



ISSUES IN MEDICINE

Cell and gene therapies at the forefront of innovative medical care: Implications for South Africa

M S Pepper,¹ MB ChB, PhD, MD; M Alessandrini,² PhD; A Pope,³ BA LLB, PG Dip Int Research Ethics;
W van Staden,⁴ MB ChB, MMed (Psych), MD, FC Psych (SA); R J Green,⁵ PhD, DSc

¹ South African Medical Research Council Extramural Unit for Stem Cell Research and Therapy; and Institute for Cellular and Molecular Medicine, Department of Immunology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa

² Department of Pathology and Immunology, Faculty of Medicine, University of Geneva, Switzerland

³ Emeritus Associate Professor, Department of Private Law, Faculty of Law, University of Cape Town, South Africa

⁴ Centre for Ethics and Philosophy of Health Sciences, Faculty of Health Sciences, University of Pretoria, South Africa

⁵ Department of Paediatrics and Child Health, School of Medicine, Faculty of Health Sciences, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa

Corresponding author: M S Pepper (michael.pepper@up.ac.za)

The fields of cell and gene therapy are moving rapidly towards providing innovative cures for incurable diseases. A current and highly topical example is immunotherapies involving T-cells that express chimeric antigen receptors (CAR T-cells), which have shown promise in the treatment of leukaemia and lymphoma. These new medicines are indicative of the changes we can anticipate in the practice of medicine in the near future. Despite their promise, they pose challenges for introduction into the healthcare sector in South Africa (SA), including: (i) that they are technologically demanding and their manufacture is resource intensive; (ii) that the regulatory system is underdeveloped and likely to be challenged by ethical, legal and social requirements that accompany these new therapies; and (iii) that costs are likely to be prohibitive, at least initially, and before economies of scale take effect. Investment should be made into finding novel and innovative ways to introduce these therapies into SA sooner rather than later to ensure that SA patients are not excluded from these exciting new opportunities.

S Afr Med J 2019;109(1):20-22. DOI:10.7196/SAMJ.2019.v109i1.13425

Altering the human genome for therapeutic purposes is now a reality. Several forms of change are possible, but essentially they involve the addition, removal or alteration of DNA. Changes can be effected in various ways such as introducing DNA sequences into cells using viral vectors or using gene editing techniques. From an ethical perspective, gene editing is globally acceptable when performed on somatic cells (i.e. cells of the body excluding gametes – ova and sperm). Gene editing of gametes in humans, particularly for purposes of enhancement, is not condoned.

CAR T-cells

Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is an effective new therapy for patients with aggressive B-cell malignancies including leukaemia and lymphoma. It genetically engineers T-cells to express a synthetic antigen receptor (i.e. the CAR), consisting of an extracellular antigen-recognition receptor (targeting CD19 on B-cells in this therapeutic application) coupled to intracellular signalling domains that allow T-cell activation following recognition of the antigen. The therapy produces a redirected, effector T-cell anti-tumour immune response in a major histocompatibility complex-independent manner. Although CD19 is expressed on all B-cells, malignant and non-malignant, eradication of normal B-cells seems at this time to be well tolerated, and a recovery in non-malignant polyclonal B-cell expansion has been shown in patients with complete response to CD19 CAR T-cell therapy.^[1,2]

Two CAR T-cell therapies (both targeting CD19, Table 1) were approved by the US Food and Drug Administration (FDA) in 2017. The first, tisagenlecleucel, is indicated for relapsed/refractory

(R/R) B-cell acute lymphoblastic leukaemia in paediatric and young patients (<25 years of age). In the pivotal clinical trial with 75 participants (followed up to date), a complete remission rate of 81% was reported.^[3] This response rate is impressive considering that the participants had failed on two or more prior therapies, including allogeneic haematopoietic stem cell transplantation.

The second therapy, axicabtagene ciloleucel, is indicated for R/R B-cell lymphoma in adults. The pivotal clinical trial with 101 participants reported a complete response rate of 54%.^[4] This response is a notable improvement over the outcome of the prior standard of care, namely high-dose chemotherapy and autologous haematopoietic stem-cell transplantation, where overall response rates of <30% and a median overall survival of 6 months are generally observed.^[5]

The European Commission and the National Institute for Health and Care Excellence (NICE) in the UK have recently also approved the use of both CAR T-cell therapies.^[6] Initially, NICE stated that one of the treatments was too expensive to be eligible for coverage by the National Health Service; however, this decision was reversed once a way was found to reduce cost.^[7]

Although these CAR T-cell therapies are approved for different indications and populations (Table 1), their functionality or mode of action is virtually identical: both target and kill CD19-expressing B-cells. Subtle differences do, however, exist in the architecture of the CAR (transmembrane and co-stimulatory domains), which may differentiate the rate of tumour killing and persistence of the CAR T-cells.^[8] The risk of adverse events and even mortality related to neurotoxicity and a systemic immune response (cytokine release

Table 1. Approved CAR T-cell therapies

	Tisagenlecleucel (Kymriah; Novartis)	Axicabtagene ciloleucel (Yescarta; Gilead/Kite Pharma)
Description	CD19-directed genetically modified autologous T-cell therapy	
Indication	Paediatric and young (<25 years) patients with B-cell precursor ALL that is refractory or in second or later relapse	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Includes DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Dosage	0.2 - 5.0 × 10 ⁶ CAR T-cells/kg (for patients <50 kg) 0.1 - 2.5 × 10 ⁸ total CAR T-cells (for patients >50 kg)	2 × 10 ⁶ CAR T-cells/kg (maximum 2 × 10 ⁸)
Gene delivery	Lentiviral vector	Gamma-retroviral vector

CAR = chimeric antigen receptor; ALL = acute lymphoblastic leukaemia; DLBCL = diffuse large B-cell lymphoma.

syndrome) that is associated with CAR T-cell therapies^[9] precludes interchangeability. This means that extrapolation of the CAR T-cell therapies to other patient populations, particularly children, when they have only been tested in adults,^[10] should not be considered lightly. Safety of patients is the priority, followed by efficacy.

Accessibility and socioeconomic status

Often questioned is whether technological advances such as novel immunotherapies, gene therapy and genome editing are relevant to low- and middle-income countries (LMICs), given more pressing priorities such as delivery of basic healthcare services, education, and food and water security. Is it ethically justifiable for LMICs to support use of advanced technologies in the face of challenges in meeting the basic needs of the general population?

Distributive justice concerns the socially just allocation of goods in a society. Although reflecting a noble principle, it is problematic to enforce in resource-strapped settings. A simple egalitarian approach to distributive justice may, however, insist on meeting basic needs first, and it may be justifiable to allocate some resources to all populations who need healthcare. However, resource constraints require careful rationing decisions, often based on finding the most cost-effective treatments for commonly occurring diseases.

Antiretroviral therapy (ART) for HIV in South Africa (SA) provides a pertinent illustration. The principles of health economics lead to the view that it makes sense from both a clinical and an economic perspective to provide ART, because everyone stands to benefit. In practical terms, gene therapy for HIV leading to a 'cure' would be possible and sensible, if the once-off cost of such gene therapy were less than the lifetime cost of HIV treatment, the anticipated medical complications and costs to society more broadly. Currently, the cost of gene therapy in SA would far outweigh the cost of lifetime ART for HIV, although the cost of anticipated medical complications and the costs to society are more difficult to define. Nonetheless, by analogy, the use of CAR T-cell therapies in SA is not currently sensible from a health economics perspective, since the infrastructure, equipment and manufacturing costs are likely to be prohibitive. In the USA, the costs for the FDA-approved CAR T-cell therapies are USD475 000 and USD373 000 for tisagenlecleucel and axicabtagene ciloleucel, respectively.^[11] In general, lower costs are expected for provision of these treatments in Europe and the UK.^[7,12] Cost reductions are likely to occur in the future as these technologies are refined and adapted to local settings. One should also bear in mind that economies of scale are likely to result in significant cost reductions.

According to the World Bank, SA has the highest Gini coefficient globally, which reflects large inequalities in individual/household incomes. This inequality is clearly visible in the healthcare sector,

where more than 50% of total annual health expenditure in the country is in the private health sector (<20% of the population), while less than 50% is in the public health sector (which serves >80% of the population). Several high-end (expensive) technologies are available in the private sector but not in the public sector, which is challenged by budget constraints. It is therefore possible that innovative medicines such as CAR T-cell therapies may enter the SA market initially through the private sector. Although it is regrettable that public sector patients may not benefit initially, being able to demonstrate the efficacy of these innovative medicines in SA patients may persuade the funders of public healthcare to allocate resources for the application of these new medicines, albeit at a significantly lower cost.

This state of affairs raises the question whether SA should refrain from participation and simply be a bystander in the development of rapidly evolving and highly efficacious, albeit costly, new medicines. Arguably, the answer is a resounding negative. To refrain from participation in relevant research and innovative medical practice that, in time, may benefit all South Africans, merely because of current resource constraints, is not sensible or reasonable.

Regulatory oversight

Although manufacture of CAR T-cell and other immune and gene therapies is technologically demanding and resource intensive, it will be possible to overcome these limitations in SA once facilities are constructed and personnel are appropriately trained. The healthcare regulatory system, on the other hand, is markedly underdeveloped and is likely to be challenged by the ethical, legal and social requirements implicated by these new therapies. The challenges must be addressed as soon as possible using guidance and lessons learnt from the USA and EU. It may be noted that on 11 June 2018, the US FDA published detailed and comprehensive draft guidance for the development, review and approval of gene therapies, which addresses issues related to manufacturing, testing and long-term follow-up. In addition, specific guidance was provided for gene therapy for haemophilia, retinal disorders and rare diseases.^[13]

Conclusions

It is critical that SA's diverse populations are involved in research on these new therapies to ensure that they will be safe and effective for local use. Time and effort should be devoted as a matter of urgency to finding novel and innovative ways to introduce innovative therapies such as those described here into the healthcare sector in SA while recognising the diverse needs in our society. This will allow all deserving patients, irrespective of socioeconomic status, to benefit from these new developments and not simply to be bystanders in a rapidly evolving field.

Declaration. None.

Acknowledgements. None.

Author contributions. MSP: initial manuscript conception, initial drafting and subsequent editing; MA: conceptual refinement and manuscript editing; AP: conceptual refinement and manuscript editing; WvS: conceptual refinement and manuscript editing; RJG: conceptual refinement and manuscript editing.

Funding. Work in MSP's group is funded by the South African Medical Research Council (University Flagship and Extramural Unit awards).

Conflicts of interest. None

- Kochenderfer JN, Somerville RPT, Lu T, et al. Long-duration complete remissions of diffuse large B cell lymphoma after anti-CD19 chimeric antigen receptor T cell therapy. *Mol Ther* 2017;25(10):2245-2253. <https://doi.org/10.1016/j.ymthe.2017.07.004>
- June CH, Sadelain M. Chimeric antigen receptor therapy. *N Engl J Med* 2018;379(1):64-73. <https://doi.org/10.1056/NEJMra1706169>
- Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med* 2018;378(5):439-448. <https://doi.org/10.1056/NEJMoa1709866>
- Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med* 2017;377(26):2531-2544. <https://doi.org/10.1056/NEJMoa1707447>
- Crump M, Neelapu SS, Faraooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the International SCHOLAR-1 Study. *Blood* 2017;130(16):1800-1808. <https://doi.org/10.1182/blood-2017-03-769620>
- The Scientist. Two CAR T-cell therapies greenlighted in Europe. <https://www.the-scientist.com/news-opinion/two-car-t-cell-therapies-greenlighted-in-europe-64720> (accessed 20 November 2018).
- Pharmaphorum. NHS to reimburse Gilead's CAR-T in adults. <https://pharmaphorum.com/news/nhs-to-reimburse-gileads-car-t-in-adults/> (accessed 20 November 2018).
- Tran E, Longo DL, Urba WJ. A milestone for CAR T cells. *N Engl J Med* 2017;377(26):2593-2596. <https://doi.org/10.1056/NEJMe1714680>
- Le RQ, Li L, Yuan W, et al. FDA approval summary: Tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 2018;23(8):943-947. <https://doi.org/10.1634/theoncologist.2018-0028>
- Pepper MS, Pope A, Kling S, Alessandrini M, van Staden W, Green RJ. Ethical considerations in the application of cell and gene therapies in children. *S Afr Med J* 2018;108(12):1027-1029. <https://doi.org/10.7196/SAMJ.2018.v108i12.13585>
- American Journal of Managed Care. Evidence-based Oncology. With approval of CAR T-cell therapy comes the next challenge: Payer coverage. 21 February 2018. <https://www.ajmc.com/journals/evidence-based-oncology/2018/february-2018/with-approval-of-car-t-cell-therapy-comes-the-next-challenge-payer-coverage> (accessed 20 November 2018).
- Savage P, Mahmoud S, Patel Y, et al. Cancer drugs: An international comparison of postlicensing price inflation. *J Oncol Pract* 2017;13(6):e538-e542. <https://doi.org/10.1200/JOP.2016.014431>
- US Food and Drug Administration. Vaccines, Blood & Biologics. Cellular & Gene Therapy Guidances, July 2018. <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm> (accessed 20 November 2018).

Accepted 23 August 2018.