Review Article

THE UNEXPLORED POSSIBILITIES, PERCEPTIONS AND ETHICAL IMPLICATIONS OF GENE-EDITING ALLERGIC DISEASE: ENGAGING STAKEHOLDERS IN SOUTH AFRICA

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ABSTRACT

Clinically approved cell and gene therapies are opening up future possibilities to treat and prevent myriad diseases, which may include allergic diseases. In South Africa, this could help alleviate the high disease burden and economic cost of treating such diseases. However, even if viable gene-editing options to treat, cure and prevent allergic diseases become safe, effective and affordable for the South African market within the next few decades, the ethical implications and challenges of perceptions, regulation and oversight to ensure safety and equitable access remain. It would be important for all stakeholders involved, including the public and physicians, clinicians and ethicists on clinical and research ethics committees, to be informed about the possibilities, to engage in discussions with one another and to redress any gaps in knowledge. It would be especially important to determine whether cases for gene-editing aimed at allergy would be applied for therapeutic purposes or for enhancement. Much research and discussion remain to be embarked upon; however, it is imperative that research and engagement are expanded and prioritised.

Keywords: allergic disease, gene-editing, enhancement, therapeutic, equitable access

INTRODUCTION

Genome-editing tools such as Clustered Regularly Interspaced Palindromic Repeats and its associated proteins (CRISPR-Cas) are opening up the possibilities of safe therapeutic applications, including the successful prevention of HIV and the treatment of certain cancers, sickle-cell disease (SCD) and allergic diseases.[1,2,3] CRISPR and its associated proteins act like molecular scissors that can edit specific sections of genetic material accurately. At present, 1 200 cell and gene-therapy clinical trials are ongoing and it is expected that 50 such treatments will be available clinically in the United States by 2030.[4] According to Centerwatch.com, no gene-editing clinical trials are currently registered in South Africa.[5] A search on the Clinicaltrials.gov website using search terms 'allergy' and 'gene therapy' indicated 139 studies globally.[6] The search included broader search terms such as 'hypersensitivities' and 'sensitivities'. Gene-therapy clinical trials focusing on allergic disease seem not to be a reality just yet. However, in the long term, it is inevitable that South Africa will be influenced by the growing market of gene therapy. Physicians may be faced with choices whether to offer these treatment options to their patients in the future.

The South African population has a high disease burden, one further exacerbated by severe inequality in its healthcare sector.[7] The private healthcare sector serves 16% of the population and offers access to world-class therapies, whereas the public healthcare sector serves 84% of the population and faces severe resource constraints.[4] In the public healthcare sector, those treatments most beneficial to the largest number of patients are prioritised.[4] Genome-editing may have the potential to relieve the high disease burden by delivering single-dose effective treatments. In addition, it could also relieve the long-term economic burden of treating certain diseases if early screening and prevention takes place. It would, however, be critical that gene-editing therapeutic services develop in such a way that equitable access is ensured so as not to increase inequalities further. The development and delivery of gene-editing therapies would require rigorous and intensive processes of capacity-building, education, training and data production.[4]

CURRENT POSSIBILITIES OF GENE-EDITING FOR ALLERGIC DISEASES

One-third of South Africans suffer from allergic diseases, of whom 40% are children.[8] The cost of allergic disease to the South African economy is difficult to estimate. A pharmaceutical company estimated the cost to be more than ZAR600 million a year in 2018.[9] Current treatment methods include the avoidance of allergens, administering medication such as antihistamines, nasal and oral corticosteroids, mast-cell stabilisers, adrenaline and immunotherapies. Although lifelong treatment strategies and management of allergic disease are well described and implemented by physicians, no long-lasting treatments or cures exist.

A good therapeutic application of CRISPR could be to prevent lethal allergies and severe asthma.[10] The prevalence of allergic reactions could be reduced by the genetic modification of common allergy-causing culprits so as to prevent the production of allergenic proteins.[11] For example, promising gene-editing research in the domain of food allergies has been done on various allergenic proteins found in peanuts, wheat and soybeans.[1] CRISPR-Cas could also be programmed to eliminate the Fel d1 allergen in cats, which could prevent a Th2-type immune response in human beings, usually brought about by exposure to cat dander.[1] Genetic modification such as gene-editing plants and other organisms, as has been done, is generally acceptable in society. Ethical challenges remain, nonetheless, depending on specific applications and societal perceptions.

More contentious possibilities are research and translational pathways involving human gene-editing with the goal of curbing the allergic reaction itself. Current research is limited to cell and non-human animal models. For example, studies have shown that the Th2-type immune response of an asthma flare-up can be modified through CRISPR-Cas by wiping the memory of Th2 cells.[7,11,12] Gene-editing for therapeutic purposes may eventually form part of current existing immunotherapies.[11,13,14]

Even if viable options to treat, cure and prevent allergic diseases become safe, effective and affordable for the South African market within the next few decades, the ethical implications and challenges of perceptions, regulation, oversight to ensure safety, and equitable access remain.

PERCEPTIONS AND ETHICAL IMPLICATIONS

Perceptions about gene-editing have been shaped throughout history. Many gene-editing tools have been developed and have shaped perceptions. These include restriction enzymes, transcription activator-like effector nucleases, zinc finger nucleases and epigenetic editing. In the 1970s, genetically modified organisms (GMOs) were developed using gene-editing tools. Examples are recombined bacterial genomes that produce human insulin to treat diabetes, and herbicide-resistant soybeans. Perceptions about human-gene manipulation have a tainted past and have rightly faced scrutiny. An example of the beginnings of manipulation of the human genetic code is eugenics, which emerged during World War Two. The pseudoscience of eugenics was used to perpetuate the idea that a genetically superior race could be bred by allowing people only with certain traits to reproduce.[15] Doctors and geneticists working for the Nazi regime conducted numerous unethical experiments on prisoners.[16] This led to the Nuremberg trials being conducted from 1947 to 1949[17] and in their wake the Nuremberg Code, whose ten principles were drawn up to guide experimentation involving human beings.[17]

In the 1990s, the potential use of gene-editing for therapeutic purposes became prominent.[18] Perceptions of gene therapy were shaped by the pivotal case of Jesse Gelsinger, who was the first person to die in a gene-therapy clinical trial.[19] Gelsinger suffered from an X-linked genetic disease, Ornithine transcarbamylase, which prevented his body from breaking down ammonia.[19] He underwent an experimental procedure by which a viral vector carrying an unaffected gene was injected. He died four days later, probably due to an immune reaction to the virus vector.[19]

Now, more than two decades later, advancements in science are driving clinically approved, safe, efficacious therapeutic gene-editing applications. CRISPR far surpasses other gene-editing tools based on its accuracy and cost-effectiveness. CRISPR's potential use as a safe and cost-effective gene-editing tool with broad applications was first described by Doudna and Charpentier in 2012.[20] Perceptions are being shaped further by (dis)trust in technology, scientific understanding, proven efficacy and safety in the long term.[21] The safety and efficacy of CRISPR has to do with possible off-target effects and mosaicism being present in an individual undergoing somatic or heritable gene-editing. CRISPR's most contentious use is that of heritable human genome-editing which involves genetic edits being made to the gametes of an individual that enable traits to be passed on from one generation to the next.[21] For example, in 2018, the scientific community reacted with outrage when a Chinese scientist reportedly gene-edited and brought to full term two HIV-immune baby girls.[22] The general understanding in the scientific community up to that point was that no one would proceed without consensus being reached that it was safe to do so.[23] The Chinese scientist's application of CRISPR was considered to be an enhancement rather than a therapeutic application, considering that there are safer ways to ensure that HIV-resistance exists, such as semen-washing followed by in vitro fertilisation, intrauterine insemination or intracytoplasmic sperm injection.

During the COVID-19 pandemic, CRISPR's broad applications were exemplified by its application in rapid diagnostic testing. A collaboration between a biotechnology company and a university developed rapid diagnostic tests that could determine not only whether a person was infected with SARS-CoV-2, but also with which variant they were infected.[24,25] CRISPR's use in diagnostic-testing applications is not limited to SARS-Cov-2 and could also be used for the Ebola virus and other virus-detection systems.[26] This could shape perceptions of CRISPR further, possibly prompting greater acceptance.

REGULATION AND OVERSIGHT ENSURING SAFETY AND EQUITABLE ACCESS

Currently, CRISPR is seen as a controversial tool that has the potential to be misused, whether for therapeutic or for enhancement purposes. Governments and societies across the world have reacted in various ways to the development of gene-editing applications in the form of statements, reports, policies and guideline documents.[27] The National Academies of Medicine, the National Academies of Sciences and the Royal Society formed the International Commission on the Clinical Use of Human Germline Genome Editing.[27] The commission was tasked to 'address the scientific considerations that would be needed to inform broader societal decision-making'. In 2020, they published their report, which identifies six categories (A–F) of the potential use of heritable human genome-editing. The categories include:

- prospective parents' children who would inherit a serious monogenic disease;
- monogenic diseases with a less serious impact;
- polygenic diseases; and

- cases involving changes that would enhance or introduce new traits or eliminate certain diseases.

They suggested establishing clear and transparent translational pathways that the International Scientific Advisory Panel (ISAP) would assess, review, and provide input and advice on. An international mechanism should also be established to which concerns about research can be submitted so that the relevant authorities can be informed and act, if necessary.

Concurrently, the World Health Organisation (WHO) aimed to address the ethical and public-health considerations of genome-editing. In 2021, they released a position paper, recommendations and a governance framework for heritable human genome-editing.[28,29,30] Accordingly, global cooperation and coordination is necessary. In order to enhance this coordination and cooperation, the WHO established a global registry for clinical trials of genome-editing. These and other measures put in place are important to ensure the safety and efficacy of and equitable access to gene-editing therapies. Equitable access would require, first, that the need for genome-editing therapies be established and then building a registry of eligible patients.

In South Africa there is a gap in the regulation of these technologies: currently, no legislation governs the manufacture and importation of cell and gene therapies. Any gene-editing therapy would need to be approved by the South African Health Products Regulatory Authority (SAHPRA). It is, therefore, important that binding regulations and committees are in place to ensure that patients who need these treatments the most can access them.

THERAPEUTIC OR ENHANCING CRISPR APPLICATIONS: WHAT ABOUT GENE-EDITING ALLERGIC DISEASES?

The first therapeutic gene-editing applications, as recommended by the ISAP, will be limited to monogenic diseases that cause severe morbidity or premature death.[27] In the case of prospective parents wanting to gene-edit an embryo, it is recommended that they must have no other means of producing genetically related children without the monogenic disease.[27] Allergic diseases are considered polygenic and therefore belong to Category D of potential applications of gene-editing as described by ISAP. According to ISAP, this category requires a lot more research due to the complexity of the interplay of genes and the environment. If the scientific and translational pathways were developed, it could be assumed that the first possible therapeutic applications of gene-editing for allergies would be for those suffering from potentially lethal allergies and who have no other therapeutic options.

Beside lethal allergies, deciding when the gene-editing of allergic diseases would be considered an enhancement or therapeutic entails applying underlying value judgements that have not yet been explored. 'Enhancement' is a broad and conceptually laden term: it can be defined as a change in the state of a person (whether biological or psychological) that is experienced or judged by the person, or people, as being good.[31] Most people suffering from allergies would agree that, depending on the severity of the condition, allergies impair and hinder everyday functioning and well-being. It is likely that, at first, determining in which cases gene-editing allergies would be either enhancing or therapeutic would have to be evaluated case by case. Gene-editing for lethal allergic diseases will most probably come to the market first. These kinds of application will probably be considered acceptable and are likely to be welcomed by the sufferers. When, however, it comes to pre-conception genetic testing, prenatal genetic testing, pre-implantation genetic testing and gene-editing to ensure that a child does not develop allergies, this may be considered enhancement rather than therapeutic.

CONCLUSION

Whether gene-editing allergic diseases is considered therapeutic or enhancement is based on underpinning value judgements.[32,33] These value judgements have not yet been explored clearly or sufficiently. Along with the scientific progress to ensure safety and efficacy, research is still needed to evaluate in which cases clinical applications of gene-editing would be considered acceptable and good. These technological developments are opening an array of unexplored possibilities, ethical implications and perceptions. It is, therefore, important that all stakeholders involved – including physicians, clinicians, patients, patient advocates, ethicists on clinical and ethics committees, and the lay public – be informed about the current possibilities and challenges to remedying any gaps in knowledge. This, in turn, should spark discussions that drive the equitable development and deployment of these technologies.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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