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STUDY PROTOCOL

REVISED Efficacy and safety of chimeric antigen receptor T-cell (CAR-T) therapy in hematologic malignancies: a living systematic review (protocol)

[version 2; peer review: 1 approved, 2 approved with reservations]

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Abstract

Objective

To determine the efficacy and safety of CAR-T therapy in the treatment of patients with hematologic malignancies, in comparison with other current therapies.

Design

A living systematic review

Methods

We will include randomized trials evaluating the effect of CAR-T therapy versus other active treatments, hematopoietic stem cell transplantation, best supportive care or any other intervention in patients with hematologic malignancies. Non-randomized primary studies will be searched in case we found no direct evidence from randomized controlled trials. Two reviewers will independently screen each study for eligibility, extract data, and assess the risk of bias. Efficacy measures will include overall survival rate, overall response rate, complete response/remission (CR) rate, partial response/remission (PR) rate, relapse from CR, progression-free survival, and time from CAR-T infusion to transplantation. Safety measures will include serious adverse events, the incidence of

Open Peer Review

Approval Status ✓ ? ?

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version 2 (revision) 21 May 2024	✓ view		
version 1 15 Mar 2022	? view	? view	? view

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Any reports and responses or comments on the article can be found at the end of the article.

cytokine release syndrome, graft-versus-host disease, neurotoxicity, and total adverse events. Quality of life will also be assessed. Meta-analyses will be carried out to summarize the results. We will apply the GRADE approach to assess the certainty of the evidence for each outcome. A living, web-based version of this review will be openly available until there is solid evidence to respond to the review objective. We will resubmit it for publication every time the conclusions change or whenever there are substantial updates.

Plain language summary
Research has been carried out over the last few years to assess the efficacy and usefulness of Chimeric Antigen Receptor T-Cell (CAR-T) therapy in hematologic malignancies. The present review aims to determine the efficacy and safety of CAR-T therapy in the management of patients suffering hematologic malignancies.

Randomized controlled trials (RCT) that answer our research question or non-randomized primary studies, in case we found no direct evidence of RCT, will be retrieved. The Epistemonikos database will be used for the identification of potentially eligible studies. We will identify studies meeting our inclusion criteria. We will evaluate the risk of bias and the quality of the evidence will be determined with specific tools. We will monitor the newly published evidence every two months, searching for relevant studies that could indicate changes in the available evidence. This monitoring process will last until a high certainty of evidence is reached or at least 36 months.

Keywords
Living systematic review; Chimeric Antigen Receptor T- Cell therapy; living evidence synthesis; hematologic malignancies; CAR-T infusion to transplantation.



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This article is included in the Immunological Disruptions and Interventions collection.

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REVISED **Amendments from Version 1**

The modifications made to the previous version of the protocol address several key concerns raised by the reviewers and aim to enhance the overall quality and comprehensiveness of the study. These include extending the monitoring period to 36 months, adding "time to response" as an outcome measure, considering non-randomized studies, clarifying quality of life measurement methods, conducting separate analyses for diseases and CAR-T products, acknowledging real-world data's importance, excluding economic considerations for focus, and expanding the background section for context. These changes aim to strengthen the study's methodology and relevance in evaluating CAR-T therapy for hematologic malignancies.

Any further responses from the reviewers can be found at the end of the article

Background

Condition or domain being studied

Chimeric antigen receptors (CARs) show a high affinity to bind effector cells of the immune system, such as T cells[1]. This cancer immunotherapy enables enhancement of the immunological response against malignant cells. Although the development of CAR T-cell (CAR-T) cell therapy started more than 20 years ago[2], the first steps in their transfer to clinical practice are now taking place, following the recent authorization of different CAR-T therapies by the U.S Food and Drug Administration and the European Medicines Agency.

Why it is important to do this review

The earliest and most extensive research with CAR-T therapy has been carried out in hematologic malignancies, where it has pointed to high response rates in patients who generally have very poor prognosis such as refractory acute lymphoblastic lymphoma, diffuse large B-cell lymphoma, or multiple myeloma[3–5]. Few therapeutic options are available in this setting, and CAR-T therapy is showing encouraging results.

B-cell maturation antigen (BCMA) and CD19-targeting CAR-T cell therapies are the ones that are at a more advanced stage of research and have shown the best results so far[6]. At this time, CAR-T cells directed to other targets for treating solid tumors and infectious or autoimmune diseases are emerging[7,8].

Clinical studies have suggested that CAR-T cell therapies can be even curative in patients who are responsive. However response rates can vary in different pathologies or depending on the characteristics of the patient or the disease. There is also a possibility of resistance and relapses. Moreover, these therapies can associate important adverse events such as cytokine release syndrome, neurologic adverse events and B-cell aplasia, which may lead to serious consequences[1]. To date, clinical trials have been mainly performed in terms of a single-arm design. Consequently, systematic reviews have focused on synthesizing overall response rates of CAR-T cell therapy, without providing results compared with a control group[9–12].

A recently published systematic review focused on randomized controlled trials (RCTs) analyzing the efficacy and safety of CAR-T therapies versus high-dose salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment of relapsed or refractory large B-cell lymphoma[13]. However, this review shows several limitations, such as the lack of diverse comparators and hematologic diseases, and methodological concerns with the pooled analysis strategy. A second systematic review showing remarkable differences with our living project was also identified, providing mixed results in adults and children, an updated search 6 months shorter than our study, less detail on pre-specified exploratory outcomes and no data available on complementary observational evidence[14].

Although more than a thousand CAR-T trials are being conducted[15], those with the highest quality, randomized clinical trials are still scarce. Some data from RCTs in different hematological pathologies have already been published (BELINDA[16], ZUMA-7[17], TRANSFORM[18], KarMMa-3[19] or CARTITUDE-4[20]), and other studies are currently underway (KarMMa-4, CARTITUDE-5, CARTITUDE-6 or DALY 2-EU).

The encouraging results obtained in non-comparative studies have allowed the approval of these therapies and their progressive introduction into clinical practice. However, all the above limitations do not make it possible to clarify in which patients there is a clearly favorable risk-benefit ratio or what place in therapy should be reserved to the existing therapies. Numerous phase III randomized clinical trials are already underway that will shed light on these questions in the near future. The development of CAR-T cell therapies will continue to expand and new CAR-T cells will emerge. Therefore, a living synthesis of the evidence with regular updates can be positioned as the best method to incorporate emerging evidence in a timely manner.

Considering the characteristics of the available evidence, the width variability of the SRs currently published, and taking into account that the evidence on this therapy is on the rise (*i.e.* new studies have been published and other studies are going to be published in the near future), we propose to carry out a living systematic review that will make it possible to develop a rigorous and updated synthesis of the evidence on the efficacy and safety of CAR-T therapy in patients suffering from hematological malignancies. This SR will be developed as part of the *Living Evidence to Inform Health Decisions* project, which supports health system organizations in the implementation of a living process for the development of the synthesis of the evidence to inform health decisions[21].

Objective

To determine the efficacy and safety of CAR-T therapy in the treatment of hematologic malignancies, in comparison with other current therapies

Methods

A living systematic review. This protocol is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P). It shares a common methodological approach that has been defined on the basis

of previous developments, as part of the Living Evidence to inform health decisions project[21] for developing multiple living systematic reviews and living overviews of reviews.

Types of studies

Randomized controlled trials (RCTs) will be prioritized. In the absence of evidence from RCTs, non-randomized controlled studies (quasi-experimental studies, cohort studies, case-control studies) will be considered for inclusion. Studies with other designs, such as those with historical controls and single-arm studies will not be considered. Studies must analyze at least one primary or secondary outcome.

Types of participants

Studies including participants diagnosed with hematologic diseases, such as multiple myeloma, leukemia and lymphoma of any type will be included. Both adults (≥ 18 years) and pediatric patients will be considered. Untreated patients, as well as patients previously treated, will be included, irrespective of the type of treatment or treatment line.

Intervention

Any CAR-T therapy type will be considered regardless of the T-cell origin (allogenic or autologous), target antigen, costimulatory domain, or infusion dose.

Comparator

The comparator will consist of chemotherapy or any other active pharmacologic treatment, hematopoietic stem cell transplantation (HSCT), best supportive care or any other intervention.

Outcome variables

Efficacy assessment

The primary outcome will be overall survival (OS).

Secondary efficacy variables will be mainly based according to the Center for International Blood & Marrow Transplant Research (CIBMTR) criteria (https://www.manula.com/manuals/cibmtr/fim/1/en/pdf) and consist of:

Overall response rate (ORR) (proportion of patients who have a PR or CR)

- Complete Response/Remission (CR) rate (including Stringent Complete Response (sCR) and negative minimal residual disease (MRD) when provided)
- Partial Response/Remission (PR) rate (including Very Good Partial Response (VGPR) and positive MRD when provided)
- Relapse from CR
- Progression-free survival (PFS)
- Time period between CAR-T administration and transplantation

Safety assessment

Secondary safety outcomes will be the following:

- Serious adverse events (SAE)
- Incidence of cytokine-release syndrome (grade ≥3)
- Graft-versus-host disease
- Neurotoxicity (grade ≥3)
- Total adverse events (grade ≥3)
- Quality of life (QoL)

All efficacy and safety outcomes will be measured at the longest reported follow-up. For analyzing efficacy outcomes, variables will be considered as reported by the individual studies as long as internationally accepted criteria are used. The homogeneity of the criteria used for determining the outcomes in the different studies will be analyzed. The definition established by the authors of the primary publications will be acceptable if decided by consensus among the research team and it is consistent with the internationally accepted criteria. Results will not be combined when substantial heterogeneity (I^2>60%) is found.

The International Conference on Harmonization Guidelines defined SAE as any event that led to death, was life-threatening, caused hospitalization or prolongation of existing hospitalization, led to persistent or significant disability, or any congenital anomaly or birth defect[22]. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) will be followed for the grading of the adverse events (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

Methods for identification of studies

The literature search will be designed and launched through the Epistemonikos-L·OVE platform (https://app.iloveevidence.com). This platform has been validated as a repository for the COVID-19 showing to be a highly comprehensive source of evidence[23,24]. The following approach will be used:

1. Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology to the corpus of documents available in Epistemonikos Database.
2. Discussion of terms with content and methods experts to identify relevant, irrelevant and missing terms.
3. Creation of a sensitive boolean strategy encompassing all the relevant terms.

The main search source will be the Epistemonikos database (https://www.epistemonikos.org), a comprehensive database of systematic reviews and other types of evidence, maintained by screening multiple information sources to identify systematic reviews and their included primary studies, including

Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library[24].

An additional search will be performed on MEDLINE in order to identify randomized trials and non-randomized studies. The searches will cover the inception date of each database. No publication status or language restriction will be applied to the searches in Epistemonikos or to the additional searches. We will apply validated filters to identify clinical trials in the MEDLINE database.

Boolean search strategy

Epistemonikos

(leukem* OR leukaem* OR leucem* OR leucaem* OR lymphoma* OR lymphobl* OR ((hemato* OR haemato* OR lymph* OR myelo*) AND (malignan* OR malignan*))) AND ((("car-engineered" OR "car-modified" OR "receptor-modified" OR chimeric* OR adoptive* OR redirected* OR engineered*) AND ("t cell" OR "t cells" OR "t-cell" OR "t-cells")) OR "car-t" OR "car t" OR "car-ts" OR "car ts" OR "car t-cell" OR "car t-cells")

Medline. PUBMED

(leukem* OR leukaem* OR leucem* OR leucaem* OR lymphoma* OR lymphobl* OR ((hemato* OR haemato* OR lymph* OR myelo*) AND (malignan* OR malignan*))) AND ((("car-engineered" OR "car-modified" OR "receptor-modified" OR chimeric* OR adoptive* OR redirected* OR engineered*) AND ("t cell" OR "t cells" OR "t-cell" OR "t-cells")) OR "car-t" OR "car t" OR "car-ts" OR "car ts" OR "car t-cell" OR "car t-cells")

Results from these searches will be automatically included in the L.OVE platform of the Epistemonikos Foundation (https://iloveevidence.com/).

Other sources

We will carry out a manual search for reviewing the reference list of included studies, guidelines, narrative reviews and any other document of interest in an attempt to identify additional references that might be potentially eligible and to keep monitoring for the new evidence.

Study selection

The L·OVE platform repository will automatically incorporate all the references that meet the criteria of the research question. The titles and abstracts of the identified references will be independently screened by at least two authors. Full texts of all potentially eligible references will be retrieved to make a final decision on their inclusion. Reasons for the exclusion of the identified references will be registered. The screening process will be conducted through Rayyan-Intelligent Systematic Review software whenever necessary (https://www.rayyan.ai/). Results of the screening process will be shown in a PRISMA[25] flow diagram.

Data extraction

A specific data extraction form will be designed to incorporate data obtained from the included studies. Information will be independently extracted by two authors, and cross-checked by another author. Discrepancies will be addressed by discussion, and if necessary a third author will be also involved.

The following information will be extracted: 1) general information of the studies, study design, number of participants, follow-up time, type of centre (Unicenter, multicenter), country, study sponsor and sources of funding; 2) Trial methods and conduction, such as randomization, blinding and follow-up time; 3) characteristics of the participants including age, sex, type of pathology, stage, number of previous lines, previous HSCT, the median time from diagnosis, percentage with high-risk cytogenetics, percentage with extramedullary disease; 4) Intervention characteristics such as T-cell origin (allogenic or autologous), transfection/transduction method (lentivirus, retrovirus, electroporation, or others), target antigen, CAR costimulatory domain, infusion dose; 5) Characteristics of the comparator; 6) Results of the measured outcomes.

The need for interleukin receptor antagonists to treat cytokine-release syndrome in the participants in the CAR-T arm will be analyzed.

We will contact the authors of the primary studies in case of missing information in the retrieved studies. Whenever possible, individual patient data and clinical study reports of included studies will be obtained by contacting corresponding authors, sponsors and promoters.

Data analysis

Risk of bias assessment

In the case of RCTs, the risk of bias will be evaluated using the Cochrane Risk of Bias Tool. This tool considers the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias[26]. We will rate the overall risk of bias of each study as low, moderate, high or unclear risk of bias.

The risk of bias of non-randomized studies of intervention will be assessed using the ROBINS-I tool[27]. The tool evaluates the following domains: bias due to confounding, selection of participants, classification of interventions, deviation from intended interventions, missing data, measurement of outcomes, and bias in selection of the reported result. According to these domains, we will judge the overall risk of bias as low, moderate, serious, critical or no information.

Measures of treatment effect

In the case of binary outcomes results will be presented as the proportion of patients who suffered the corresponding analyzed event. We will use hazard ratio (HR), risk ratio (RR) and Odds ratio (OR) for summarizing the results as appropriate. We will also estimate the risk difference in absolute terms and also the number needed to treat for an additional beneficial

or harmful outcome when applicable. We will determine the 95% confidence intervals (CI).

For quantitative data, mean difference (MD) or standardized mean difference (SMD) will be estimated as appropriate. We will also determine the 95%CI.

We will accept any general or specific validated scale used to estimate QoL. Results that refer to specific domains of a QoL scale will be analyzed separately from results that refer to the overall results of the scale. In the event the identified studies reported QoL using the same scale, these data will be meta-analyzed and reported as MD with 95%CI. On the contrary, if the studies included in the review were to use different validated scales for reporting QoL, data will be standardized before an aggregated SMD with 95%CI is calculated.

Data synthesis

Results will be analyzed separately according to each specific study design and type of hematologic disease. Data will be analyzed following an intention-to-treat approach. We will combine outcomes across trials using a fixed-effects model when applicable.

The heterogeneity of treatment effect among studies will be analyzed by estimating the I^2 statistic. We will consider I^2>60% as indicative of substantial heterogeneity, whose possible reasons will be explored by carrying out subgroup analyses. We will carry out meta-analyses when data from more than one study are available and unless substantial heterogeneity (I^2>60%) is found, whose results will be represented using forest plots. We will carry out meta-analyses using Review Manager Software (RevMan version 5.4).

Results will be presented in a narrative form in case there is one only study that provides data for an outcome variable or when data obtained from different studies cannot be combined.

Subgroup analysis

When possible, overall survival rate, overall response rate and total grade 3 or higher adverse events will be analyzed according to the following aspects:

- Type of CAR-T therapy (antigen type, costimulatory domain)
- Type of comparator
- Age group (≥18 years and <18 years)
- Treatment line
- Tumor burden
- Cancer stage

Sensitivity analysis

Sensitivity analyses will be performed in terms of the following criteria:

- Analysis excluding studies with a high risk of bias.
- Analysis excluding industry-sponsored studies.

Certainty of evidence

The quality of the evidence for each outcome variable will be analyzed using GRADE methodology, which includes the assessment of five main aspects: risk of bias, directness of the evidence, consistency among trials' results, the precision of effect estimates, and risk of publication bias[28].

Two reviewers will independently assess the quality of the evidence. All possible discrepancies will be discussed until consensus and by the involvement of a third author, if necessary. Results of this assessment will be presented in a Summary of Findings table generated in the tool GRADEpro ® (https://www.gradepro.org/)

Evidence monitoring and surveillance plan

In order to maintain the living evidence process for this review, the Epistemonikos-L.OVE platform (https://iloveevidence.com/) will be used as a technological enabler to support evidence identification, screening, and selection. We will keep a living search in the L·OVE platform to detect systematic reviews and randomized controlled trials. Additionally, every three months, we will manually search for ongoing studies in the WHO International Clinical Trials Registry Platform and in clinicaltrials.gov.

One reviewer will be in charge of assessing the evidence that has entered the specific question in the L.OVE platform every month and applying the selection criteria presented above. If a potentially eligible study is found, a second reviewer will confirm its eligibility by reading the full text. Results of evidence surveillance will be collected and kept as part of the study records. Information on the PRISMA figure will be updated accordingly. The PICO question and criteria for selecting studies will be revised and changed accordingly during the Living Evidence process every time new eligible studies are incorporated into the evidence synthesis on main outcomes or every four months, whichever is reached first.

We will carry out data extraction for all new eligible studies. The data synthesis will be updated immediately after that, and the quality of the evidence will be evaluated following the GRADE approach accordingly, looking for changes on the certainty assessment results.

The living process for this question will end when the certainty of the evidence on the updated estimates for the desirable and undesirable effects becomes high or after 36 months of surveillance, whatever is reached first.

Statistical considerations for the living evidence synthesis

The inclusion of new studies identified as part of evidence surveillance and reporting on the outcomes of interest will follow this approach: We will perform an updated meta-analysis for each of the outcomes of interest including data obtained from the new studies. Data will be analyzed using a fixed-effect model. Heterogeneity among included studies will be analyzed by using the I^2 statistics. If new heterogeneity is detected (compared to the previous meta-analysis, new heterogeneity appears or increases), we will explore its potential sources by reviewing the new studies against previously included studies in order to identify reasons that may explain inconsistent results among studies. In the presence of unexplained heterogeneity (I^2> 60%), data will not be meta-analyzed, and the results of the evidence synthesis will be explained narratively.

Dissemination plan

We plan to communicate our review results (from baseline review and its updates) by publication in a scientific journal. We will elaborate technical reports to the healthcare providers, decision-makers, and clinical committees. We will share the results through our social media channels and in Open Science Framework (https://osf.io/). The base line report as well as the periodical updates will be available on the Living Evidence to Inform Health Decisions project website (https://livingevidenceframework.com/en/).

If during the living process, new relevant results that imply changes in the current clinical practice are identified, we will update the report of this review and disseminate the new evidence and conclusions among potential users through all the above described communication channels.

Study status

The searching and screening phases have been completed at the time of this submission.

Data availability

Underlying data

No data are associated with this article.

Extended data

Open Science Framework: LIVING EVIDENCE TO INFORM HEALTH DECISIONS. 10.17605/OSF.IO/V6HDX

Reporting guidelines

Open Science Framework: PRISMA-P checklist for "Efficacy and safety of Chimeric Antigen Receptor T-Cell (CAR-T) therapy in hematologic malignancies: a living systematic review (Protocol)". 10.17605/OSF.IO/V6HDX

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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Open Peer Review

Current Peer Review Status: ✔ ? ?

Version 2

Reviewer Report 30 May 2024

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✔ **Lee M Greenberger**
The Leukemia and Lymphoma Society, Rye Brook, NY, USA

All the edits are acceptable and ths work should be accepted.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Grant and venture philanthropy funding for blood cancer.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 04 December 2023

https://doi.org/10.21956/openreseurope.15530.r36013

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? **Le Wang**
[1] Jiangsu University, Zhenjiang, Jiangsu, China
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Strengths:

- Clear Objectives: The paper sets a defined goal to determine the efficacy and safety of CAR-T therapy in hematological malignancies and compare it with other current therapies.

- Sound Methodology: The use of an active systematic review approach adheres to the PRISMA-P guidelines.
- Comprehensive Study Design: Inclusion of both randomized controlled trials and non-randomized original studies offers a well-rounded research design.

- Detailed Data Extraction and Analysis: Utilization of the Cochrane risk of bias tool and ROBINS-I for bias risk assessment, and fixed effect model analysis for results, is commendable.

Suggestions for Improvement:

- Data and Timeframe Scope: Given the rapid advancements in the CAR-T field, the 12-month monitoring period might be insufficient to reflect the latest research and long-term outcomes.

- Quality of Life Measurements: The methodology and integration of quality of life (QoL) results need clearer delineation.

- Real-world Data Application: Incorporation of real-world data could enhance the breadth and applicability of the analysis.

- Economic Considerations: Given the high cost of CAR-T therapy, analyzing its economic impact is crucial for clinical decision-making.

- Completeness of Reporting: Enhance the detailing of ongoing and completed trials for a better understanding of the study's context and setting.

Conclusion and Recommendation:
This paper presents a promising study aimed at comprehensively evaluating the efficacy and safety of CAR-T therapy in hematological malignancies. However, it is recommended that the authors consider extending the monitoring period, including analyses of economic and real-world data, and clarifying the methodology for comparing QoL data. These improvements will enhance the practical applicability and impact of the research.

Recommendation for indexing: Major Revision Required

Rationale: The study is valuable but requires significant enhancements in terms of data scope, economic analysis, and methodological clarity to be suitable for publication. After addressing these major concerns, the paper could provide a more impactful and comprehensive insight into the CAR-T therapy landscape in hematological malignancies.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: CAR-T, breast cancer

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Apr 2024

Maria Ximena Rojas Reyes

Strengths:

- Clear Objectives: The paper sets a defined goal to determine the efficacy and safety of CAR-T therapy in hematological malignancies and compare it with other current therapies.
- Sound Methodology: The use of an active systematic review approach adheres to the PRISMA-P guidelines.
- Comprehensive Study Design: Inclusion of both randomized controlled trials and non-randomized original studies offers a well-rounded research design.
- Detailed Data Extraction and Analysis: Utilization of the Cochrane risk of bias tool and ROBINS-I for bias risk assessment, and fixed effect model analysis for results, is commendable.

Suggestions for Improvement:

- Data and Timeframe Scope: Given the rapid advancements in the CAR-T field, the 12-month monitoring period might be insufficient to reflect the latest research and long-term outcomes.

Thank you for the comment. We have broadened the initial follow-up to set a 36-month monitoring period based on our existent resources. In any case, we agree CAR-T field is rapidly evolving and a longer monitoring duration would be ideal. In this regard, our team is committed to extend the monitoring process as long as new high quality evidence arises and our resources allows for it.

- Quality of Life Measurements: The methodology and integration of quality of life (QoL) results need clearer delineation.

QoL constitutes in our project a secondary safety outcome. We will accept any general or specific validated scale used to estimate QoL. Results that refer to specific domains of a QoL scale will be analyzed separately from results that refer to the overall results of the scale. In the event the identified studies reported QoL using the same scale, these data will be meta-analyzed and reported as mean difference (MD) with 95% confidence interval (95%CI). On the contrary, if the studies included in the review were to use different validated scales for reporting QoL, data will be standardized before an aggregated standardized mean difference (SMD) with 95%CI is calculated.

- Real-world Data Application: Incorporation of real-world data could enhance the breadth and applicability of the analysis

Thank you for this appreciation. As stated in the current version of the protocol, randomized controlled trials (RCTs) have been prioritized given their higher quality of evidence, but observational studies with comparative designs have also been taken into consideration, specifically in cases where the evidence from RCTs is not sufficient. We agree that real-world data are also of great interest in this field, particularly when safety issues are assessed, and are not excluded in our inclusion criteria. Nonetheless, our experience with the original version of this review has showed us the great complexity of mixing experimental and observational designs in just one paper. Consequently, we highly appreciate your suggestion, which could probably be considered and addressed in separate publications.

- Economic Considerations: Given the high cost of CAR-T therapy, analyzing its economic impact is crucial for clinical decision-making.

Thank you. This living systematic review has been designed to focus on CAR-T efficacy and safety. We agree on the importance of economic considerations, but these are out of the scope in the current project, as they may depend on the setting, context and time point in which CAR-T therapy is applied. Therefore, results from studies conducted at distant moments in time, and in diverse countries and settings cannot be directly extrapolated to other contexts, since unit costs can be highly variable.

- Completeness of Reporting: Enhance the detailing of ongoing and completed trials for a better understanding of the study's context and setting.

Thank you for this valuable comment. Following your suggestion, the Background section has been broadened including two recent systematic reviews and several published and ongoing clinical trials on the topic. In our view, both of them help understand the context of past, present and future CAR-T evidence. In this sense, the following text has been added: *"A recently published systematic review focused on randomized controlled trials (RCTs) analyzing the efficacy and safety of CAR-T therapies versus high-dose salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment of relapsed or refractory large B-cell lymphoma (13). However, this review shows several limitations, such as the lack of diverse comparators and hematologic diseases, and methodological concerns with the pooled analysis strategy. A second systematic review showing remarkable differences with our living project was also identified, providing mixed results in adults and children, an updated search 6 months shorter than our study, less detail on pre-specified exploratory outcomes and no data available on complementary observational evidence (14)." "Although more than a thousand CAR-T trials are being conducted (15), those with the highest quality, randomized clinical trials are still scarce. Some data from RCTs in different hematological pathologies have already been published (BELINDA (16), ZUMA-7 (17), TRANSFORM (18), KarMMa-3 (19) or CARTITUDE-4 (20)), and other studies are currently underway (KarMMa-4, CARTITUDE-5, CARTITUDE-6 or DALY 2-EU)."*

Conclusion and Recommendation:

This paper presents a promising study aimed at comprehensively evaluating the efficacy and safety of CAR-T therapy in hematological malignancies. However, it is recommended that the authors consider extending the monitoring period, including analyses of economic and real-world data, and clarifying the methodology for comparing QoL data. These improvements will enhance the practical applicability and impact of the research.

Recommendation for indexing: Major Revision Required
Rationale: The study is valuable but requires significant enhancements in terms of data

scope, economic analysis, and methodological clarity to be suitable for publication. After addressing these major concerns, the paper could provide a more impactful and comprehensive insight into the CAR-T therapy landscape in hematological malignancies. **Is the rationale for, and objectives of, the study clearly described?** Yes **Is the study design appropriate for the research question?** Yes **Are sufficient details of the methods provided to allow replication by others?** Yes **Are the datasets clearly presented in a useable and accessible format?** Yes

Competing Interests: No competing interests were disclosed.

Reviewer Report 22 November 2023

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LaQuisa Hill
[1] Department of Medicine, Baylor College of Medicine, Houston, TX, USA
[2] Department of Medicine, Baylor College of Medicine, Houston, TX, USA

The authors describe a protocol to develop a "living" systematic review of published CAR-T studies for hematologic malignancies.

The rationale for the study is clearly described. However, it may be difficult to meet the objectives of efficacy and safety as many of the currently available studies are non-randomized single center or single arm multii-center studies (which will be excluded per methods). Also the timeframe of ongoing review for only 12 months will likely be insufficient to establish rigorous review and updated findings given the number of ongoing studies, and many new ones in development. It typically takes several years for randomized study data to be available so 12 months will likely be too short.

Other endpoints to consider are time from diagnosis to CAR-T treatment, time to response and duration of responses.

While QoL outcomes are becoming increasingly important and utilized, it is not clear from the protocol how different methods for QoL will be compared and/or grouped to determine true impact.

Also will there be separate reports for individual diseases? CAR-T products?

No datasets were provided so unable to assess usability or accessibility.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: Speakers Bureau for Kite/Gilead; Consultant for March Biosciences

Reviewer Expertise: Stem cell transplantation and cellular therapy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Apr 2024

Maria Ximena Rojas Reyes

The authors describe a protocol to develop a "living" systematic review of published CAR-T studies for hematologic malignancies. The rationale for the study is clearly described. However, it may be difficult to meet the objectives of efficacy and safety as many of the currently available studies are non-randomized single center or single arm multii-center studies (which will be excluded per methods). Also the timeframe of ongoing review for only 12 months will likely be insufficient to establish rigorous review and updated findings given the number of ongoing studies, and many new ones in development. It typically takes several years for randomized study data to be available so 12 months will likely be too short. Thank you for the comments. As stated in the protocol, randomized controlled trials (RCTs) have been prioritized given their higher quality of evidence, but non-randomized and observational studies with comparative designs have also been taken into consideration, specifically in cases where the evidence from RCTs is not sufficient. Nonetheless, we have experienced high complexities to combine results from different study designs within a single publication. Thus, we are planning to focus on RCTs in subsequent versions of our living systematic review. We have broadened the initial follow-up to set a 36-month monitoring period based on our existent resources. In any case, we agree CAR-T field is rapidly evolving and a longer monitoring duration would be ideal. In this regard, our team is committed to extend the monitoring process as long as new high quality evidence arises and our resources allows for it.
Other endpoints to consider are time from diagnosis to CAR-T treatment, time to response and duration of responses. Thank you for the suggestion. We agree on including “time to response” and “duration of response” as additional secondary outcomes.
While QoL outcomes are becoming increasingly important and utilized, it is not clear from the protocol how different methods for QoL will be compared and/or grouped to determine true impact. Thank you for the comment. We have expanded the information in the protocol

to clarify this point: "*We will accept any general or specific validated scale used to estimate QoL. Results that refer to specific domains of a QoL scale will be analyzed separately from results that refer to the overall results of the scale. In the event the identified studies reported QoL using the same scale, these data will be meta-analyzed and reported as MD with 95%CI. On the contrary, if the studies included in the review were to use different validated scales for reporting QoL, data will be standardized before an aggregated SMD with 95%CI is calculated.*" Also will there be separate reports for individual diseases? CAR-T products? Thank you for the comment. We have clarified in the protocol that we will perform separate analysis for individual diseases: "*Results will be analyzed separately according to each specific study design and type of hematologic disease*". As stated in the protocol, subgroup analyses of the main outcomes (overall survival rate, overall response rate and total grade 3 or higher adverse events) will be conducted according to the type of CAR-T product, among other factors.
No datasets were provided so unable to assess usability or accessibility. **Is the rationale for, and objectives of, the study clearly described?** Yes **Is the study design appropriate for the research question?** Yes **Are sufficient details of the methods provided to allow replication by others?** Yes **Are the datasets clearly presented in a useable and accessible format?** Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Report 17 July 2023

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Lee M Greenberger
[1] The Leukemia and Lymphoma Society, Rye Brook, NY, USA
[2] The Leukemia and Lymphoma Society, Rye Brook, NY, USA

This protocol describes a systematic review of CAR T therapy for hematologic malignancies. The work will rely on previous CAR T studies, most of which have been conducted without randomized control arms. So, while the output of this protocol is needed and will assess performance of CAR Ts, trials, comparisons between CAR T results from independent trials are difficult. Ultimately, the analysis will be replaced by phase 3 comparison trials (e.g. vs SOC), which are just beginning to be conducted for early stage disease treatment.

The endpoints for analysis are comprehensive, although time to response was not listed as an analysis endpoint.

The monitoring process is only for 12 months. As the CAR T field is rapidly changing, is this a long enough period to conduct the study? What is the justification for only 12 months?

Will there be any effort to assess the financial toxicity of CAR T therapy as well as access and response in underserved populations?

Are the authors considering data generated in real-world experience? There are multiple reports of real-world CAR T data including CD19 CAR T for ALL and CD19 CAR T for lymphoma.

What quality of life instruments will be used and how do the authors intend to compare QoL if the measurements are done with different methods?

It is not possible to evaluate the datasets, as no datasets were presented.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Grant and venture philanthropy funding for blood cancer.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Apr 2024

Maria Ximena Rojas Reyes

This protocol describes a systematic review of CAR T therapy for hematologic malignancies. The work will rely on previous CAR T studies, most of which have been conducted without randomized control arms. So, while the output of this protocol is needed and will assess performance of CAR Ts, trials, comparisons between CAR T results from independent trials are difficult. Ultimately, the analysis will be replaced by phase 3 comparison trials (e.g. vs SOC), which are just beginning to be conducted for early stage disease treatment.

The endpoints for analysis are comprehensive, although time to response was not listed as an analysis endpoint. Thank you for this suggestion. We agree on including “time to response” as an additional secondary outcome. The monitoring process is only for 12 months. As the CAR T field is rapidly changing, is this a long enough period to conduct the study? What is the justification for only 12 months? Thank you for this question. We have

broadened the initial follow-up to set a 36-month monitoring period, based on our existent resources. In any case, we agree CAR-T field is rapidly evolving and a longer monitoring duration would be ideal. In this regard, our team is committed to extend the monitoring process as long as new high quality evidence arises and our resources allows for it.
Will there be any effort to assess the financial toxicity of CAR T therapy as well as access and response in underserved populations? Thank you. This living systematic review has been designed to focus on CAR-T efficacy and safety. We agree on the importance of economic considerations but these are out of the scope in the current project, as they may depend on the setting and context in which CAR-T therapy is applied.
Are the authors considering data generated in real-world experience? There are multiple reports of real-world CAR T data including CD19 CAR T for ALL and CD19 CAR T for lymphoma. Thank you for this question. As stated in the current version of the protocol, randomized controlled trials (RCTs) have been prioritized given their higher quality of evidence, but observational studies with comparative designs have also been taken into consideration, specifically in cases where the evidence from RCTs is not sufficient. Nonetheless, we have experienced high complexities to combine results from different study designs within a single publication. Thus, we are planning focus on RCTs in subsequent versions of our living systematic review. We agree that real-world data are also of great interest in this field and are not excluded in our inclusion criteria but, in our view, it should be addressed in a separate publication.
What quality of life instruments will be used and how do the authors intend to compare QoL if the measurements are done with different methods? Thank you for this interesting comment. We will include the following statement in the “Data analysis” section of the protocol: “*We will accept any general or specific validated scale used to estimate QoL. Results that refer to specific domains of a QoL scale will be analyzed separately from results that refer to the overall results of the scale. In the event the identified studies reported QoL using the same scale, these data will be meta-analyzed and reported as MD with 95%CI. On the contrary, if the studies included in the review were to use different validated scales for reporting QoL, data will be standardized before an aggregated SMD with 95%CI is calculated*.”
It is not possible to evaluate the datasets, as no datasets were presented. Thank you. As it is a protocol, there are no datasets associated with it. **Is the rationale for, and objectives of, the study clearly described?** Yes **Is the study design appropriate for the research question?** Yes **Are sufficient details of the methods provided to allow replication by others?** Yes **Are the datasets clearly presented in a useable and accessible format?** No

Competing Interests: No competing interests were disclosed.