16]. Data are primarily gathered from an interview design, and data analysis is largely inductive, which allows meaning to emerge from the data rather than the more deductive, hypothesis-centered approach of quantitative research [15]. Therefore, the attitudes, opinions, and experiences (when available) of experts regarding the ethical issues in translational clinical RM research for musculoskeletal disorders were examined by means of qualitative interview design [16,17]. This study was conducted as part of the Dutch BioMedical Materials–funded consortium IDiDAS (New Early Therapies for Intervertebral Disc Diseases. Drug Delivery and Augmentation through Smart Polymeric Biomaterials). IDiDAS involves four academic medical centers, one technical university, and industrial partners and is in the preclinical phase of developing RM interventions for the treatment of intervertebral disc disease. In our workpackage ethics, IDiDAS is used as an example to identify ethical issues that will arise in translating RM interventions for orthopedic disorders from bench to bedside.

Respondents

Respondents were recruited using the network of the IDiDAS consortium and by following recommendations from the interviewees (so-called snowball sampling) [18]. Inclusion criteria were that the respondent is involved in (pre)clinical orthopedic RM research, and/or has experience with conducting clinical research or practice in degenerative musculoskeletal disorders. These latter respondents were included to provide insight in the general challenges in conducting orthopedic research. One-on-one, in-depth interviews were mainly held with scientists working at the bench in orthopedic RM and with surgeons in different areas of orthopedic surgery (primarily spine) who were involved in the field of RM or orthopedic research (Table). We aimed to collect a range of attitudes, opinions, and experiences as wide as possible, termed contrast maximization, by selecting respondents of different professions, specializations, and nationalities [16].

In total, 36 interviews were conducted; 12 people did not respond and 4 rejected the invitation. Recruitment was ended when saturation was reached (ie, when no new thematic content was found) [19].

Interview strategy

The interviews were conducted by S.N. between April and November 2012. The interviews lasted between 30 and 75 minutes and most interviews took place at the workplace of the respondent. Five interviews were done by telephone.