RESEARCH ETHICS

Ethical and policy issues relating to progenitor-cell-based strategies for prevention of atherosclerosis

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Objective: To examine important ethical and societal issues relating to the use of progenitor-cell-based strategies for disease prevention, particularly atherosclerosis.

Background: Several nascent lines of evidence suggest the feasibility of using progenitor cells to reverse the health consequence of atherosclerosis. Such potential uses of progenitor cells are scientifically exciting, yet they raise important ethical and societal issues.

Method: The Working Group on Ethics of Progenitor Cell-based Strategies for Disease Prevention met to discuss the relevant issues. Several drafts of a report were then circulated to the entire Working Group for comments until a consensus was reached.

Results: Scientific evidence suggests the appropriateness of using progenitor-cell-based strategies for some rare conditions involving atherosclerosis, but additional preclinical data are needed for other, more prevalent conditions before human trials begin. All such trials raise a set of ethical issues, especially since trials aimed at prevention rather than treatment may involve persons who do not yet have disease but will be exposed to the risks of interventions. In addition, enrolment in prevention trials may be hazardous and harmful if participants erroneously believe experimental interventions will necessarily prevent disease. Finally, given the high prevalence of atherosclerosis, there are some important public policy implications of taking such an approach to prevention, including the sources of progenitor cells for such interventions as well as the allocation of health resources.

Conclusion: Potential uses of progenitor-cell-based strategies for preventing atherosclerosis must be considered in the context of a range of social and ethical issues.

Progenitor-cell-based therapies offer significant possibilities for changing the nature, goals and meaning of medical interventions. To date, both the medical community and the general public have largely conceived of progenitor-cell-based strategies as potentially powerful new ways of curing established diseases. However, it may also be possible to use progenitor cells to prevent diseases—either by stopping them from occurring or, if they are established, by modifying their progress. There has been almost no discussion of the ethical and policy issues relating to the use of progenitor cells for prevention.

Several nascent lines of evidence suggest the feasibility of using progenitor cells to reverse the health consequence of atherosclerosis—both in children with a specific genetic predisposition to develop atherosclerosis and in adults with established disease. Such potential uses of progenitor cells are scientifically exciting, given the extraordinarily high prevalence of atherosclerosis and its associated morbidity and mortality. The prospect of using intensive and costly progenitor-cell-based interventions that involve immune ablation is problematic, because these interventions pose certain risks to people who are merely at risk of developing disease. In addition, the development and testing of safer modes of progenitor-cell-based treatments raise complex ethical and policy issues.

The Working Group on Ethics of Progenitor Cell-based Strategies for Disease Prevention was established to examine such issues. It is composed of individuals with expertise in many disciplines, including the basic science and clinical practice of using progenitor cells for treating diseases, ethics, social science and the law. In this report, we review the scientific feasibility and ethical issues relating to the use of progenitor-cell-based strategies for disease prevention,

particularly atherosclerosis. Next, we identify and describe some of the ethical issues in research that arise when evaluating and developing progenitor-cell-based therapies for atherosclerosis. Finally, we address some of the public health policy implications of using progenitor-cell-based strategies for the prevention of atherosclerosis.

SCIENTIFIC FOUNDATIONS

The scientific foundations for considering cell-based therapies for the prevention of atherosclerotic disease derive from both clinical and pre-clinical research. In the following analysis, we distinguish different types of disease prevention, since they can have different implications for science, ethics and policy. Primary prevention is aimed at preventing the occurrence of a disease, while secondary prevention involves intervening after the disease has first developed but before it becomes advanced.¹

For instance, umbilical cord blood (UCB) cells have been used to treat children with Hurler syndrome (MPS-I; mucopolysaccharidosis type I). This syndrome is a clinically complex disorder caused by the accumulation of mucopolysaccharides in various tissues as a result of alpha-L-iduronidase deficiency. The syndrome is characterised by severe mental retardation, facial deformities, joint stiffness, corneal opacification and bone deformities, and it also leads to accelerated atherosclerosis and cardiovascular death. Thus far, UCB transplantation following immunoablation among 6–9-month-old children with Hurler syndrome has had short-term success (with benefit lasting up to 7 years) in modifying the disorder's multiple features, possibly including atherosclerosis.^{2,3}

Abbreviation: UCB, umbilical cord blood

While this treatment might eventually prove curative, at the very least, UCB treatment for Hurler syndrome could be aptly described as secondary prevention—modifying the progression of an already established disease. Given the severity and lethality of the untreated illness, progenitor-cell-based therapy for such a disease is ethically justifiable. Almost any potential amelioration of the disease will seem proportionately beneficial compared with not intervening, even if the long-term consequences of intervention are not yet known. And while there has been demonstrable short-term success, questions do remain about the long-term consequences. For example, will the treated child have a normal lifespan? Will there be late complications?

Nevertheless, there is currently greater scientific uncertainty regarding whether progenitor-cell-based approaches would be appropriate for primary or secondary prevention of atherosclerosis among individuals without other indications for such a treatment. Yet, several lines of evidence support the feasibility of such approaches. For instance, preliminary experiments in genetically modified murine models suggest that progenitor cells from bone marrow may be used to prevent atherosclerotic disease by enhancing endothelial repair mechanisms. A possible explanation of this finding is that progenitor cells continuously repair arteries affected by atherosclerosis but that the supply of progenitor cells capable of carrying out this repair diminishes with age. A growing body of evidence supports this hypothesis. For example, the long-term administration of bone marrow cells can prevent atherosclerosis in established recombinant murine models of human vascular disease (ie, apolipoprotein E (apoE) knock-out B6 mice fed high fat diets), even if the injurious mechanisms that promote atherosclerosis (eg, a cholesterol level in excess of 1200 mg/dl) are not removed.⁴ In addition, it has been observed that while bone marrow cells from young ApoE^{-/-} mice are capable of preventing atherosclerosis, these precursors lose this capacity as they age.⁵ These studies suggest that with ageing, organisms may simply become depleted of progenitor cells that are capable of maintaining cardiovascular homeostasis. If this is correct, introducing progenitor cells from external sources may make it possible to stimulate the cardiovascular repair process to attenuate atherosclerosis.⁶ In fact, in the damaged heart of a child undergoing treatment with UCB, more than 15% of the cells were found to be derived from the donor's UCB.⁷

However, it is currently unknown whether, in the absence of clear injury, progenitor cells migrate to tissues or organs at risk. For example, in familial hypercholesterolaemia, a known genetic defect in cholesterol metabolism (most frequently the absence or mutations of the hepatic low-density lipoprotein receptor) causes a profound acceleration of atherosclerosis and leads to severe cardiovascular manifestations.⁸ There is currently no specific treatment for familial hypercholesterolaemia in its homozygous form. Therefore, although the use of a prevention strategy in childhood before the onset of atherosclerosis is desirable, it is unclear whether progenitor-cell-based therapy has the potential to be helpful in such cases, partly because there is insufficient knowledge about the mechanisms by which UCB cells locate and identify damaged cells.

Thus, given the risks associated with immunoablation and progenitor cell transplantation, it would currently be ethically inappropriate to pursue human trials for primary or secondary prevention of atherosclerosis that does not manifest itself with an obvious injury. Additional scientific areas that warrant examination before initiating clinical trials using progenitor cell transplants for prevention of atherosclerosis include (1) how long after transplantation progenitor cells remain capable of providing therapeutic benefit and (2) the degree of certainty in identifying which individuals will ultimately be affected by

the disease for which they putatively have a genetic predisposition.

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Assuming that clinical trials to evaluate and use progenitor-cell-based strategies for the prevention of atherosclerosis will be conducted in the future, it is essential to address the other challenging issues in research ethics besides a careful assessment of the potential risks and benefits. While these other issues may not be unique, they have yet to be satisfactorily resolved, and they emerge here in a distinctive and particularly vexing form.

First, a critical characteristic of some types of research involving primary prevention of atherosclerosis is that most of those enrolled in a research study may not be symptomatic, and the majority of enrolled subjects who are considered to be at risk may never become ill as a result of their atherosclerotic disease.¹⁹ These factors must be considered in weighing the risks and benefits of proposed research, since many individuals will necessarily be exposed to risk even though many of them will not benefit. Such exposure is especially difficult to justify when proposed preventive interventions are particularly burdensome or risky. In addition, this issue is likely to pose challenges to the informed consent process for research, since it may be difficult to communicate the notion of population-based benefits for the individuals who will be asked to enrol and be exposed to risk.

Related to these challenges of obtaining meaningful informed consent are those associated with the potential hazards of participants believing, perhaps erroneously, that the experimental interventions will certainly be effective. In short, those enrolled in preventive intervention trials might discontinue, or choose not to adopt, alternative preventive practices, assuming that the experimental preventive intervention will protect them from disease. In HIV vaccine trials, for example, those enrolled might fail to use condoms, assuming that the experimental vaccine will protect them from infection with HIV. Similarly, an individual enrolled in a trial to prevent atherosclerosis might ignore other currently proven means of preventing heart disease. Such “disinhibition” may have important implications both for being able to properly interpret data from the trial and for the individuals enrolled. The behaviours that might be disinhibited as a result of enrolment in an atherosclerosis trial encompass both objectively dangerous ones (such as smoking) and those that are on the border between lifestyle and objectively dangerous behaviours. Borderline behaviour might include relatively low levels of exercise, difficulty controlling stress, and even religiously or spiritually based resistance to allopathic medicine (resulting, perhaps, in a failure to diagnose and treat hypertension). In some cases, the disinhibition could outweigh the advantages of the preventive measure even if it is effective. Any intervention that decreases motivation to quit smoking, for example, invites a continued risk for atherosclerosis as well as risk for a variety of cancers and respiratory illnesses. In other cases, it could undermine an already stuttering public health campaign, such as those under way to increase physical activity among children and adults. Overall, then, a model of disinhibiting effects is needed, and so is an evaluation of whether those effects are objectively harmful and if they meaningfully affect the integrity of research designed to evaluate preventive interventions.

Finally, as with other innovative approaches such as maternal-fetal surgery for meningomyelocele or spina bifida, what may be considered a standard of care in one treatment setting might be considered investigational in others.¹⁰ Indeed, while progenitor-cell-based therapy for atherosclerosis or myocardial infarction is considered investigational in the US,

patients may already be able to access these treatments in Germany.¹¹ As in other settings, once some success in this type of research has been published, there may be a demand for access to such approaches even without a scientific consensus regarding safety and efficacy. This may have implications for the design of future studies or the ability of investigators to recruit adequate numbers of participants into clinical trials.

IMPLICATIONS FOR HEALTH POLICY

Assuming that progenitor-cell-based strategies are shown to be safe and effective for the prevention of atherosclerosis, important questions arise for public health policy. These relate to the sources of progenitor cells for research and treatment and to the allocation of public health resources.

Sources of progenitor cells

Among the possible sources of progenitor cells for the prevention of atherosclerosis, UCB is particularly attractive for several reasons. First, early experimentation suggests that it may be effective in this setting. Second, adult bone marrow progenitor cells may be less available than UCB. Third, using UCB can avoid some of the difficult ethical and political issues surrounding the use of embryonic stem cells.

Despite the appeal of using UCB for the prevention of atherosclerosis, the possibility raises some interesting questions about UCB banking. On the one hand, the high prevalence of atherosclerosis would seem to bolster strong arguments that support the development and maintenance of public UCB banks.¹² After all, properly constructed public banks should provide many persons with a source of allogeneic progenitor cells. On the other hand, the use of UCB for the prevention of atherosclerosis calls into question the assumption made by many experts that private UCB cell banking for most persons is unnecessary because of the extremely small likelihood that autologous cells will ever be needed for transplantation.¹³ Since atherosclerosis is so prevalent and autologous cells may eliminate the need for ablation, this assumption may need to be revisited. Furthermore, some have argued that the quality of privately banked samples may be questionable, because of problems in ensuring appropriate collection, shipping, testing and long-term storage.¹⁴ Should progenitor-cell-based therapies prove efficacious in preventing atherosclerosis, there will be a clear need to examine the quality of privately banked UCB.

Allocation of health resources

Anticipating the introduction of effective strategies for the prevention of atherosclerosis involves considering the implications for the allocation of health resources. Historically, atherosclerosis in adults was considered to be a normal consequence of ageing—that is, it is due to a gradual, universal, age-related decline of circulatory functioning.¹⁵ Delaying the initiation and clinical manifestation of atherosclerosis is likely to increase life expectancy, because circulatory disease is a major cause of death, both by itself and because it degrades the function of other organs (eg, brain and kidney). Therefore, changing the process of atherosclerosis (which is experienced almost universally) at late ages seemingly can modify multiple age-specific norms for functioning. If so, it reflects a change in basic parameters of ageing dynamics in human populations.

Accurate projections of benefits of interventions to prevent atherosclerosis would obviously be of great benefit in determining the appropriate distribution of health resources. Nevertheless, some subtle ethical issues are related to the study of health outcomes, especially the methodology and data used to project the benefits of preventive interventions. While estimates of effects on individuals may be made based solely on clinical evidence, the effects, regarding both economic and

human capital, on a population are even more complex. Such effects must be estimated from other types of evidence on the distribution of people in a given population who could benefit from the interventions—using a mathematical model for combining and stochastically forecasting or extrapolating results of selected health interventions to a larger (and probably more physiologically heterogeneous) population into the uncertain future. This aspect of evaluating the future consequences of medical innovations has been little studied and evaluated, even though it is often done and has tremendous effects on the societal perception of the utility of any given medical innovation and on the mix of health services ultimately made available to the population. Therefore, close attention should be paid to making projections that are consistent with evidence on health outcomes in the individual and the potential distribution of outcomes in the population.

In generating and interpreting these projections, it is essential to guard against the possibility of assuming a pre-conceived goal—for example, to prove the significance of the consequence of an intervention, or to generate controversy, possibly to attract additional funding to a particular area of study (eg, obesity as opposed to smoking).^{16 17} This forecasting of therapeutic activity and benefit has important effects on research on new medical therapies and their availability, and also on an individual's perception of the likelihood of successful treatment for a condition, on whether other well-established therapies would be provided and on whether these established therapies would be provided to persons with a certain comorbidity. For example, an individual might receive a reduced level of publicly provided services for a given physical health problem, such as myocardial infarction, if the individual has also received a diagnosis of a condition such as Alzheimer disease.¹⁸

CONCLUDING COMMENTS

The prospect of using progenitor-cell-based therapies as a means of preventing atherosclerosis is scientifically exciting. Like other potential preventive uses of such therapies, however, the prospect raises important ethical and societal concerns. Although additional scientific evidence may help to resolve some of these concerns, new ones are likely to arise if progenitor-cell-based therapies become part of medical practice in fields such as atherosclerosis prevention. In particular, these powerful new approaches could significantly exacerbate the already difficult questions about access to healthcare that will need to be faced in the coming years.

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