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Review

Access to CAR T-cell therapy: Focus on diversity, equity and inclusion

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ABSTRACT

Chimeric antigen receptor T-cell (CAR T-cell) therapy has revolutionized the treatment of hematologic malignancies in patients with relapsed or refractory disease without other treatment options. However, only a very small proportion of patients with an indication for CAR T-cell can access the treatment. The imbalance between supply and demand is magnified in minority and vulnerable populations. Limited access is multifactorial and in part a result of factors directly related to the cellular product such as cost, complex logistics and manufacturing limitations. On the other hand, the impact of diversity, equity, and inclusion (DEI) and their social and structural context are also key to understanding access barriers in cellular therapy and health care in general. CAR T-cell therapy provides us with a new opportunity to better understand and prioritize this gap, a key step towards proactively and strategically addressing access.

The aim of this review is to provide an analysis of the current state of access to CAR T therapy with a focus on the influence of DEI. We will cover aspects related to the cellular product and the inseparable context of social and structural determinants. Identifying and addressing barriers is necessary to ensure equitable access to this and all future novel therapies.

1. Introduction

Chimeric antigen receptor T-cell (CAR T) therapy has revolutionized the treatment of several hematologic malignancies, leading to increased rates of remission and improved outcomes in patients with relapsed or refractory disease without other treatment options [1]. Based on the success of CAR T-cell therapy in hematologic malignancies, researchers have expanded their application to oncology and other areas of medicine. There are currently >1300 registered clinical trials in blood cancers, solid tumors, HIV, and autoimmune disease [2]. CAR T-cell therapy is a type of immunotherapy involving engineering a patient's T-cells to express synthetic proteins on their surface called chimeric antigen receptors (CARs) which can then recognize and target cancer cells [3]. Several clinical trials in CAR T-cell therapy in hematologic malignancies have demonstrated promising results in terms of overall survival and long-term outcomes, surpassing standard care options [4,5]. Six CAR T-cell therapies have been approved by the US Food and Drug Administration (FDA) for the treatment of various hematologic malignancies since 2017 [6].

In recent years, concerns regarding equitable access to healthcare, particularly access to novel, more expensive therapies such as CAR T-cell, have garnered increasing attention. While major progress has been made regarding the science, therapeutic applications, and management of complications, access to CAR T-cell remains suboptimal, and only a very small proportion of patients with an indication for CAR T-cell therapy receive the treatment. This limited access is thought to be due to several unique challenges associated with CAR T-cell therapy including cost, complex logistics and manufacturing limitations which can further exacerbate existing disparities [7].

It is well known that promotion of equitable delivery of healthcare, and thus access, has the potential to improve overall health outcomes for underrepresented populations [8]. CAR T-cell therapy provides us with a new opportunity to better prioritize and address this gap. The impact of diversity, equity, and inclusion (DEI) is key to understanding access barriers in cellular therapy and health care in general. Diversity encompasses a range of human differences, including but not limited to race, ethnicity, gender, sexual orientation, age, social class, physical abilities or attributes, religious or ethical values, national origin, and political beliefs [9]. Equity involves providing different levels of support and assistance adjusted to specific needs to ensure fair processes and

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outcomes [10]. Finally, inclusion allows for involvement and empowerment through acknowledgement of the inherent worth and dignity of all people [9]. These principles of DEI are connected and influenced by the complexity of social and structural determinants of health, as shown in Fig. 1.

Presently, there are about 200 health care centers spread throughout 39 states that report to the US Cellular Immunotherapy Data Resource (CIDR). In 2021 the Center for International Blood and Marrow Transplant Research (CIBMTR) reported a total of 2000 CAR T-cell treatments, 95% done by US centers [14]. This same year in the United States, there were 81,560 new cases of Non Hodgkin Lymphoma (NHL) of which 30%–40% were diffuse large B-cell lymphoma (DLBCL) [15]. Using DLBCL as an example, 45% of patients will relapse or develop refractory disease, which leads to over 10,000 patients yearly who may benefit from CAR T-cell therapy [16].

Thus, there is a large discrepancy between the number of disease-eligible patients and the number of patients who received it. Compromised health care capacity, along with social and structural determinants exacerbates regional and national disparities. The situation is even more problematic globally, where there is even more limited access to CAR T-cells.

The aim of this review is to provide an analysis of the current state of access to CAR T-cell therapy with a focus on the influence of DEI. We will initially cover aspects of the cellular product and then the inseparable context of social and structural determinants (Fig. 1). All of these are, to some extent, linked to DEI. Addressing barriers in necessary to ensuring equitable access to novel therapies.

2. Why such an imbalance?

CAR T-cell therapy requires on-demand manufacturing to create an individualized product [17]. Commercial CAR T-cells are produced in a centralized system, and the process requires many steps including transportation of patient blood samples to and from the manufacturing site, the isolation of T-cells, transduction of these T-cells using lentivirus to introduce the CAR gene, and then expanding and activating those modified T-cells so that they can be used for this therapy [17,18]. This process results in a turnaround of approximately 3–6 weeks to produce each CAR T-cell product [19]. The lengthy manufacturing process results in a delay that is particularly risky for patients with aggressive disease. For instance, 9% of all patients who underwent leukapheresis for collection of autologous T-cells in the KarMMa trial, did not ultimately proceed with the infusion due to progression of disease, physician decision, or death [17,19]. Decentralized CAR T-cell manufacturing from industry to the point-of-care at academic centers might save time [20]. However, the logistics of this process requires an infrastructure, training and quality standards that are absent in most health care centers, which may also be unwilling or unable to absorb the implementation costs. Alternative strategies to improve scalability, such as faster manufacturing or the use of allogeneic product are currently in development [21–23].

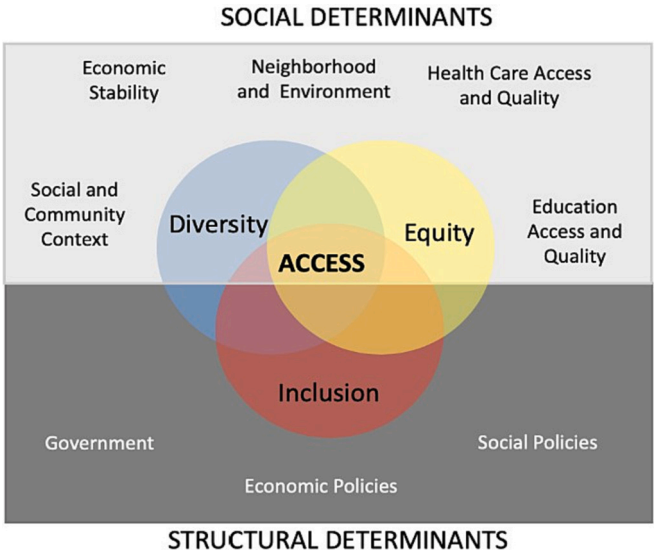

Fig. 1. Diversity, equity, and inclusion depend on one another and are influenced by the environment, illustrated in this figure in two shades of gray. The influence of the environment is represented by social and structural determinants of health. Social determinants include the conditions under which people are born, grow, live, work and age [11]. Structural determinants of health include the social, economic, and political mechanisms which generate social class inequalities and inequities in society [12,13].

Access is not only limited by the complex logistics mentioned above, but also by the cost of the therapy itself. Palani et al. published their experience and found that the cost of manufacturing was approximately $35,107 when excluding cost of the lentivirus [20]. This is still far away from the average cost of a single product of an FDA-approved CAR T-cell therapy which is between $373,000 to $475,000 [24,25]. There are additional costs that include the procedures necessary to produce the infusions (i.e. leukapheresis and lymphodepletion therapy), as well as the cost of inpatient admission and management of adverse effects [25,26]. The price of CAR T-cell therapy is clearly high. The prejudice related to its value can only be addressed by collecting relevant data and reducing the payer's uncertainty of cost-effectiveness analysis [27,28].

CAR T-cell therapy is available in <4% of health care centers in the US, most of which are large academic medical centers. This results in additional travel and lodging costs which are exacerbated by the fact that patients are required to have a caregiver and to remain in the vicinity of the institution in which they receive their therapy for at least one month after infusion. Thus, there is also the short-term loss of income for both the patient and their caregiver which must be factored into the overall cost of treatment. Taken together, the real-world cost of CAR T-cell therapy can range from $700,000 to $1 million which may make the treatment unaffordable to those patients without robust financial and/or social support [29]. The degree to which this cost is covered is currently unclear and dependent on type of insurance coverage, especially private versus public coverage [29]. Increasing availability by involving and preparing community.

hospitals and other health care facilities that can deliver CAR T-cell therapy safely should be an immediate priority to improve access.

3. General social and structural determinants in health care

Social and structural determinants of health are outlined in Fig. 1. These factors are complex and interdependent, influencing patients' overall health outcomes and ability to access healthcare [30,31]. Access disparities are pervasive across race, gender, age, and income.

The United States has a high ethnic diversity. According to the 2020 Census, Caucasians represented only 61.6% of the US population. The other 38.4% was formed by Hispanic (18.7%), African American (12.4%), Asian (6%), American Indian (1.1%), and others (0.2%) [32]. With such a diverse populace, it follows that cultural background and belief systems can influence how, when, and where community members seek care [33]. Furthermore, racism and discrimination are deeply ingrained in the social, political, and economic structures of our society [34,35]. For minorities, these differences result in unequal access to quality education, healthy food, livable wages, affordable housing, and health [36].

Nearly 78.5% of the US population speak English as their primary language. Spanish is the second most spoken language (13.2%) [32]. Language barriers in healthcare may lead to miscommunication between medical professionals and patients. This, in turn, can result in decreased quality of healthcare, decreased satisfaction with the healthcare received, and detrimental effects on patient safety. In

addition, interpreter services contribute indirectly to increased cost and the length of treatment visits [37].

The census estimates that 12.8% of the population lives in poverty [32]. There is a positive relationship between income and healthcare outcomes [38–40]. The income determines where a person lives, what kind of health insurance they have and how much out of pocket costs they can afford. Poverty also hinders people from participating in community life, engaging in healthy activities, or accessing healthcare services when needed [41]. In the 2020 Census 13.9% of people lived in nonmetropolitan counties and 86.1% lived in metropolitan counties [42]. Residing at a farther distance from healthcare facilities also decreases health service utilization and imposes socioeconomic and clinical disparities on patients [13,41], particularly for those receiving later-line oncology therapy who may have poorer performance status [41].

The US is supported by one of the most complex and expensive healthcare systems in the world, with 18.6% of the gross domestic product ($4.3 trillion) spent on healthcare in 2021. However, it has the lowest life expectancy among large wealthy countries [43–45].

The data on health insurance in 2021 shows that 8.3% of Americans were uninsured, and that 66% of those with insurance coverage had private health insurance, versus 35.7% covered by public health insurance providers including Medicaid, Medicare, Veterans, and Military Health Service [42,46]. American Indian and Hispanic groups were significantly less likely to be insured as well as for those from low-income households, minority communities, and “inner city” and “rural” areas [47,48].

4. DEI and access to cellular therapy

DEI is an important framework that influences the fair and inclusive treatment of individuals from diverse backgrounds. When considering CAR T-cell therapy within the context of DEI, it is crucial to ensure equitable access, eliminate disparities, and promote inclusivity in all aspects of the treatment. To foster diversity, it is essential to accept the goal that CAR T-cell therapy should be accessible for all eligible patients, regardless of their background. However, according to the CIBMTR, 79% of patients who received CAR T-cell therapy were Caucasian, 6% were African American, and 8% Hispanic or Latinos [14].

Medicare reported that 87% of patients receiving CAR T-cell therapy for B-cell lymphoma were Caucasian [49]. Finally, Ahmed et al. used the Vizient Clinical Database to capture and analyze 4396 patients who received CAR T-cell therapy; only 5.9% of patients were African American [50]. This clear lack of diversity is a major barrier that needs to be analyzed and systematically addressed.

Minority groups are also underrepresented in clinical trials [50]. The number of African American participants in 7 CAR T-cell pivotal trials ranged from 1 to 12 participants (2%–5%), with an extremely low participants/prevalence ratio (0.02), especially in multiple myeloma, which is more common among African American persons [51]. One explanation for this is that geographic distribution of clinical trials for CAR T-cell did not include 60% of the states with the highest proportion of African American residents [52]. This means that new therapies are studied in populations that could differ dramatically from those to whom the therapies will be applied [53]. These differences could have a major impact on real-world outcomes.

There are some special populations that are also underrepresented and require special attention based on their higher incidence of hematological malignancies**.** Patients with Down syndrome have an increased risk of leukemia and historically have poor outcomes post-relapse with severe toxicity with salvage chemotherapy and stem cell transplant [54]. For this reason, there is a need for new interventions in this patient population and CAR T-cell therapy may be a new option. There is no data available about CAR T-cell therapy access, and the number of patients with Down syndrome in the ELIANA trial was small (7 of 97 patients) [5]. Patients who are living with HIV have been excluded from clinical trials evaluating this cell therapy. However, they are not excluded in the package insert for currently approved CAR T-cell therapy [55]. There is no data available about patients living with HIV and access to CAR T-cell. It is necessary to increase their participation to improve our understanding of their safety and efficacy in a group that has been excluded from such trials in the past.

As discussed briefly above, socioeconomic status is an important barrier to equitable health care, and access to CAR T-cell therapy is not an exception. Ahmed et al. reported that 321 of the 4396 CAR T-cell patients (7.3%) were from low-income neighborhoods [50]. Furthermore, patients with household incomes less than $50,000 were approximately 30% less likely to participate in CAR T-cell therapy clinical trials.[56.] In another study, patients with household poverty who received treatment with CAR T-cell therapy for acute lymphoblastic leukemia (ALL), whether commercial or academic, had similar response rates and survival outcomes compared to other patients, regardless of socioeconomic status and neighborhood opportunity. Thus, access to CAR T-cell therapy may ameliorate factors influencing disparate outcomes observed in other treatment settings for children with ALL [57].

Geographic accessibility is another crucial factor, as patients are required to remain near the treatment facility for a month after CAR T-cell infusion. In Ahmed et al.'s study, 29% patients lived >120 min from the facility [50]. Snyder et al. [58] used geographic information system techniques to calculate the shortest travel distance and time between patients with relapse/refractory DLBCL and the nearest center with CAR T-cell therapy. Of 3922 patients eligible for CAR T-cell therapy, >37% had to travel more than one hour to the nearest academic hospital. They also found that longer travel times were significantly associated with higher poverty rates and particular races/ethnicities [58].

Referral patterns from the community to CAR T-cell therapy centers have also shown to impact timely access. CAR T-cell therapy is limited to well-resourced academic medical centers with hematopoietic transplantation experience, adequate training, technologies and accredited by the Foundation for the Accreditation of Cellular Therapy (FACT) [17]. However, NHL and multiple myeloma (MM) patients are mainly treated by community oncologists. For this reason, enhancing communication between the CAR T-cell center and the referring oncologist is necessary [56,59]. Reducing wait times by 2 months increased the number of eligible patients receiving CAR T-cell by at least 10.7% and generated a 3.3% increase in survival gains per treated patient [60]. A study performed in 2019 reported that 29% of US community-based.

hematologists/oncologists had never referred any patients for CAR T-cell therapy. The top two barriers to prescribing/recommending CAR T-cell therapy, as reported by the physicians, were the cumbersome logistics of administering therapy and following patients (52%), and the cost of the therapy (46%). Other top concerns included high toxicity (24%) and lack of long-term survival data (19%) [61].

Finally, health insurance coverage is a major determinant of high-quality cancer care and CAR T-cell access [62,63]. Insurers and governments are slow to cover expensive CAR T-cell therapy. For example, Tisagenlecleucel was approved in the United States in august 2017, but Medicare did not issue a national coverage determination until August 2019 [64]. Some Medicaid programs still do not cover the therapy, and commercial insurers generally offer coverage on an individual basis. However, the case-by-case approval process can add weeks of delay, particularly among smaller insurers plans where the CAR T-cell technology or urgency of request is not well understood.

5. What is happening outside of the United States?

There is a wide use of CAR T-cell therapy in Europe and China, but access is limited in developing countries in Southeast Asia, Africa, and Latin America [65].

Europe has four autologous CAR19-T-cell products and one BCMA approved and available [66]. In February 2021, the Spanish pharmaceutical regulator authorized the first CAR T-cell therapy approved by a.

European national authority, the ARI-0001 CAR T-cell developed by

the Hospital Clinic in Barcelona [67,68].

Despite the EU's efforts to tackle variable access across the continent with initiatives like the European Cancer Inequalities Registry, access to CAR T-cell therapies is not the same in all European countries and the EU member states in Central and Eastern Europe still struggle compared to Western countries [67]. Recently, CAR T-cell centers have expanded to several locations in countries like Czechia and Poland, which have also initiated funding schemes, but other states such as Romania and Slovakia are still at earlier stages of adoption [67].

In the Asia-Pacific region, "off the shelf" CAR T-cell therapies are available in Australia, Japan, South Korea, China, and Singapore [66]. China developed Relmacabtagene Autoleucel, approved by the China National Medical Products Administration (NMPA) in 2021 [69]. China is also the country with the most CAR T-cell clinical trials registered on ClinicalTrials.gov (accessed on 10 March 2022), with 460 studies, even higher than the USA with 286 studies [70]. India also developed their own CAR T-cell product, Varnimcabtagene autoleucel [65,20].

In Latin America, Brazil is the only country with two CAR T-cell therapies approved [71,72] and locally developed CAR T-cell therapy that has been used to treat individuals with B cell lymphoma in a compassionate use protocol. There are a few clinical trials in Mexico, Brazil, and Argentina, but most of them are associated with studies that are registered in another country [70].

There are no currently CAR T-cell therapy products approved in Africa and determining the size of the potential CAR T-cell market is impossible due to the absence of a registry [73]. Africa has a high disease burden of HIV, tuberculosis, malaria, and childhood treatable diseases. Therefore, moving resources from these entities to cell therapy is unlikely [73,74]. The gap between Latin America and Africa with the other continents is the result of limited capacity in terms of money, human resources, and infrastructure. And is compounded by the lack of sufficient/appropriate legislation and government support and cultural sensitivities related to traditions and belief systems [73,74].

6. Discussion

CAR T-cell therapy is an effective and lifesaving therapy for patients with no more treatment available. This therapy has experienced an impressive advance in the last 5 years and its indication will soon be extended to other pathologies. But the question is, what can we do to ensure equitable access, eliminate disparities, and promote inclusivity in all aspects of CAR T-cell treatment? The current challenge is clearly an economic and financial one, with direct ethical implications.

Access to CAR T-cell therapy depends on the availability of economic resources and specialized medical care. There is still an imbalance between the supply and the demand that needs to be resolved. Once the.

CAR T-cell is available, there remains an obligation by institutions and providers to decrease disparities by addressing DEI and recognizing opportunities for increased inclusion.

Improving CAR T-cell access from a DEI approach involves implementing strategies and initiatives that address the barriers and disparities faced by diverse populations. Currently every aspect of CAR T-cell therapy challenges access for vulnerable populations [75]. Some of these strategies are listed on Table 1 and includes addressing social and structural determinants of health, financial assistance programs, education and awareness, cultural competency training, collaborative partnerships, research representation, policy, and advocacy.

To guarantee universal availability, a change in culture is required, by both the scientific community and governments, who must develop health legislations and health economics that focus on DEI. Cost reduction is important [17]. Innovative technologies such as faster strategies will soon be available, and this will further shorten manufacturing times [17]. "Inhouse" production of CAR T-cells can reduce the cost of centralized production [75], which requires investment and intensive training. It is vital that every country develops new health legislation, invests in cell therapy research and production, and improves networking with organizations that regulate its synthesis and distribution, and especially entities that can guarantee its quality. Every center in which allogeneic bone marrow transplants are performed has all the necessary hospital and human resources to apply this new cell therapy. Increasing academic CAR T-cell production at points of care and decreasing the demand for commercial sources is also a helpful strategy to enhance access, with the limitation of a low number of contributing centers relative to a large and increasing demand [17].

Table 1
Strategies to address barriers to cell therapy access according to social and structural determinants of DEI

Social determinants of health
• Identify and address disparities in health care access • Cultural competency training for health care providers • Psychosocial and financial support for patients and caregivers • Health care education for patients and caregivers • Collaborations and partnerships to share knowledge and expertise to improve quality and outcomes nationally and globally • Increase DEI in clinical trial participation

Structural determinants of health
• Infrastructural development to promote geographic access • Policies addressing product cost reduction and transparency • Policies to expand and provide adequate health insurance • Policies to facilitate social strategies • Public Health Advocacy • Funding for health care innovation

Finally, health equity is a complex, multifaceted roadblock to health care access, and organizations should think about how they approach it [76]. Racism and discrimination are present in every society and explain why African Americans, Asian communities, and Latinos born in the U. S., face illnesses earlier, more severely, and suffer higher rates of impairment and death compared to Caucasians [77]. Many of these problems start before they even approach the health care system for help. That is because their socioeconomic status puts them at a disadvantage [77]. We believe this disadvantage may be exacerbated by DEI-related issues. Organizations should consider each community's demographic, its culture, history of racism, and local events that might influence whether people are hesitant to seek care when needed [78]. National programs and drug companies need to participate more in supporting patients, financial infrastructure equipped to offset costs and diminish logistical burdens in providing equitable care that led to equitable outcomes regardless of socioeconomic status and neighborhood opportunity. The long-term goal is to make these therapies available to everyone, across all health care barriers. This will require international networking, collaborations and global partnerships that will likely involve both the public and private sectors.

7. Future considerations

Universal access to CAR T-cell cell therapy is a unique challenge, especially for minorities and those in a lower socioeconomic stratum. Improving CAR T-cell access from a DEI perspective involves a multifaceted approach implementing strategies and initiatives that address the barriers and disparities faced by diverse populations. Addressing issues more directly related to the product itself, such as escalating manufacturing and increasing cell therapy delivery sites, will likely provide the most immediate improvements. However, this will only provide a partial fix to a much deeper problem.

Socioeconomic factors significantly impact access to immunotherapy. High costs, limited insurance coverage, healthcare infrastructure disparities, and educational barriers contribute to disparities in accessing these life-saving treatments. Addressing these socioeconomic disparities requires a multifaceted approach involving policy

interventions, patient support programs, education, and increased equity in clinical trials. To improve access to CAR T-cell therapy for minorities such as underrepresented ethnic groups and individuals of low socioeconomic status, it is crucial to address these social and structural determinants of health. This requires implementing policies and initiatives that prioritize equitable healthcare delivery, reduce financial barriers, and enhance representation in clinical trials. Furthermore, collaborations between healthcare providers, policymakers, and community organizations can help identify and overcome barriers to access, promote culturally competent care, and develop targeted outreach programs.

While specific interventions may vary depending on regional contexts, the overarching goal should be to create a healthcare system that ensures universal access to novel immunotherapies like CAR T-cell therapy. By addressing diversity, equity, and inclusion within healthcare delivery, we can strive towards a more equitable and accessible landscape for patients from underrepresented ethnic groups and low socioeconomic status, ultimately improving health outcomes and reducing disparities.

The future is here, though unevenly distributed. By addressing the current challenges and working collaboratively across various stakeholders, we can pave the way for a more widespread and equitable adoption of CAR T-cell therapy, ultimately benefiting a larger number, ideally all of the patients in need.

Practice points

- There are clear barriers to the access of new cellular therapies, with an increasing imbalance in supply and demand
- These barriers are partially related to product-related issues such as cost, complex logistics and manufacturing
- Outside product-related factors, social and structural determinants of health and their impact on DEI are major barriers to cellular therapy

Research Agenda

- New cellular therapies represent an opportunity to better understand barriers to complex health care
- There should be more effort and focus on research addressing DEI and its impact on resulting disparities in US and global access to cellular therapy.
- Research should include development and support of US and global databases that gather relevant datapoints contributing to a better understanding of how socioeconomic disparities and DEI affect access and outcomes.

Declaration of Competing Interest

None.

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