In response to the letter by Howard JF and colleagues (eclinm-D-24-00922)

Raffaella Greco,[a,*] Tobias Alexander,[b] Ibrahim Yakoub-Agha,[c,e] and Dominique Farge[d,**]

[a]Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy
[b]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Rheumatology and Clinical Immunology, Berlin, Germany
[c]CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000, Lille, France
[d]Internal Medicine Unit (04): CRMR MATHEC, Maladies Auto-immunes et Thérapie Cellulaire, Centre de Référence des Maladies auto-immunes Systémiques Rares d'Ile-de-France, AP-HP, St-Louis Hospital Paris-Cite University France and Department of Medicine, McGill University, Montreal, QC, Canada
[e]Chair of the Practice Harmonization and Guidelines Committee of EBMT, Barcelona, Spain

eClinicalMedicine 2024;78: 102917
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102917

Dear Editor

We would like to thank James Howard et al. for their insightful comments on our paper titled "*Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee.*"[1] We appreciate their interest in the approach developed by the EBMT to standardize Good Clinical Practice (GCP), as outlined in detail on the EBMT webpage (https://www.ebmt.org/practice-harmonisation-and-guidelines-committee).

It is important to clarify that, contrary to their first statement, the present EBMT recommendations are not *"restricted based on conventional, integrating vector-based CAR-Ts, which require lymphodepletion chemotherapy, inpatient administration, and prolonged post-infusion monitoring."* As stated on page 5 of the manuscript, these recommendations are "*intended to be general in scope and applicable to all mentioned diseases and types of innovative CTs adopted as standard clinical practice.*" Whether the Chimeric Antigen Receptors T cells (CART) will be DNA or RNA construct, the use of new immune effector cell therapy requires the same GCP and prerequisites in terms of healthcare pathway, especially considering that 40 patients with ADs have been treated with various types of CART, as reported in the literature.

As also stated in the EBMT-EHA CART textbook (*2024 Edition*): "*in contrast to integrating DNA transfer technologies, mRNA transfer via electroporation or cationic lipid-mediated transfection produces T cells with transient CART expression for a few days and has been found to produce antitumor reactivity for a limited time to avoid undesirable effects in patients. However, very few clinical trials using RNA-modified CART cells have been registered.*" The 14 patients with myasthenia gravis reported by Granit et al.[2] treated with the mRNA CART strategy is still limited experience. Therefore, it does not allow the conclusion that all these severe patients undergoing CART mRNA treatment can yet be treated "as outpatients", outside a clinical trial. They still require the same careful follow-up recommended for early clinical trials using cell and gene therapies.

Additionally, we respectfully disagree with the assertion that "*In phase 1/2 trials in generalized myasthenia gravis, mRNA CAR-Ts were administered outpatient, without lymphodepletion, and resulted in no cytokine release syndrome or neurotoxicity.*" This is because, as stated by Granit and colleagues in their original paper, "all 14 participants assigned in part 1 (3 ascending doses of Descartes-08) of their trial were admitted to the hospital for at least 3 days for their first doses and thereafter daily as an outpatient for 7 days." Out of the 11 individuals assigned to part 2 originally planned to be administered as outpatients, 2 withdrew, and 2 serious adverse events (SAE) were reported necessitating readmission. It is important to note that the definition of outpatient care may vary among different medical teams and regions worldwide. In all cases, these highly fragile patients with myasthenia gravis receiving CART therapy require the same close monitoring. Furthermore, the two SAEs reported in part 2 of Granit clinical trial included grade 3 urticaria occurring 24 h after the third infusion and a non-ST segment elevation myocardial infarction occurring 72 h after the sixth infusion in an 83-year-old man with a history of hypertension and hyperlipidemia. Thus, although the Descartes-08 study

DOI of original article: https://doi.org/10.1016/j.eclinm.2024.102918
*Corresponding author. Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, via Olgettina 60, 20132, Milano, Italy.
**Corresponding author. Internal Medicine Unit (04): CRMR MATHEC, Maladies Auto-immunes et Thérapie Cellulaire, AP-HP, St-Louis Hospital, 1 avenue Claude Vellefaux, 75010, Paris, France.
E-mail addresses: greco.raffaella@hsr.it (R. Greco), dominique.farge-bancel@aphp.fr (D. Farge).

demonstrated the feasibility of preparing autologous mRNA CART for individuals on immunosuppressive therapy, using the cells without lymphodepletion chemotherapy, and administering this CART product in the outpatient setting for 7 patients with minimal monitoring needed after infusion due to the notable safety profile of the product, we strongly believe that RNA-based CART, like DNA-based CART, still require "*close monitoring after infusion, with daily clinic visits and reservation of hospital beds in case severe toxicities develop,*" as stated by our colleagues themselves.

We are pleased that our colleagues have concurred with the latter phrasing, "in case of fluctuating or inadequate clinical response to second-line immunosuppressive treatment," and would like to offer clarification if necessary. Effectively, CART may not be proposed if the patient is clinically stable and not refractory to previous lines of therapy. In order to avoid any confusion, 'stable disease' is mentioned as a contraindication in Table 3[1] to specify clearly that the recommendation is on to consider CART in cases of refractory autoimmune diseases (AD).

We shall also be pleased to quote the consensus guidance for myasthenia gravis, especially if they have been updated since their previous publication in 2016, for next iterations of the 2024 EBMT recommendations. Additionally, we extend an invitation to a representative from their group to participate in the next iteration of these 2024 EBMT guidelines. Of note, the international consensus guidance for management of myasthenia gravis"[3] are guidance considering lower grade (ie. grade 1) of toxicities. They do not specifically address the potential side effects of CART (ie. CRS, ICANS and ICAHT), whereas these are key points detailed in the EBMT recommendations.[4,5]

As previously mentioned, the current recommendations are built upon the methodology developed by the EBMT to standardize GCP. The aim is to provide clear and practical guidance in areas where international consensus is lacking. These consensus recommendations were crafted by an international panel of experts during a two-day, in-person workshop held in Lille, France in September 2023. Prior to the workshop, participants conducted extensive preparatory work, including a comprehensive literature review, as basis for discussions. Following the workshop, a draft paper was formulated and circulated to the experts for additional review and input. Given the dearth of high-quality evidence from randomized trials in this domain, the recommendations were not graded but instead reflect the consensus views of all the authors. Our objective is to assemble experts from various countries within the EBMT, as well as from other disease-oriented specialist societies, such as the International Society for Cell and Gene Therapy (ISCT) and the Joint Accreditation Committee for ISCT and EBMT (JACIE). Collaboration with these organizations is a standard prerequisite for the treatment of patients with immune effector cell therapies.

Contributors

Conceptualization: RG, DF; Writing Original Draft: RG, DF; Writing and Editing: all authors. All authors read and approved the final manuscript.

Declaration of interests

RG discloses speaking honoraria from Biotest, Pfizer, Medac, Neovii and Magenta. TA received study support from Janssen and honoraria from Neovii, GSK, Astra-Zeneca, Abbvie. IYA discloses speaking honoraria from Kite, Janssen, Novartis and BMS. DF discloses speaking honoraria from BMS. None of the mentioned conflicts of interest were related to financing of the content of this manuscript.

Acknowledgements

We are grateful to the EBMT and ADWP.

References

1 Greco R, Alexander T, Del Papa N, et al. Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee. *eClinicalMedicine*. 2024;69:102476.
2 Granit V, Benatar M, Kurtoglu M, et al. Safety and clinical activity of autologous RNA chimeric antigen receptor T-cell therapy in myasthenia gravis (MG-001): a prospective, multicentre, open-label, non-randomised phase 1b/2a study. *Lancet Neurol*. 2023;22(7):578–590.
3 Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. *Neurology*. 2016;87(4):419–425.
4 Yakoub-Agha I, Chabannon C, Bader P, et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Haematologica*. 2020;105(2):297–316.
5 Rejeski K, Subklewe M, Aljurf M, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. *Blood*. 2023;142(10):865–877.