INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Efficacy and safety of intravenous Daratumumab for patients with AL Amyloidosis: A systematic review

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Review question / Objective: **To explore the efficacy and safety of intravenous daratumumab-based therapy for patients with Light-chain amyloidosis (AL).**
Participant or population: **Studies enrolling patients with AL Amyloidosis. There will be no limitation on age, gender, ethnic, prior lines of therapy, Mayo stage or co-morbidity, etc.**
Intervention: **We will include studies investigating the effect of intravenous daratumumab-based therapy. There will be no limitation on dosage, frequency, regimens, treatment duration or line of treatment.**
Study designs to be included: **Interventional and non-interventional studies that investigating the efficacy and safety of daratumumab-based therapy for patients with AL Amyloidosis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 June 2021 and was last updated on 17 June 2021 (registration number INPLASY202160054).

INTRODUCTION

Review question / Objective: **To explore the efficacy and safety of intravenous daratumumab-based therapy for patients with Light-chain amyloidosis (AL).**

Rationale: **A systematic review will be conducted to collect current evidence assessing the efficacy and safety of daratumumab-based therapy, including interventional and non-interventional studies. We will summarize the interventional and non-interventional studies that involves daratumumab-based therapy as a treatment arm. By doing systematic review, we will present clinical experts a whole picture of the current evidence. Firstly, we will describe the study screening process in a PRISMA flow**

diagram, to disclose that our process of selecting studies is systematic, transparent and objective. Secondly, we will describe the general evidence characteristics, for instance, the number of studies, type of evidence, location of studies, study duration, sample size and so on. Thirdly, for controlled studies (interventional and non-interventional), we will describe the population characteristics, administration of intervention and comparator, and outcome category, definition and time point of measurement. For single arm trials, we will summarize the population characteristics, administration of treatment regimens, and outcome category, definition and time point of measurement. Meanwhile, a meta-analysis will be performed to pool the clinical outcome data when the characteristics of studies, i.e., study design, characteristics across population, interventions and outcomes are considered as homogeneous. The data used for meta-analysis will be extracted from daratumumab-based therapy group from all interventional and non-interventional studies that reported administration, hematologic responses, median time to hematologic response, etc. The systematic review and meta-analysis will be performed according to the preferred reporting items for systematic review and meta-analysis (PRISMA) extension statement.

Condition being studied: Immunoglobulin light chain (AL) amyloidosis is characterized by a clonal population of bone marrow plasma cells that produces a monoclonal light chain of κ or λ type as either an intact molecule or a fragment. This insoluble protein deposits in tissues and interferes with organ function. Treatment of systemic AL relies primarily on multiple myeloma (MM) regimens aimed at suppressing the underlying PC clone secreting amyloid forming monoclonal free light chains (FLCs). Standard treatment with melphalan and prednisolone or with cyclophosphamide and dexamethasone has been replaced with newer drugs used for the treatment of multiple myeloma—bortezomib, carfilzomib and ixazomib or thalidomide, lenalidomide and pomalidomide. High dose melphalan supported by autologous stem cell transplantation remains the therapeutic option for patients with low-risk status. These treatment options prolong survival from months to years and improve the prognosis in a majority of patients. While these results are encouraging there remain a significant proportion of patients that do not respond to these agents and alternative options are needed. Patients with AL amyloidosis who are not eligible for ASCT have limited options, particularly those with advanced Mayo Stage who have a poor prognosis. Daratumumab has the potential to become a powerful therapeutic option in this area of unmet need for the treatment of AL amyloidosis. Daratumumab is a first-in-class human IgG1k monoclonal antibody (mAb) that binds with high affinity to a unique epitope of CD38, an antigen that is highly and uniformly expressed on the surface of multiple myeloma cells. Daratumumab induces myeloma cell death via a variety of mechanisms including complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis and direct cellular apoptosis. Trials of daratumumab in combination with other novel agents in relapsed myeloma have shown dramatic response rates and improved progression free survival. Given the abnormal plasma cell clone in AL amyloidosis also expresses CD38; it is only natural to consider daratumumab as a therapeutic option for this disorder. Recently, daratumumab has emerged as an attractive option in this indication, based on retrospective and prospective trials. A retrospective review of 25 AL amyloidosis patients treated with intravenous daratumumab by Kaufman and colleagues at Stanford University shows the hematologic response rate was 76% with 36% achieving a complete response (CR) and 24% achieving a very good partial response (VGPR) with a median time to deepest response of 1 month.

METHODS

Search strategy: 1, embase #1.'Daratumumab'/exp OR "humax

CD38":ab,ti,kw OR darzalex:ab,ti,kw | #2. 'AL amyloidosis'/exp OR ((amyloid OR immunoglobulin) NEAR/1 "light-chain" NEAR/1 amyloidos* OR primary NEAR/1 amyloidos* OR "AL amyloidos*"):ab,ti,kw | #3.#1 AND #2. | 2, PubMed, #1. "daratumumab" [Supplementary Concept] OR Daratumumab[tw] OR "humax CD38"[tw] OR darzalex[tw] | #2. "Immunoglobulin Light-chain Amyloidosis"[Mesh] OR "Light chain Amyloidos*"[tiab] OR "AL amyloidos*"[tiab] OR Primary Amyloidos*[tiab] | #3.#1 AND #2 | 3, web of science #1. TS=(Daratumumab OR "humax CD38" OR darzalex) | #2. TS=((amyloid OR immunoglobulin) NEAR/1 "light-chain" NEAR/1 amyloidos* OR primary NEAR/1 amyloidos* OR "AL amyloidos*") | #3.#1 AND #2 | 4, cochrane library #1 Daratumumab OR "humax CD38" OR darzalex | #2 MeSH descriptor: [Immunoglobulin Light-chain Amyloidosis] explode all trees | #3 ((amyloid OR immunoglobulin) NEAR/1 light NEAR/1 chain NEAR/1 amyloidos* OR primary NEAR/1 amyloidos* OR "AL amyloidos*"):ti,ab,kw | #4 #2 OR #3 | #5 #1 AND #4.

Participant or population: Studies enrolling patients with AL Amyloidosis. There will be no limitation on age, gender, ethnic, prior lines of therapy, Mayo stage or co-morbidity, etc.

Intervention: We will include studies investigating the effect of intravenous daratumumab-based therapy. There will be no limitation on dosage, frequency, regimens, treatment duration or line of treatment.

Comparator: There will be no other comparator treatments.

Study designs to be included: Interventional and non-interventional studies that investigating the efficacy and safety of daratumumab-based therapy for patients with AL Amyloidosis.

Eligibility criteria: Studies enrolling patients with AL Amyloidosis, those recieved daratumumab-based therapy. But we will exclude literatures not reported in English or Chinese; studies without outcome data; studies based investigating the PK/PD of daratumumab.

Information sources: A systematic search in the databases of PubMed, EMBASE, the Cochrane Library and Web of Science will be conducted in literatures published in English and Chinese from inception without limitations on date/time and document type. The following items will be used to develop our search strategy: "Daratumumab" "AL amyloidosis" "(amyloid OR immunoglobulin) NEAR/1 "light-chain" NEAR/1 amyloidos*" , "primary NEAR/1 amyloidos* OR "AL amyloidos*"" "Immunoglobulin Light-chain Amyloidosis","Light chain Amyloidos*"[tiab] OR "AL amyloidos*"[tiab] OR Primary Amyloidos*[tiab]. The details on search strategies are presented in Appendix 1. Reference lists of included studies will be checked for relevant studies to identify any additional published or unpublished material (grey literature) not retrieved by the electronic search.

Main outcome(s): (1) ≥very good partial response rate (VGPR), defined as complete response (CR) or VGPR. Complete response (CR) defined as normalization of the FLC levels and ratio, negative serum and urine immunofixation, or defined as original studies. VGPR defined as reduction in the dFLC to <40 mg/L or defined as original studies.

Additional outcome(s): (1)Very good partial response (VGPR) rate, defined as reduction in the dFLC to 30% and >300 ng/L decrease in patients with baseline NT-proBNP 2650 ng/L) or NYHA class response (22 class decrease in subjects with baseline NYHA class 3 or 4). Renal response rate, defined as ≥30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 h in the absence of renal progression. Liver response rate, defined as 50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm. Peripheral nervous system response rate, defined as improvement in electromyogram nerve

conduction velocity (rare). (7)Progression-free survival (PFS), defined as original studies. (8)Overall survival (OS), defined as original studies. (9)Association between early hematologic responses and survival. Early hematologic response was defined as hematologic response within 1 month. (10)Adverse events (AEs) ✓Rates of most common grade 3-4 adverse effects (AEs), defined as AEs reported in ≥ 5% (Grade 3-4) of patients ✓Rates of infusion-related reactions (IRRs). Notes: a. We will collect the outcome data measured as original studies. The definition criteria used here according to NCCN Clinical Practice Guidelines Version 2.2021. b. We will collect the primary and secondary outcomes data when hematologic response results were reported by more than 1 paper. For the timepoint of outcome measurement, the goal of Amyloidosis treatment is to achieve a fast hematologic response then organ responses and the median time to hematologic response was about 1~2 months for intravenous Daratumumab in the treatment of AL Amyloidosis. Therefore, we will pool response rate measured at about 1 - 3 months follow-up.

Data management: (1) Study selection: Two reviewers will independently make the selection after reading titles and abstracts of the search results. All potentially relevant citations will be requested and inspected in detail using the full-text version. Disagreements will be resolved by discussion, with assistance from a third party if necessary. A PRISMA flow diagram will be constructed to show the full study-selection process. (2) Data extraction: Data from each study will be extracted independently by two reviewers using a standardized data extraction form. Any disagreements will be resolved by discussion, with the assistance from a third party if necessary. Where more information relating to a potentially included study is lacking, we will contact study authors and request further information. A PICOS structure will be used to formulate the data extraction, as follows: 1)General study characterizes: the first author's name, the published year, country, center, funding sources. 2)Participants: diagnosis, diagnostic criteria, clinical stage, inclusion criteria, exclusion criteria, sample sizes, gender and age of patients, prior lines of therapy, dFLC, Mayo stage, organ involvement, epidermal growth factor receptor (eGFR). 3)Interventions: treatment frequency, dosage, and treatment duration. 4)Outcomes: types of outcomes, definitions, measurement timepoints. 5)Results: all relevant dichotomous results. 6)Study design: RCT, non-randomized studies of interventions (NRSI), single-arm studies.

Quality assessment / Risk of bias analysis: Two reviewers will independently assess the risk of bias in the included studies. We will use the Cochrane risk of bias tool to assess the risk of bias of RCTs, and the Newcastle-Ottawa Scale (NOS) instrument for Non-Randomized Studies of Interventions. For single arm studies, we will evaluate every domain of risk of bias, basis on the standard criteria (Before-After (Pre-Post)) outlined by National Institutes of Health (NIH). Disagreements will be resolved by discussion, with assistance from a third party if necessary.

Strategy of data synthesis: The statistical analysis will be conducted following Cochrane handbook for systematic reviews. (1) Measurement of effects: For dichotomous outcomes (hematologic response, organ response), we will use rates and its 95% credible intervals (CI) to describe and pool the data. For studies with no events in one or both arms, in accordance with specific conditions, we will handle the data following methods described in Cochrane handbook. For time-to-event outcomes (such as OS, PFS), we will use hazard rates and its 95% credible intervals (CI) to describe and pool the data. For data expressed as median and interquartile range (IQR)/range, we will narratively describe the data. (2)Meta-analysis and model selection: Before doing meta-analysis, we will consider the homogeneity on clinical characteristics for all studies that included by the systematic review. Meta-analysis will only be performed when the homogeneity is good.

We will consider the clinical homogeneity according to the following factors: Age, Type of regimen, Line of therapy, dFLC level; Mayo staging, Organ involvement, eGFR level, etc. We will group the included studies according to the above factors separately, and perform meta-analysis where data is available. Considering the situation of our proposed research question, fixed-effects model will be used to synthesize data. However, when heterogeneity was significant (P≤0.1 and I2≥ 50%) and the source of heterogeneity was not identified, we will change to a random-effects model to pool the result or narratively describe the results of each included studies. (3) Assessment of Heterogeneity: Heterogeneity between studies includes clinical heterogeneity, methodological heterogeneity and statistical heterogeneity. Meta-analysis will only be performed, when clinical heterogeneity and methodological heterogeneity are acceptable between included studies. Clinical and methodological heterogeneity will be tested by statistical heterogeneity. The amount of statistical heterogeneity is measured by I2 and Chi2, and I2 >= 50% coupled with P< 0.1 will be interpreted as evidence of substantial levels of heterogeneity. Where substantial heterogeneity is identified, we will explore the sources of heterogeneity. If the sources of heterogeneity are identified, we will conduct subgroup analysis to pool the data, however, if the sources of heterogeneity are not identified, we will use random-effects model to pool the data or narratively describe the results of each included studies. (4) Assessment of publication biases: The funnel plot will be used to visually inspect the small study effect; when there are sufficient numbers of studies (n >=10), the Egger's test will be used for a quantitative inference.

Subgroup analysis: We plan to perform subgroup analysis on primary outcomes according to clinical prognostic factors and different study design below: 1) Age (≥65y vs.＜65y); 2) Type of regimen (D vs. Dd vs. DVd vs. DRd); 3) Line of therapy (newly diagnose vs. non-newly diagnose); 4) dFLC (≥180mg/L vs. ＜180mg/L); 5) Mayo stage (I vs. II vs. IIIa vs. IIIb); 6) Organ involvement (Cardiac vs. Renal vs. Liver); 7) eGFR (≤50 mL/min/1.73 m2 vs. ＞50 mL/min/1.73 m2).

Sensitivity analysis: Where meta-analysis is available to be performed, we considered that results from interventional studies might be different with results from non-interventional studies. Therefore, to test the robustness of the pooled results, we will conduct sensitivity analysis by excluding data from interventional studies and including data from non-interventional studies only.

Language: No language limitation on the search. Records with language other than in English will be excluded when screening.

Country(ies) involved: China.

Keywords: intravenous daratumumab; AL amyloidosis; meta-analysis.

Contributions of each author:

Author 1 - Chunyan Sun drafted and revised the protocol, collect the data, then perform or supervise analyses, provide substantive suggestions for revision or critically reviewed subsequent iterations of the manuscript.
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Author 2 - Xiaohong Wang drafted the protocol, assess the risk of bias in the included studies, perform analyses, then write the initial draft.
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