



## Reconsidering REMS Mandate May Improve CAR T-Cell Therapy Accessibility



**Nausheen Ahmed, MD**, Associate Professor, Division of Hematologic Malignancies and Cellular Therapeutics at the University of Kansas Medical Center, Kansas City, KS

**Q / What was your rationale for the study?**

Investigators of a study recently published in *Blood Advances* assessed toxicity onset and duration in patients receiving chimeric antigen receptor (CAR) T-cell therapy to test the viability of FDA Risk Evaluation and Mitigation Strategy (REMS) mandates.<sup>1</sup>

*CancerNetwork* spoke with the study's lead author, Nausheen Ahmed, MD, an associate professor in the Division of Hematologic Malignancies and Cellular Therapeutics at the University of Kansas Medical Center in Kansas City. She shared post-CAR T-cell therapy toxicity findings and discussed their implications regarding patient accessibility and a potential revision to FDA guidelines.

Ahmed highlighted the relatively low occurrences of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) at 2 weeks after CAR T infusion. Cooperation between a patient's primary care physician and a specialized care center may ensure that physical and financial constraints are reduced for patients without sacrificing access to care. Additionally, the findings supported a more flexible approach, whereby patients undergo a 2-week monitoring period within a certain distance of a specialized care center followed by a collaborative assessment of a patient's individualized needs beyond that period.

**Ahmed /** The rationale for this study started from my background in understanding more about accessibility issues with CAR T. Currently, CAR T-cell therapy is not your regular off-the-shelf drug that, if prescribed, patients just get the next day. It's one of those therapies that have a lot of upfront investment with the patient's time. It does carry some financial and physical burden on the patient from the time of collection of the cells all the way up to the postmonitoring period. Some of my prior work demonstrated that there are groups of patients who are not able to get CAR T or have a lower likelihood of getting CAR T, such as those from lower socioeconomic classes and those who may be from ethnic and racial minority groups, especially African American groups.

I demonstrated that in 2022 in one of my papers,<sup>2</sup> as well as one in 2024, which we recently published in *Transplantation and Cellular Therapy*.<sup>3</sup> We also found that there are some other groups of people, such as those living more than 2 hours from a treatment center, who may not have adequate access to CAR T.

Putting it all together, the question was, “Is there any part of this whole CAR T process that is contributing to the physical and financial burden and is not of much value? Is there anything that we can do to make it easier for the patients without compromising safety or efficacy?” One thought that came to my mind was that there’s an FDA REMS mandate [stating that] patients have to relocate to be within 2 hours of the center for up to 4 weeks and they should avoid driving for up to 8 weeks from the day that they get their CAR T-cell therapy. Are those restrictions necessary?

[These mandates] were specifically put in place for monitoring 2 initially unique toxicities of CAR T, which are ICANS and CRS. My study of 475 patients with non-Hodgkin lymphoma [included patients] who received axicabtagene ciloleucel [Yescarta], tisagenlecleucel [Kymriah], or lisocabtagene maraleucel [Breyanzi]. These are the 3 CAR T-cell products they received as the standard of care. We wanted to see whether these toxicities occur up to the 4-week mark [of treatment]. Do they occur beyond that to justify those [REMS] restrictions?

We found that after 2 weeks, the incidence of CRS was 0% and the incidence of ICANS was [approximately] 1%. Our study, based on these data, gives us some grounds to revisit those requirements and see whether we can reduce that time to a 2-week mandatory period, making it more flexible so that patients

and their doctors can decide how long the patient needs to be monitored beyond the 2 weeks. This might help [improve] access because patients [currently] have to relocate close to a center. The FDA mandate is 2 hours [within proximity to a center], but a lot of times, our centers have even stricter mandates.

“[CAR T-cell therapy] does carry some financial and physical burden on the patient from the time of collection of the cells all the way up to the postmonitoring period.”

—Nausheen Ahmed, MD

They may say within 30 minutes, 45 minutes, or 60 minutes. If [one goes] to different centers, there will be different requirements. A patient may have to relocate closer to the center and bring a caregiver with them and then not be able to drive for 8 weeks. The study results pretty much demonstrate that these [requirements] need to be revised.

**Q / Aside from ICANS and CRS, can you provide a brief general overview of the results of your study?**

**Ahmed /** We also explored causes of death. Although we focused on neurotoxicity and CRS, we wanted to know whether we were missing something or whether patients were dying due to something else that needed to be monitored closely for 4 weeks. We found that within the first 4 weeks, neurotoxicity and infections were the main causes of death. Beyond 4 weeks—we went up to 90 days—the incidence of death did not

go down. In fact, there were still patients dying; they were dying of infections, primarily.

That [outcome] was instructive in at least 2 ways. First, there’s no magic to day 28. This is a whole continuum of care for the patient. A lot of times, it’s the primary referring physician who takes over the care of the patient after the 28 days, and they may not be completely in tune with managing or recognizing these infections or understanding the complications of CAR T-cell therapy. These data inform us that we need to have more of a collaborative approach with our referring doctors in order to improve survival of the patients. The answer is not to keep the patients near the center for 90 days; the answer is more about allowing them to go back to their homes and then to

empower, educate, and involve them and collaborate with their community doctors to improve their survival. The level of involvement of the treatment center must be individualized based on the locally available infrastructure and expertise.

**Q / What do you propose as the new monitoring guidelines?**

**Ahmed /** We saw that the incidences of CRS and ICANS were as expected, as they usually occurred within the first 2 weeks [of therapy]. [Therefore], monitoring can be [conducted] in an inpatient or outpatient [setting] by the treatment center. It’s important in the first 2 weeks that the patient is monitored very closely, which they are right now. Patients are either admitted to the hospital for a period of time, or they’re monitored almost on a daily basis with 24/7 access to care bypassing the emergency department for at least 2 weeks. Beyond that, [monitoring] would have to depend on

what's going on with the patient. Are their blood counts very low? Are they at a high risk of infection? It has to involve more [individual-based] decisions on whether the patient can go back, stay home, and be monitored locally. In this day and age, we're still monitoring them very closely, but that can be more flexible and more individualized for each patient.

**Q / Are there plans to evaluate other CAR T-cell therapies for adverse effects [AEs] beyond those listed in the study?**

**Ahmed /** Our group has [previously] looked at multiple myeloma and at the 2 CAR T-cell therapies that are available for myeloma, which are idecabtagene vicleucel [ide-cel; Abecma] and ciltacabtagene autoleucel [cilta-cel; Carvykti]. We recently published [findings] in *Transplantation and Cellular Therapy* demonstrating that the chances of CRS or ICANS starting after 2 weeks are extremely low.<sup>4</sup> We also looked at what the causes of death were with the same question in mind for those constructs. We found that infections, again, were predominantly the reason for death, even in the population of patients who had not progressed.

In our multiple myeloma findings, there was also a different AE that was not seen in our lymphoma findings, which is hemophagocytic syndrome. Immunotherapy [may be] associated with hemophagocytic syndrome. There were some deaths from that as well, which is another thing to watch out for with CAR T in general. That's one of the newer AEs that we're becoming more aware of. The onset of that is sometimes a little beyond CRS, but at the same time, if a patient is doing well beyond 2 weeks, there's no reason to keep monitoring [them on site]. They need to be monitored, but it can be done via comanagement with their primary doctors, and it should be more individualized.

**Q / How should clinicians utilize and implement the data into their clinical practice?**

**Ahmed /** Right now, we're still bound to the REMS mandates. We wouldn't be able to let patients leave before 4 weeks, and we wouldn't be able to tell them [they can] drive. The next step is seeing what the FDA thinks about these data and whether they think that this is enough evidence for them to reconsider their REMS mandates.

**Q / Can you comment on the recent findings that CAR T-cell therapy may lead to secondary malignancies? Would this affect the use of these agents?**

**Ahmed /** My study did not capture second primary malignancies because the follow-up was just up to day 90. Within the first 3 months, there aren't many second malignancies. There are some real-world data coming out [showing] that, even as early as within 2 years [of treatment], there are second primary malignancies. Mostly, those second primary malignancies would be myelodysplasia, leukemia, or skin cancers. The FDA has raised concerns about T-cell malignancies [following] CAR T-cell therapy. That is very rarely seen and is not a major concern. The other second primary malignancies are something that we will be seeing more of as we use more of these therapies.

Would that deter me from using CAR T-cell therapy? I don't think so. We have more choices these days, [such as] bispecifics. Still, the outcomes with CAR T-cell therapy in lymphoma and myeloma are still better than the outcomes with some of these other drugs. [Clinicians] have to think about the efficacy and all those [risks] when considering a therapy. The patients should [also] be informed and know what the risks are.

**Q / Is there anything else that you'd like to highlight within your study?**

**Ahmed /** The main take-home message is that we have a [long way to go] in order to improve outcomes for these patients who are receiving CAR T-cell therapy. Specifically, one of the areas where we can make a difference is infection prevention and management. [Considering] the way things have been divided into such blocks of time [before patients] go to the referring physician, there may be a gap in that transition. There has to be more of a hybrid model of care. There has to be more involvement of our referring doctors or community doctors in detecting and managing these infections or working with the specialized center in order to bypass the [emergency department] with other strategies to help these patients. That's going to be important. If there are enough data to say that the patients do not need extra restrictions beyond 2 weeks, which is what [data from] our studies show, then reconsidering the requirements will be one step toward decreasing disparities in access [to CAR T-cell therapy]. There are many other things that can be done at many other levels. This will be one of the things that I will be looking forward to seeing [progress]. ■

**References**

1. Ahmed N, Wesson W, Lutfi F, et al. Optimizing the post-CAR T monitoring period in recipients of axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel. *Blood Adv*. Published online July 23, 2024. doi:10.1182/bloodadvances.2023012549
2. Ahmed N, Shahzad M, Shippey E, et al. Socioeconomic and racial disparity in chimeric antigen receptor T-cell therapy access. *Transplant Cell Ther*. 2022;28(7):358-364. doi:10.1016/j.jtct.2022.04.008
3. Ahmed N, Sun F, Teigland C, et al. Chimeric antigen receptor T-cell access in patients with relapsed/refractory large B-cell lymphoma: association of access with social determinants of health and travel time to treatment centers. *Transplant Cell Ther*. 2024;30(7):714-725. doi:10.1016/j.jtct.2024.04.017
4. Wesson W, Dima D, Suleman N, et al. Timing of toxicities and non-relapse mortality following CAR T therapy in myeloma. *Transplant Cell Ther*. Published online June 11, 2024. doi:10.1016/j.jtct.2024.06.012