Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

adjustment for all other known clinical risk factors did not affect the main outcome. Most importantly, the study presents a new locus with overt molecular relevance. However, the data must be verified in independent studies using a similar approach, and ideally in prospectively designed cohort studies. Further functional experiments using genetically modified animals could shed light on the protective role of rs708113 in *WNT3A-WNT9A* in hepatocarcinogenesis. Also, integrating the novel locus with previously known loci in *PNPLA3*, *TM6SF2*, and *HSD17B13* to generate a polygenic risk score would be an attractive approach to test its utility in supporting clinical decisions. For that, it could be interesting to calculate the population-attributable risk of each locus individually, and in combination. This study is highly laudable and the key finding should stimulate others to address questions unanswered so far.

We declare no competing interests.

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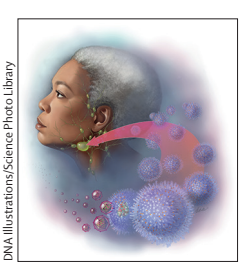
Early immunomodulators with CAR T-cell immunotherapy in the COVID-19 era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The safety endpoints in ongoing immunotherapy trials need reevaluation. With regard to chimeric antigen receptor (CAR) T-cell management, corticosteroids and interleukin-6 (IL-6) blockers are being administered earlier (or in a prophylactic setting) to treat and prevent CAR T-cell therapy-related toxic effects. Pivotal trials are exploring the use of immunomodulators (corticosteroids, IL-1 blockers, and IL-6 blockers) not only to treat CAR T-cell therapy-related toxic effects, but also to prevent them. In the ever-growing research effort to design sophisticated and durable CAR constructs, targeting novel and often multiple tumour antigens, toxic effects are likely to occur more often with a corresponding increase in cumulative immunosuppressant use. Whether early or preemptive corticosteroids and immunomodulators should continue to be used to mitigate CAR T-cell therapy-related toxic effects, when such a strategy is associated with an increased risk of infections and diminished SARS-CoV-2 vaccine responses, remains a timely question and probably will involve a balancing act.[1] To that end, Topp and colleagues[2] and Caimi and colleagues[3] provided a set of results showing the potential of preemptive corticosteroids and tocilizumab, respectively, to mitigate the risks of severe cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[2,3]

A subgroup analysis by Topp and colleagues from the pivotal ZUMA-1 trial evaluated the incidence and severity of CRS and ICANS (primary endpoints in cohort 4) with early administration of corticosteroids and tocilizumab. The results showed that the efficacy outcome (objective and complete response rates) and the incidence of any grade CRS and ICANS were similar to the ZUMA-1 trial. Although there were no grade 4 or worse toxic effects reported, grade 3 CRS and ICANS

occurred at rates of 2% and 17%, respectively.[2] Despite earlier dosing, the cumulative corticosteroid dose in patients who needed corticosteroid therapy to treat on-target-off-tumour toxicities was lower than those in the pivotal ZUMA-1 cohorts. Similarly, Caimi and colleagues examined prophylactic tocilizumab administration 1 h before CD19-directed CAR T-cell infusion in 20 patients with relapsed or refractory non-Hodgkin lymphoma. They found that none of the 20 patients developed grade 3 or worse CRS, and only one patient developed grade 4 ICANS. Although no adverse events were reported with tocilizumab, the cumulative incidence and density of infections were not described in the study.[3] Other studies have shown that preemptive administration of corticosteroids and tocilizumab substantially reduced CAR T-cell therapy-related toxic effects.[4,5] Studies have further shown that early corticosteroid use might not affect CAR T-cell expansion, persistence, and efficacy.[4,6]

However, extensive data show an increased risk of infections with CAR T-cell therapy.[7] Although this risk is dependent upon several factors, including CRS severity, the use of corticosteroids has independently been shown to confer an increased risk of infections. The association between cumulative corticosteroid dose and duration and increased risk of infections has been shown in several studies examining CD19 and B-cell maturation antigen-targeted CAR T-cells.[7] This is an important safety consideration as infections are among the most common causes of mortality in CAR T-cell therapy recipients, second only to CRS and ICANS.[8]

In the era of an ongoing pandemic and continuous emergence of variants of concern, clinical practice and research related to CAR T-cell therapy needs redirection. In-vivo CAR T-cell persistence is considered a surrogate marker of CAR T-cell therapy efficacy and B-cell aplasia is often a clinical surrogate of CAR T-cell persistence. Although patients might have a durable response without B-cell aplasia, B-cell aplasia has been shown to be correlated with clinical benefit in pivotal trials. By contrast, patients might maintain durable remission without B-cell aplasia.[9] Despite the limitation of B-cell aplasia being a toxicity endpoint and its association with clinical efficacy needing to be determined, the contemporary focus of designing sophisticated and durable CARs might not be clinically meaningful when patients are predisposed by design (ie, sophisticated CARs will be durable and hence will have more B-cell aplasia, cytopenia, and infections engineered into the construct) to infections for a prolonged period. The unexplored complication of prolonged cytopenia further compounds the toxicity profile of CAR T-cell therapies and brings the durability endpoint into question.

Furthermore, prolonged use of corticosteroids has been shown to affect viral kinetics in immuno-compromised patients and could lead to prolonged shedding of the replication-incompetent virus. Importantly, evolving data related to SARS-CoV-2 vaccine responses in patients with cancer suggest that humoral immune responses might be substantially blunted in CAR T-cell therapy recipients, with cortico-steroids being identified as the primary driver of diminished vaccine responses.[7]

Although there might not be an immediate solution to the problem, exploratory studies showing the feasibility of CAR.λ and CAR.κ T cells hold potential for a minimal effect on humoral immunity. While sophisticated CARs are developed with better immune reconstitution profiles, the timing and intensity of early and prophylactic corticosteroid use should be reevaluated. Additional mitigation strategies could include bridging therapy to reduce disease burden before CAR T-cell therapy, secondarily decreasing the risk of CRS and infections, which has potential but has not been proven in a clinical setting. The data relating to bridging therapy are controversial thus far in terms of insufficient outcome improvement and potential for increased infectious complications.[10] Until large-scale prospective data are available, more stringent infection surveillance and monitoring procedures combined with protocol-specified use of prophylactic antimicrobials, starting from lymphodepletion until at least 6 months after CAR T-cell infusion, might be needed.

I declare no competing interests.

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