GENE THERAPY IN THE DEVELOPING COUNTRIES

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ABSTRACT

Gene therapy is treatment directed to curing genetic disease by introducing normal genes into the patients in order to overcome the effects of abnormal genes using technique of genetic engineering. The most radical approach involves applying this at the early stage in the embryo, so that the new gene would be incorporated into the germ cells and hence will be inheritable. This approach is not considered to be safe either safe or ethical because the consequences may affect the descendants of the patients. Therefore, this review throws more light on gene therapy, its application and consequences in the developing countries.

Keywords: Gene, Therapy, Genetic engineering, Application, Consequences, Developing countries.

Contribution/ Originality

This study contributes in the existing literature, in new gene therapy approach that repairs errors in messenger RNA derived from defective genes. It is now theoretically possible to cure all genetic diseases. It is now imperative that developing countries should embrace gene therapy technology.

1. INTRODUCTION

Gene is the functional component of the deoxyribonucleic acid (DNA) which is the cell responsible for the inherited traits in an individual. However Gene therapy is the use of drug-like DNA. In order words DNA is used as a drug to treat disease by delivering therapeutic DNA into patients cells. The most common form of gene therapy involves using DNA that encodes a functional therapeutic gene to replace a mutated gene. Other forms involve directly correcting a mutation, or using DNA that encodes a therapeutic proteins drug (rather than a natural human gene) to provide treatment [1]. Gene therapy was first conceptualized in 1972, with the authors urging caution before commencing gene therapy studies in humans. The first FDA – approved

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gene therapy experiment in the United States occurred in 1990, when Ashanti Desilva was treated for ADA – SCID \[2\]. By January 2014, about 2000 clinical treats had been conducted or had been approved using a number of techniques for gene therapy.

Although early clinical failures led many to dismiss gene therapy as over-hyped, clinical successes since 2006 have bolstered new optimism in the promise of gene therapy. These include successful treatment of patients with the retinal disease, leber’s congenital amaurosis \[3\].

In gene therapy, DNA that encodes a therapeutic protein is packaged within a “Vector” which is used to get the DNA inside cells within the body. Once inside, the DNA becomes expressed by the cell machinery, resulting in the production of therapeutic protein, which in turn treats the patients disease. Although this should, in theory, be highly effective in counteracting genetic disorders and hereditary diseases, some jurisdiction, including Australia, Canada, Germany, Israel, Switzerland and Netherlands, prohibit this for application in human begins at least for the present, for technical and ethical reasons, including insufficient knowledge about possible risks to future generations.

These clinical successes have led to a renewed interest in gene therapy, with several articles in scientific and population publications calling for continued investment in the field \[4\]. It has been documented that between 2013 and April 2014, US companies invested over 600 million Dollars in gene therapy \[5\]. In 2012, Glybera became the first gene therapy treatment to be approved for clinical use in either Europe or the United States after its endorsement by the European commission \[6\]. Included in the success story is the Parkinson’s disease \[7\].

Following early advances in genetic engineering of bacterial, cells, and small animals, scientists started considering how this technique could be applied to medicine, could human chromosomes be modified to treat disease? Two main approaches have been considered – adding a gene to replace a gene that wasn’t working properly, or disrupting genes that were not working properly (U.S National library). Scientists focused on diseases caused by single-gene defects, such as cystic fibrosis, hemophilia, muscular dystrophy, thalassemia, and sickle cell anemia. As of 2014, gene therapy was still generally an experimental technique, although in 2012 Glybera became the first gene therapy treatment to be approved for clinical use in either Europe or the United States after its endorsement by the European commission, as a treatment for a disease caused by a defect in a single gene, lipoprotein lipase \[6\].

In gene therapy, DNA must be administered to the patient, get to the cells that need repair, enter the cell, and express a protein (U.S National Library). Generally the DNA is incorporated into an engineering virus that serves as a vector, to get the DNA through the blood stream, into cells, and incorporated into a chromosome \[1, 8\]. However, so called naked DNA approaches have been explored, especially in the context of vaccine development.

Generally, effects have focused on administering a gene that causes a protein to be expressed, that the patient directly needs. However, with development of our understanding of the function of nucelases such as zinc finger nucelases in humans, efforts have begun to in corporate gene encoding nucelases into chromosomes; the expressed nucelases then “edit” the chromosome,
disrupting genes causing disease. As of 2014, these approaches have been limited to taking cells from patients, delivering the nuclease gene to the cells, and then administering the transformed cells to patients [9]. There are other technologies in which nucleic acids are being developed as drugs, such as antisense, small interfering RNA, and others. To the extent that these technologies do not seek to alter the chromosomes, but instead are intended to directly interact with other bimolecules such as RNA, they are generally not considered “gene therapy” per se.

2. TYPES OF GENE THERAPY

Gene therapy may be classified into the two following types, only one of which has been used in humans.

**Somatic gene therapy**: As the name suggests, in somatic gene therapy, the therapeutic genes are transferred into the somatic cells (non-sex-cells) or body, of a patient. Any modifications and effects will be restricted to the individual patient only, and will not be inherited by the patient’s offspring or later generations. Somatic gene therapy represents the mainstream line of current basic and clinical research, where the therapeutic DNA transgenic (either integrated in the genome or as an external epitome or plasmid) is used to treat a disease in an individual.

**Germ line gene therapy**: In germ line gene therapy, germ cells (sperm or egg) are modified by the introduction of functional genes, which are integrated into their genomes. Germ cells will combine to form a zygote which will divide to produce all the other cells in an organism and therefore if a germ cell is genetically modified then all the cells in the organism will contain the modified gene. This would allow the therapy to be heritable and passed on to later generations. Although this should, in theory, be highly effective in counteracting genetic disorders and hereditary disease, some jurisdictions including Australia, Canada, Germany, etc. prohibits this for application in human being. The U.S.A has no federal legislation specifically addressing human germ-line or somatic genetic modification (beyond the usual FDA testing 2006) regulations for therapies in general [10].

3. VECTORS IN GENE THERAPY AND ADVANCES

Gene therapy utilizes the delivery of DNA into cells, which can be accomplished by a number of methods. The two major classes of methods are those that use recombinant viruses (some times called biological nano-particles or viral vectors) and those that use naked DNA or DNA complexes (Non viral methods).

3.1. Viruses

All viruses bind to their hosts and introduce their genetic material into the host cell or part of their replication cycle. Therefore this has been recognized as a plausible strategy or gene therapy by removing the viral DNA and using the virus as a vehicle to deliver the therapeutic DNA. A number of viruses have been used for human gene therapy, including retrovirus, adenovirus, lentivirus, herpes simplex virus, vaccinia, pox virus and adeno-associated virus [5].
4. NON VIRAL METHODS

Non viral methods can present certain advantages over viral methods, such as large scale production and low host immunogenicity. Previously low levels of transfection and expression of the gene held non-viral methods at a disadvantage. However, recent advance in vector technology have yielded molecules and techniques and approach the transfection efficiencies of viruses.

There are several methods for non-viral gene therapy, including the injection of naked DNA, electroporation, the gene gun, sonoporotion, magnetofection, and the use of oligonucleotide, lipoplexes, dendrimers, and inorganic monoparticles.

4.1. Deaths

The patient's deaths have been reported in gene therapy trials, putting the field under close scrutiny. One X-SCID patient died of leukemia following gene therapy treatment in Sheridan [2]. In 2007, a rheumatoid arthritis patient died from an infection in a gene therapy trial, a subsequent investigation conducted that the death was not related to her gene therapy treatment.

4.2. Advances

4.2.1. Development of Gene Therapy Technology

In 1970s and earlier, freedman and Roblin authorized a paper in science titled “Gene therapy for human genetic disease in 1972) was cited for proposing the exogenous good DNA be used to replace the defective DNA in those who infer from genetic defects.

In 1990s, the first approved gene therapy case in the United States took place on 14th September 1990, at the institute of health, under the dissection of professor William French Anderson. It was performed on a four year old girl named Ashanti Desilva. It was a treatment for a genetic, defect that left her with ADA-SCID, a severe immune system deficiency. The effects were temporary but successful [11].

New gene therapy approach repairs errors in messenger RNA derived from defective genes. This technique has the potential to treat the blood disorder thalassaemia-, cystic fibrosis, and some cancer researchers at case western reserve University and Copernicus therapeutics are able to create tiny liposomes, 25 nanometers across that can carry therapeutic DNA through pores in the nuclear membrane (DNA nano balls toost gene theraphy).

Sickle – cell disease is successfully treated in mice [12]. The nice – which have essentially the same defect that causes sickle cell disease in humans – through the use of a viral vector, were made to express the production of fetal hemoglobin (HbF), which normally ceases to be produced by an individual shortly after birth. In humans, the use of hydroxyurea to stimulate the production of HbF has long been shown to temporarily alleviate the symptoms of sickle cell disease. The researchers demonstrated this method of gene therapy to be a more permanent means to increase the production of the therapeutic HbF [13].

In 1992 Doctor Claudio Bordignon working at the vita-salute San Raffaele University. Milan, Italy performed the first procedure of gene therapy using hematopoietic stem cells as vector to
deliver gene intended to correct hereditary disease [14]. In 2002 this work led to the publication of the first successful gene therapy treatment for adenosine deaminase-deficiency (SCID).

The success of a multi-centre trial for treating children with SCID (Severe combined immune deficiency or “bubble boy” disease) held from 2000 and 2002 was questioned when two of the ten children treated at the trial’s Paris center developed a leukemia-like condition. Clinical trials were halted temporarily in 2002, but resumed after regulatory review of the protocol in the United States, the United Kingdom, France, Italy, and Germany [15].

In 1993, Andrew Gobes was born with severe combined immunodeficiency (SCID). Genetic screening before birth showed that he had SCID. Blood was removed from Andrew’s placental and Umbilical cord immediately after birth containing stem cells. The allele that codes for ADA was obtained and was inserted into a retrovirus. Retrovirus and stem cells were mixed, after which the viruses entered and inserted the gene into the stem cells chromosomes. Stem cells containing the working ADA gene were injected into Andrew’s blood system via a vein. Injections of the ADA enzyme were also given weekly. For four year T cells (white blood cells) produced by stem cells, made ADA enzymes using the ADA gene. After four years more treatment was needed.

The death of Jesse Gelisinger in 1999, in a gene therapy clinical trial resulted in a significant setback to gene therapy research in the United States [16]. As a result, the U.S. FDA suspended several clinical trials pending the re-evaluation of ethical and procedural practices in the field [17].

In 2003, a University of California, Los Angeles research team inserted gene into the brain using liposomes coated in a polymer called polyethylene glycol. The transfer of genes into the brain is a significant achievement because viral vectors are too big to get across the blood brain barrier. This method has potential for treating Parkinson’s disease [18]. RNA interference or gene silencing may be a new way to treat Huntington’s disease. Short pieces of double – stranded RNA (short interfering RNAs or siRNAs) are used by cell to degrade RNA of a particular sequence. If a siRNA is designed to match the RNA copied from a faulty gene, then the abnormal protein product of that gene will not be produced [19].

In March 2006, an international group of scientists announced the successful use of gene therapy to treat two adult patriots for X-linked chronic granulomatous disease, a disease which affects myeloid cells and which gives a defective immune system. The study published in Nature medicine, is believed to be the first to show that gene therapy can cure diseases of the myeloid system [20].

In May 2006, a team of scientists led by Dr. Luigi Naldini and Dr. Brian Brown from the San Raffaele Telethon institute for gene therapy (HSR – TIGET) in Milan, Italy reported gene-therapy in which they developed a way to prevent the immune system from rejecting a newly delivered gene [21]. Similar to organ transplantation, gene therapy has been plagued by the problem of immune rejection. So far, delivery of the normal gene has been difficult because, the immune system recognizes the new gene as foreign and rejects the cells carrying it. To overcome
this problem, the (HSR-TIGET group utilized a newly uncovered network of genes regulated by molecules known as micro-RNAs. Dr. Naldini's group reasoned that they could use this natural function of micro RNA to selectively turn off the identify of their therapeutic gene in cells of the immune system and prevent the gene from being found and destroyed. The researchers injected mice with the gene containing an immune-cell micro RNA target sequence, and the mice did not reject the gene, as previously occurred when vectors without the micro RNA target sequences were used. This work will have important implications for the treatment of hemophilia and other genetic disease by gene therapy.

In August 2006, scientist at the National institutes of Health (Bethesda, Maryland) successfully treated metastatic melanoma in two patients using killer T cells genetically retargeted to attack the cancer cells. This study constitutes one of the first demonstrations that gene therapy can be effective in treating cancer [22].

In November 2006 Preston Nix from the University of Pennsylvania school of medicine reported on VR x 496, a gene – based immune therapy for the treatment of human immunodeficiency virus (HIV) that uses a lentiviral vector for delivery of an antisense gene against the HIV envelope. In the phase I trial enrolling five subjective with chronic HIV infection who had failed to respond to at least two antiretroviral regimes, a single intravenous infusion of autologous CD, T cells genetically modified with VRX 496 was safe and well tolerated. All patients had stable or decreased viral load; four of the five patients had stable or increased CD, T cells counts. In addition, all five patients had stable or increased immune response to HIV antigens and other pathogens. This was the first evaluation of a lent viral vector act ministered in U.S. food and Drug Administration – approved human clinical trials for any disease [23]. Data from an ongoing phase I/II clinical trial were presented at CROI 2009.

On May I 2007 More Fields Eye Hospital and University College Houdon’s institutes of ophthalmology announced the world’s first gene therapy trial for inherited retinal disease. The first operation was carried out on a 23 year old British male Robert Johnson, in early 2007. Leber’s congenital amaurosis is an inherited blinding disease caused by mutations in the RPE65 gene. The results of a small clinical trial in children were published in New England journal of medicine in April 2008 [9]. They researched the safety of the subretinal delivery of recombinant adeno-associated virus (AAV) carrying RPE65 gene, and found it yielded positive results, with patient having modest increase in vision, and perhaps more importantly, no apparent side effects.

In May 2008, two more groups, one at the University of Florida and an other at the University of Pennsylvania, reported positive results in independent clinical trials using gene therapy to treat leber’s congenital amaurosi. In all the three clinical trails, patients recovered functional vision without apparent side effects. These studies which used adeno-associated virus, have spawned a number of new studies investigating gene therapy for human retinal disease.

In September 2009, the journal Nature reported that researchers of the University of Washington and university of Florida were able to give trichromatic vision to squirrel monkeys using gene therapy, a hopeful precursor to a treatment for Colour blindness in Humans [24].
November 2009, the journal Science reported that researchers succeeded at halting a fatal genetic disorder called adrenoleukodystrophy in two children using a lentivirus vector to deliver a functional vision of ABCDI, the gene that is mutated in the disorder \cite{25}.

A paper by Komaromy et al published in April 2010, deals with gene therapy for a form of achromatopsia in dogs. Achromatopsia or complete colour blindness is presented as an ideal model to develop gene therapy directed to cone photoreceptors. Cone function and day vision have been restored for of least 33 months in two young dogs with achromatopsia. However, the therapy was less efficient for older dogs \cite{26}. In September 2010, it was announced that an 18 year old male patient in France with beta-thalassemia major had been successfully treated with gene therapy \cite{27}. Beta thalassemia major is an interested blood disease in which beta hemoglobin is missing and patients are dependent on regular life long blood transfusion \cite{28}. A team directed by Dr. Phillipe leboulch (of the university of Paris, Bluebird Bio and Harvard medical school \cite{29} used a lentiviral vector to transducer the human $\beta$-globin gene into purified blood and marrow cells obtained from the patient in June 2007 \cite{30}. The patients haemoglobin levels were stable at 9 to 10g/dl, about a third of the hemoglobin contained the form introduced by the viral vector and blood transfusions had not been needed Leboulch and Philippe \cite{29} and Beals Jacquelyn \cite{30}. Further clinical trials were planned \cite{31}. Bonemerros transplants are the only cure for thalessemia but 7.5% of patients are unable to find a matching bone marrow donor \cite{29}.

**Update in 2011:** In 2007 and 2008, a man being treated by Gero Hutter was cured of HIV by repeated Hematopoietic stem, cell transplantation (See also Allogeneic stem cell transplantation, Allogeneic bone marrow transplantation allotransplantation) with double-delta – 32 mutation which disabled the CCR5 receptor, this cure was not completely accepted by the medical community until 2011 \cite{32}. This cure required complete ablation of existing bone marrow which is very debilitating. In August 2011 two of three subjects of a pilot study were confirmed to have been cured from chronic lymphocytic lenkemia (CLL). The study carried out by the researcher at the university of Pennsylvania use genetically modified T cells to attack cells that expressed the CD 19 protein to fight the disease \cite{33}, in 2013, the researchers announced that 26 of 59 patients had achieved complete remission and the original patient had remained tumor free. Human HGP plasmid DNA therapy of cardiomyocytes is being examined as a potential treatment for coronary artery disease as well as treatment for the damage that occurs to the heart after myocardial infarction Yang, et al. \cite{34} and Hahn, et al. \cite{35}.

The FDA approves clinical trials of the use of gene therapy on thalassemia major patients in the U.S. Researchers at memorial Sloan Kettering cancer center in New York begin to recruit to participants for the study in July 2012 (On cancer, 2012). The study is expected to end in 2014 \cite{31}. In July 2012, the European medicine Agency recommended approved of a gene therapy treatment for the first time in either Europe or the United State. The treatment called Glybera, compensates for lipoprotein lipase deficiency, which can cause severe pancreatitis \cite{36}. The recommendation was endorsed by the European commission in November 2012 \cite{6}, and
commercial roll out is expected in late 2013. In December 2012, it was reported that 10 of 13 patients with multiple myeloma were in remission or very close to it three months after being injected with a treatment involving genetically engineered T cells to target proteins NY-ESO-I and LAGE-II which exist only on cancerous myeloma cells. This procedure had been developed by a company called Adaptimmune [37].

In March 2013, Researcher at the memorial Sloan Kettering cancer center in New York, reported that three of five subjects who had acute lymphocytic leukemia (ALL), had been in remission for five months to two years after being treated with genetically modified T cells which attack cells with CD19 genes on their surface, all β-cells, cancerous or not. The researchers believed that the patient immune systems would make normal T cells and β cells after a couple of months, however, they were given bone marrow to make sure. One patient had relapsed and died and one had died of a blood clot unrelated to the disease [37].

Following encouraging phase I trials in April 2013, researchers in the UK and the U.S. announced they were starting phase 2 clinical trails (called CUPID) and SERCA-LVAD) on 250 patients [38] at several hospitals in the US and Europe to use gene therapy to combat heart disease. These trials were designed to increase the levels of SERCA29 protein the heart muscles and improve the functions of these muscles (first gene therapy, 2014. The FDA granted this a Breakthrough therapy designation which would speed up the trial and approval process in the U.S.A.

In July 2013 the Italian San Raffaele Telethon institute for gene therapy (HSR-TIGET) reported that six children with two severe hereditary diseases had been treated with a partially deactivated lentivirus to replace a faulty gene and after 7-32 months the results were promising. Three of the children had metachromatic leukodystrophy which causes children to lose cognitive and motor skills (Biffi et al, 2013. The other children had wiskott-Aldrich syndrome which leaves them to open to infection, auto immune disease and cancer due to a faulty immune system [39].

In October 2013 the great Ormond Street hospital London reported that two children born with adenosine deaminase severe combined immuno deficiency disease (ADA-SCID) had been treated with genetically engineered stem cells 18 months previously and their immune systems were showing signs of full recovery. Another three children treated since then were also making good progress. ADA-SCID children have no functioning immune system and are sometimes known as bubble children”.

In October 2013, Amit Nathswani of the Royal Free London NHS Foundation Trust in London reported that they had treated six people with hemophilia in early 2011 using genetically engineered adeno-associated virus [40].

In January 2014, researchers at the university of oxford reported that six people suffering from choroideremia had been treated with a genetically engineered adeno-associated virus with a copy of a gene REPT. Over a six month to two year period all had improved their sight.

Choroideremia is an inherited genetic eye disease for which in the past there has been no treatment and patients eventually go blind [41]. In March 2014 researchers at the university of
Pennsylvania reported that 12 patients with HIV had been treated since 2009 in a trial with a genetically engineered virus with a rare mutation known to protect against HIV (CCRS deficiency). Results were promising (Tebas, et al. [42] and Dvorsky [43]).

5. USES AND CHALLENGES

Several uses for gene therapy have been speculated.

These include:

1. **Gene Doping:** In this use, there is a risk that athletes might abuse gene therapy technologies to improve their athletic performance. This idea is known as gene doping and is as yet not known to be in use but a number of gene therapies have potential applications to athletic enhancement.

2. **Human Genetic Engineering:** It has been speculated that genetic engineering could be used to change physical performance, metabolism and even improve physical capabilities and mental faculties like memory and intelligence, although for now these uses are limited to science fiction. These speculations have in turn led to ethical concerns and claims, including the belief that every fetus has an inherent right to remain genetically unmodified, the belief that parents hold the right to modify their unborn offspring, and the belief that every child has the right to be born free from preventable diseases (Baylis and Jason [44] and Evans [45]).

On the other hand, others have made claims that many people try to improve themselves already thought diet, exercise, education, cosmetics, and plastic surgery and that accomplishing these goals through genetics could be more efficient and worthwhile. This view sees the prevention of genetic disease as a duty to human kind in preventing harm to future generation.

**Challenges:** Some of the unsolved problems with the technology underlying gene therapy include:

(i) **Short-lived nature of gene therapy:** Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and the cells containing the therapeutic DNA must be long-lived and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients will have to undergo multiple rounds of gene therapy.

(ii) **Immune response:** Any time, a foreign objective is introduced into human tissues, the immune system is stimulated to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a possibility. Furthermore, the immune system’s enhanced response to invaders that it has seen before makes it difficult for gene therapy to be repeated in patients.

(iii) **Problems with viral vectors:** Viruses, the carrier of choice in most gene therapy studies, present a variety of potential problems to the patient toxicity, immune and inflammatory responses, and gene control and targeting issues. In addition, there is always the fear that the viral vector, once inside the patient, may recover its ability to cause disease.
Multigene disorders: Conditions or disorders that arise from mutations in a single gene are the best candidates for gene therapy. Unfortunately, some of the most commonly occurring disorders such as heart disease, high blood pressure, Alzheimer’s disease, Arthritis and diabetes, are caused by the combined effects of variations in many genes. Multigene or multifactorial disorders such as these would be especially difficult to treat effectively using gene therapy.

For countries in which germ-line gene therapy is illegal, indications that the Weismann barrier (between soma and germ-lines) can be breached are relevant, spread to the testes, therefore could impact the germ line against the intentions of the therapy.

chance of inducing a tumor suppressor gene. It could induce a tumor. This has occurred in clinical trials for X-linked severe combined immuno deficiency (X-SCID) patients, in which hematopoietic stem cells were transduced with a corrective transgene using a retrovirus, and this led to the development of T cell Leukemia in 3 of 20 patients Woods, et al. [46], and Thrasher, et al. [47]. One possible solution for this is to add a functional tumor suppressor gene to onto the DNA to be integrated. However, this poses its own problems, since the longer the DNA is, the harder it is to integrate it efficiently into cell genome. The development of CRISPR technology in 2012 allowed researcher to make much more precise changes at exact locations in the genome [48].

The cost: only a small number of patients can be treated with gene therapy because of extremely high cost (Alipogene tiparvovec or Glybera, for example, at a cost of $1.6 million per patient was reported in 2013 to be the most expensive drug in the world.

6. CONCLUSION

From the forgoing one would begin to think of the possibility of gene therapy in the developing countries. Gene therapy has been successfully carried out in the developed countries in which there has been many success stories relating to this which include gene therapy for osteoarthritis in which the therapy targets the disease process rather than the symptoms [49] and gene therapy for colour blindness which targets three major cones for normal virus designated as L, M and S and allows for absorption for differentiation within the visible spectrum from 380nm – 749nnm for correction.

These, however, show that in the developing countries, researchers could as well embark on such researches and come up with some success if adequate provision and appropriate legislations are made available for them. So far there has never been any reported break through in the literatures of a success in gene therapy in the developing countries like Nigeria. Hence, the developing countries are lagging behind in this new trend of therapeutics hoping that by the vision 2020 health for all, the developing countries should be able to join the league of nations in gene method of therapeutic, for treatment of diseases.

Funding: This study received no specific financial support.

Competing Interests: The authors declare that they have no competing interests.

Contributors/Acknowledgement: All authors contributed equally to the conception and design of the study.
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