Efficacy and safety of intravenous daratumumab-based treatments for AL amyloidosis: a systematic review and meta-analysis

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Abstract
Background: Intravenous daratumumab (DARA IV) has been increasingly used in the treatment of amyloid light-chain (AL) amyloidosis. However, the outcomes for patients administered with DARA IV have not been aggregated. The objective of this systematic review and meta-analysis was to investigate the efficacy and safety of DARA IV for AL amyloidosis.

Methods: We searched Medline, EMBASE, Cochrane Library and Web of Science up to 17 June 2021. Response rates and survival rates, and the corresponding 95% confidence intervals (CIs) were pooled and calculated using a fixed-effects model.

Results: Thirty studies (5 cohort studies and 25 single-arm studies) with 997 patients were included. In patients receiving DARA IV-based treatments, very good partial response or better response rate, complete response rate, very good partial response rate, partial response rate and overall response rate were 66% (95% CI, 62–69%), 30% (95% CI, 23–36%), 40% (95% CI, 33–46%), 17% (95% CI, 14–21%), and 77% (95% CI, 73–80%), respectively. Cardiac and renal responses were 41% (95% CI, 34–49%) and 43% (95% CI, 32–54%), respectively. 58% (95% CI, 49–66%) of patients achieved PFS one year or longer. 2.5% (range, 1–10.0%) of patients experienced grade 3 or 4 adverse events, of which the most common adverse event was lymphocytopenia (range, 13.6–25.0%).

Conclusion: This study supports the efficacy and safety of DARA IV for the treatment of patients with AL amyloidosis.

Keywords: Intravenous daratumumab, Immunoglobulin light-chain amyloidosis, Efficacy, Safety, Meta-analysis

Introduction
Immunoglobulin light chain (AL) amyloidosis is characterized by a clonal population of bone marrow plasma cells that produces θ κ or θ λ type monoclonal light protein chain as either an intact molecule or a fragment. This insoluble protein deposits in tissues and interferes with organ function [1]. Treatment of systemic AL amyloidosis relies primarily on multiple myeloma regimens by suppressing the secretion of amyloid-forming monoclonal free light chains (FLCs) by underlying plasma cell clone [2]. Autologous stem cell transplantation (ASCT) is the preferred regimen for patients with transplant-eligible AL Amyloidosis. Previous studies revealed that the median overall survival (OS) of patients with AL...
some patients are still unable to benefit from these treat-
ments, particularly those with an advanced cardiac dis-
ease [11]. Therefore, new therapies are in need for the
treatments of AL amyloidosis patients.

Daratumumab is the first-in-class antibody-based
therapy targeting the glycoprotein CD38, which is
overly expressed on the surface of abnormal plasma
cells [12, 13]. It has been reported that a higher CD38
expression is associated with adverse survival in AL
amyloidosis [14]. Plasma cell death can be induced by
daratumumab through various mechanisms, including
complement-dependent cytotoxicity, antibody-depend-
cell-mediated cytotoxicity, antibody-dependent cell-
ular phagocytosis, and direct cellular apoptosis [13].
The combination of subcutaneous daratumumab with
bortezomib, cyclophosphamide, and dexamethasone has
been demonstrated to be effective and safe for patients
with AL amyloidosis in the Andromeda study [15]. How-
ever, previously published original studies on intravenous
daratumumab (DARA IV)-based regimens are hampered
by the difference of study populations and relatively small
sample sizes [16, 17] and there has been a lack of system-
atic assessment and synthesis of the efficacy and safety of
DARA IV-based in AL amyloidosis. Therefore, this study
used meta-analysis to synthesize the efficacy and safety of
DARA IV-based therapies in the treatment of patients
with AL Amyloidosis to provide reference for the selec-
tion of treatment in clinical settings.

Materials and methods

This systematic review and meta-analysis was per-
formed in accordance with the Preferred Reporting Items
for Systematic Review and Meta-Analysis (PRISMA
2020) extension statement [18]. The protocol for this
systematic review was registered in the International
Platform of Registered Systematic Review and Meta-
alysis Protocols (INPLASY) with an identification
number “INPLASY202160054”.

Data sources and literature searches

Systematic literature searches were conducted in Med-
line, EMBASE, Cochrane Library and Web of Science
with the search terms relating to DARA IV and amy-
loidosis. Searches were performed from the database
inception to June 17, 2021 and were restricted to full
papers using human subjects and published in Eng-
lish. All document types were included in the screening
phase. A detailed search strategy is available in the Addi-
tional file 1: Methods S1. To supplement the electronic
searches, reference lists of included studies was checked
for relevant studies to identify additional published or
unpublished materials (grey literature).

Study selection

Two reviewers independently screened studies by view-
ing the titles and abstracts. All potentially relevant cita-
tions were requested and inspected in detail using the
full-text version. Disagreements were resolved by dis-
ussion, with assistance from a third party if necessary.
A PRISMA flow diagram was constructed to show the
full study selection process. The following inclusion and
exclusion criteria were used to select studies at title and
abstracts stage as well as full-text screening stage: eligi-
bility study design includes interventional and noninter-
ventional studies investigating the efficacy and safety of
DARA IV-based therapy for the treatment of patients
with AL amyloidosis. For patients with AL amyloidosis,
there was no limitation on age, gender, ethnicity, prior
lines of therapy, Mayo stage, or comorbidity. The admin-
istration of daratumumab was limited to intravenous
use. The following studies were excluded: studies not
reported in English, studies without outcome data, and
case reports.

Outcomes

The primary outcome was a very good partial response or
better response (VGPR) rate, defined as CR or VGPR.
The secondary outcomes including CR was defined as
normalization of the difference between involved and
uninvolved free light chain (dFLC) levels and ratio, nega-
tive serum and urine immunofixation, or as defined in
the original studies; VGPR was defined as a reduction in
dFLC to <40 mg/L, or as defined in the original studies;
Partial response rate (PR) was defined as a greater than
50% reduction in the dFLC, or as defined in the origi-
nal studies; Overall response rate (ORR) was defined as
the sum rate of patients with CR, VGPR, and PR; Time
to hematologic response or best hematologic response;
Cardiac response rate was defined as an N-terminal pro-
brain natriuretic peptide (NT-proBNP) response (>30%
and >300 ng/L decrease in patients with a baseline NT-
proBNP >650 ng/L) or New York Heart Association
Data synthesis and analysis
For data expressed as median and interquartile range (IQR)/range, we narratively described the data. Fixed-effects meta-analysis was performed to synthesize data using the R package “meta” (R software version 4.0.2) [20]. For dichotomous variables, we calculated risk ratios (RRs) with 95% confidence intervals (CIs). When no event was observed, we added a fixed value (typically 0.5) to the event number of intervention group. Where heterogeneity was significant (P ≤ 0.1 and I² ≥ 50%), the sources of heterogeneity were identified, we conducted a subgroup analysis to pool the data. When the source of heterogeneity was not identified by subgroup analysis, we used a random-effects model to pool the result. We performed a subgroup analysis on the primary outcome according to the type of regimen (daratumumab ± dexamethasone versus triple regimens), line of therapy (newly diagnosed versus relapsed/refractory), Mayo stage (I versus II versus III), and primary versus secondary patients. We did a sensitivity analysis, the Freeman-Tukey double arcsine transformation analysis was performed to deal 0 event, using stata package “metaprop” (Stata software version 15.0) [21]. We also did a sensitivity analysis, random-effects meta-analysis was performed when heterogeneity was not significant (P > 0.1 and I² < 50%).

Results
Results of study selection
Figure 1 shows the flow diagram displaying the literature search results. The initial search retrieved a total of 496 articles, including 476 articles from databases, and 20 articles from conferences. After deduplication, 315 unique articles remained. We excluded 221 articles by screening the titles and abstracts. 48 articles were further excluded in a full-text review, leaving 46 eligible publications from 30 study populations, including 5 cohort studies and 25 single-arm studies [2, 16, 17, 22–64].

Quality assessment
This single-arm meta-analysis was to pool data derived from single-arm study or the Dara-based treatment arm of randomized controlled trials and cohort studies. Therefore, we chose “Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group” that developed by the National Heart, Lung, and Blood Institute (NHLBI) and adapted for the purpose of our study (Additional file 1: Table S1) [19]. Two independent reviewers evaluated the quality of studies. The two reviewers resolved disagreements by discussion and if required, a third reviewer arbitrated.

Characteristics of included studies and participants
A total of 30 studies with 997 participants were included in this review (for details of included studies, see Additional file 1: Table S2). The data of these studies were contributed by ten countries, namely the US (n=15), Italy (n=3), Germany (n=2), Israel (n=2), France (n=2), Switzerland (n=1), Austria (n=1), Spain (n=1), the UK (n=1) and Greece (n=1). There was one international collaborative study (France and Italy).

The characteristics of patients included in this study are summarized in Table 1. Of 888 patients, over half (62.7%) were male; of 736 patients, the ages ranged from 34 to 91 years. Of 441 patients, 87.8% patients were λ isotype
and 12.2% were κ isotype. Of patients that reported the status of disease, most of them were at the relapsed or refractory stage (489/517). Mayo 2004 cardiac staging was available for 303 patients: 16.2% were stage I, 40.6% were stage II, and 43.2% were stage III. Mayo 2012 cardiac staging was available for 109 patients: 12.8% were stage I, 33.0% were stage II, 30.3% were stage III, and 23.9% were stage IV. The most commonly involved organs included the heart (74.3%), kidney (60.5%) and liver (8.2%).

Treatments
Of 997 patients with identified therapies, 665 (n = 665/977, 66.7%) received a daratumumab mono or combined with dexamethasone regimen (Dara±dex), Daratumumab + Bortezomib + Dexamethasone (DVd) in 108 (10.8%), Daratumumab + Lenalidomide + Dexamethasone (DRd) in 71 (7.1%) and Daratumumab + Cyclophosphamide + Dexamethasone (DCd) in 4 (0.4%) (Table 2). The median of the treatment duration ranged from 4 to 31 cycles.

Quality assessment of included studies
All 30 studies clearly stated research questions or objectives, of which 27 studies clearly prespecified and described eligibility/selection criteria for the study population. The participants lost to follow-up were less than 20% in 26 studies, while in the other four studies more than 20% of participants were lost to follow-up. Eighteen studies prespecified and clearly defined measures of outcomes. Only one study described the evaluable sample size, while in the other studies, the authors were uncertain whether sample sizes were sufficient. None of the 30 studies reported blinding of the participants. Details of the quality assessment of included studies are shown in Additional file 1: Table S1.

Hematologic response and organ response
In 26 studies that reported a robust hematologic response (Fig. 2), 536 of 769 patients (66%; 95% CI, 62–69%; I² = 41%) achieved a ≥ VGPR after treatment with daratumumab-based regimens. The overall response rate was 77% (95% CI, 73–80%), with a CR was achieved
in 30% of patients (95% CI, 23–36%), a VGPR was achieved in 40% (95% CI, 33–46%), a PR was achieved in 17% (95% CI, 14–21%). In 15 studies with 397 patients, the median time to a first hematologic response ranged from 7 to 78 days, and in 11 studies with 253 patients, the median time to the best hematologic response ranged from 30 to 336 days (Additional file 1: Tables S3, S4). Cardiac and renal responses occurred in 41% (95% CI, 34–49%) and 43% (95% CI, 32–54%) of patients, respectively (Table 3). Forest plots are presented in Additional file 1: Fig. S1-S6.

### Very good partial response or better rate

Figure 3 shows the pooled ≥ VGPR rate by categories of treatments, Mayo 2004 stage, newly diagnosis or relapsed/refractory and primary or secondary AL amyloidosis. Subgroup analyses revealed improvement in the ≥ VGPR rate following treatment with triple regimens. In three studies, 64 of 89 patients treated with a daratumumab-based triple regimens achieved ≥ VGPR (71%; 95% CI, 60–80%; I² = 35%), whereas 251 of 387 patients in 16 studies treated with daratumumab mono or combined with dexamethasone (Dara ± dex) achieved ≥ VGPR (63%; 95% CI, 58–68%; I² = 39%) (Fig. 3, Additional file 1: Fig. S7). It also showed that similar ≥ VGPR rates across different Mayo stages (Fig. 3, Additional file 1: Fig. S8-S9), and patients with primary or secondary AL amyloidosis (Fig. 3, Additional file 1: Fig. S10), whereas a higher ≥ VGPR rates were observed in newly diagnosed patients than in patients with relapsed/refractory disease (84% vs. 67%, respectively) (Fig. 3, Additional file 1: Fig. S11). Notably, interpretation of subgroup analysis result should made with caution because of the small and imbalance sample sizes in each group.

Meta-analysis with a random effects model showed heterogeneity in the rate of VGPR, CR and renal response and the source of heterogeneity could not be identified when investigated by predefined subgroup factors. Line of therapy of newly diagnosed or relapsed/refractory may be one of the sources of heterogeneity in cardiac response rate. Subgroup analysis of the cardiac response in the newly diagnosed group showed ten of the 18 (55%; 95% CI, 32–76%; I² = 12%) patients had a cardiac response, while in the relapsed or refractory group,

| Table 1 | Summary information of the characteristics of participants from included studies contributing to statistical analyses |
|-----------------------------------------------|-----------------------------------------------|
| Characteristics | No. of patients, or range of median |
| Gender, n (%) (n_total = 888) | |
| Male | 557 (62.7) |
| Female | 331 (37.3) |
| Age (years) (n_total = 736) | |
| Range | 34–91 |
| Newly diagnosed or relapsed/refractory, n (%) (n_total = 997) | |
| Newly diagnosed | 28 (2.8) |
| Relapsed/refractory | 489 (49.0) |
| Mixed population | 254 (25.5) |
| Not reported | 226 (22.7) |
| AL isotype, n (%) (n_total = 441) | |
| λ | 387 (87.8) |
| k | 54 (12.2) |
| Mayo 2004 Stage, n (%) (n_total = 303) | |
| I | 49 (16.2) |
| II | 123 (40.6) |
| III | 50 (16.5) |
| IIIA | 60 (19.8) |
| IIIB | 21 (6.9) |
| Mayo 2012 Stage, n (%) (n_total = 109) | |
| I | 14 (12.8) |
| II | 36 (33.0) |
| III | 33 (30.3) |
| IV | 26 (23.9) |
| Involved organs, n (%) (n_total = 936) | |
| Heart | 688 (74.3) |
| Kidney | 560 (60.5) |
| Liver | 76 (8.2) |
| Others* | 34 (3.7) |
| eGFR (mL/min/m²) (n_total = 330) | |
| Range of median | 34–73 |
| dFLC (mg/L) (n_total = 711) | |
| Range of median | 34.5–276.9 |

* Pulmonary, tongue, bone marrow, muscle, spleen, upper aerodigestive tract

| Table 2 | Distribution of treatment regimens |
|-----------------------------------------------|-----------------------------------------------|
| Treatment regimens | n of patients | Rate (%) |
| Dara ± dex | 665 | 66.7 |
| DVd | 108 | 10.8 |
| DRd | 71 | 7.1 |
| DCd | 4 | 0.4 |
| Mixed Daratumumab-based treatments* | 149 | 15.0 |

Dara ± dex Daratumumab ± Dexamethasone,
DVd Daratumumab + Bortezomib + Dexamethasone,
DRd Daratumumab + Lenalidomide + Dexamethasone,
DCd Daratumumab + Cyclophosphamide + Dexamethasone

* Mixed Daratumumab-based treatments indicate there were more than one kind of daratumumab-based treatment in the study (daratumumab was combined with dexamethasone, bortezomib, lenalidomide, pomalidomide, cyclophosphamide, ixazomid or carfilzomib)
77 of 200 (39%; 95% CI, 32–46%; $I^2 = 36\%$) patients had a cardiac response. However, due to the small sample size of the subgroup, the results must be interpreted with caution.

**Progression-free survival and overall survival**

Three studies [2, 48, 64] reported a PFS rate of 1 year or longer. Seventy-three of 126 (58%; 95% CI, 49–66%; $I^2 = 46\%$) patients reached PFS after 1 year or longer (Additional file 1: Fig. S12). Of 11 studies reporting OS, 411 of 534 (76%; 95% CI, 72–80%; $I^2 = 31\%$) patients survived after 1 year or longer (Additional file 1: Fig. S13). The causes of death were disease progression, infection, sepsis, immunomodulatory agent–related rejection of the transplanted heart and cardiac complication [2, 31, 54, 58, 64].

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**Table 3 Hematological and organ responses to daratumumab-based regimens**

| Secondary outcome | Studies (n) | Responses (n) | Patients (n) | Response rate % (95% CI) | $I^2$ |
|-------------------|------------|---------------|--------------|--------------------------|-------|
| Hematologic response |            |               |              |                          |       |
| CR                | 24         | 193           | 752          | 30 (23, 36)              | 65%   |
| VGPR              | 23         | 295           | 729          | 40 (33, 46)              | 61%   |
| PR                | 18         | 82            | 544          | 17 (14, 21)              | 50%   |
| ORR               | 27         | 633           | 806          | 77 (73, 80)              | 45%   |
| Organ response    |            |               |              |                          |       |
| Cardiac response  | 20         | 166           | 440          | 41 (34, 49)              | 56%   |
| Renal response    | 18         | 139           | 345          | 43 (32, 54)              | 69%   |

CI confidence interval, CR complete response, PR partial response rate, VGPR very good partial response
Adverse events

Fifteen studies reported IRRs. Of the included 276 patients, 87 experienced grade 1 or 2 IRRs (33%; 95% CI, 21–47%; \( I^2 = 76\% \)) with a median rate of 33.3% (range, 11.1–70.0%) (Additional file 1: Fig. S14), 10 of 432 patients (3%; 95% CI, 2–6%; \( I^2 = 0\)) experienced grade 3 or 4 IRRs with a median rate of 2.5% (range, 1.0–10.0%) (Additional file 1: Fig. S15).

Nine studies reported grade 3 or 4 adverse events. The most common (≥5%) grade 3 or 4 adverse events reported in more than one study were lymphocytopenia, heart failure, infection complications, pneumonia, fatigue, atrial fibrillation, neutropenia, and diarrhea. (Table 4) Other adverse events reported were presented in Additional file 1: Table S5.

Sensitivity analysis

The CR was achieved in 29% of patients (95% CI, 22–36%), a VGPR was achieved in 39% (95% CI, 32–46%), a PR was achieved in 14% (95% CI, 9–19%) (Additional file 1: Fig. S16–S18). Renal responses occurred in 41% (95% CI, 30–53%) (Additional file 1: Fig. S19). 10 of 432 patients (1%; 95% CI, 0–2%; \( I^2 = 16.64\% \)) experienced grade 3 or 4 IRRs (Additional file 1: Fig. S20). The results using Freeman-Tukey double arcsine transformation were similar to the results found. The results of the random-effects model were similar to those of the fixed-effects model, as shown in Additional file 1: Table S6.

Discussion

This systematic review and meta-analysis of 30 studies evaluated the efficacy and safety of DARA IV-based therapies for the treatment of patients with AL amyloidosis. First, the results showed 66% of patients achieved ≥ VGPR. Subgroup analysis showed a slightly increased ≥ VGPR rate in patients treated with daratumumab-based triple regimens than mono or combined with only dexamethasone (71% vs. 63%). We also observed ≥ VGPR rates were similar for patients with primary or secondary AL amyloidosis (65% vs. 64%). Furthermore, rates of ≥ VGPR were higher in patients with newly diagnosed AL amyloidosis (84%) than in those with relapsed/refractory disease (67%). However, findings from the subgroup analysis should be interpreted with caution as additional studies are needed for confirmation [65].

In this study, the CR, VGPR and PR rates were 30%, 40% and 17%, respectively. In a prospective study including 915 patients with AL amyloidosis treated with bortezomib-based therapies, the CR rate was only 25%, and the cardiac and renal response rates were 32.5% and 15.4%, respectively [66]. A retrospective analysis of 25 patients with relapsed and refractory AL amyloidosis treated with...
DARA IV reported a hematologic response rate of 76%, with 36% of patients achieving CR and 24% achieving a very good partial response (VGPR) [38]. Moreover, 77% of patients achieved an overall response, 41% of patients with cardiac involvement exhibited a cardiac response, and 43% of patients with renal involvement showed a renal response.

This study revealed that 58% and 76% of patients reached one-year or longer PFS and OS, respectively, even though most included patients had relapsed/refractory AL amyloidosis. It is important to note that due to limited studies, only four studies in this review reported 1 year or longer progression-free survival rates with no more than 2 years follow-up. For comparison, in a study assessing the efficacy and safety of lenalidomide, melphalan and dexamethasone in AL amyloidosis patients with high rates of advanced cardiac involvement, the one-year survival rate was 58% [67]. This study suggested that treatment with DARA IV may improve survival for patients with AL amyloidosis.

Most of the IRRs were grade 1 or 2. 33% of patients experienced grade 1 or 2 IRRs and 3% of patients experienced grade 3 or 4 IRRs. The most common grade 3 or 4 adverse events reported were lymphocytopenia, heart failure, infection complications, pneumonia, fatigue, atrial fibrillation, neutropenia, and diarrhea. However, caution should be exercised when interpreting the results, as cardiac-related complications due to amyloid

### Table 4 Most common (> 5%) grade 3 or 4 treatment-emergent adverse events (TEAEs) reported in more than one study

| Adverse event       | Study ID          | Intervention               | Events (n) | Total (n) | Rate (%) |
|---------------------|-------------------|----------------------------|------------|-----------|----------|
| Lymphocytopenia     | Kimmich 2021      | DRd                        | 11         | 44        | 25.0     |
|                     | Kimmich 2020      | Dara ± dex, DVd            | 27         | 142       | 20.2     |
|                     | Sanchorawala 2020 | Dara ± dex                 | 3          | 22        | 13.6     |
| Heart failure*      | Kimmich 2020      | Dara ± dex, DVd            | 15         | 168       | 9.0      |
|                     | Kaufman 2017      | Dara ± dex                 | 1          | 25        | 4.0      |
|                     | Sanchorawala 2020 | Dara ± dex                 | 3          | 22        | 13.6     |
| Infection complications | Cohen 2020  | Dara ± dex                 | 0          | 53        | 0.0      |
|                     | Dima 2020         | Mixed †                    | 3          | 40        | 7.5      |
|                     | Gounot 2020       | Mixed †                    | 2          | 25        | 8.0      |
|                     | Kaufman 2017      | Dara ± dex                 | 2          | 25        | 8.0      |
|                     | Kimmich 2020      | Dara ± dex, DVd            | 28         | 168       | 16.0     |
|                     | Milani 2020       | Mixed †                    | 3          | 72        | 4.2      |
|                     | Sanchorawala 2020 | Dara ± dex                 | 4          | 22        | 18.2     |
|                     | Shragai 2020      | Mixed †                    | 7          | 48        | 14.6     |
| Pneumonia           | Dima 2020         | Mixed †                    | 2          | 40        | 5.0      |
|                     | Kimmich 2021      | DRd                        | 7          | 44        | 15.9     |
|                     | Milani 2020       | Mixed †                    | 4          | 72        | 5.6      |
|                     | Shragai 2020      | Mixed †                    | 5          | 48        | 10.4     |
| Fatigue             | Cohen 2020        | Dara ± dex                 | 0          | 53        | 0.0      |
|                     | Sanchorawala 2020 | Dara ± dex                 | 2          | 22        | 9.1      |
| Atrial fibrillation | Kimmich 2020      | Dara ± dex, DVd            | 0          | 168       | 0.0      |
|                     | Milani 2020       | Mixed†                     | 2          | 72        | 2.8      |
|                     | Sanchorawala 2020 | Dara ± dex                 | 4          | 22        | 18.2     |
| Neutropenia         | Abeykoon 2018     | Dara ± dex                 | 3          | 44        | 6.8      |
|                     | Kimmich 2020      | Dara ± dex, DVd            | 0          | 142       | 0.0      |
|                     | Milani 2020       | Mixed †                    | 2          | 72        | 2.8      |
| Diarrhea            | Cohen 2020        | Dara ± dex                 | 0          | 53        | 0.0      |
|                     | Kimmich 2020      | Dara ± dex                 | 1          | 168       | 0.6      |
|                     | Sanchorawala 2020 | Dara ± dex                 | 2          | 22        | 9.1      |
|                     | Shragai 2020      | Mixed†                     | 1          | 48        | 2.1      |

*Dara ± dex Daratumumab ± Dexamethasone, DVd Daratumumab + Bortezomib + Dexamethasone
† Including congestive heart failure and decompensated heart failure
‡ Mixed Daratumumab-based treatments indicate there were more than one kind of daratumumab-based treatment in the study (daratumumab was combined with dexamethasone, bortezomib, lenalidomide, pomalidomide, cyclophosphamide, ixazomid, or carfilzomib)
Deposition are expected in AL amyloidosis and limitations of the meta-analysis. Besides, there were no new adverse events related to daratumumab. Overall, DARA IV therapy had an acceptable safety profile for patients with AL amyloidosis.

This study has several strengths. First, this study had good quality control. We conducted this study strictly according to the Cochrane and PRISMA standard. An information specialist performed the literature search. When necessary, a hand search was used to identify the reference lists of systematic reviews and conference abstracts. The screening and data extraction processes were performed independently by two reviewers and checked by a third independent assessor, ensuring the accuracy of the data. Second, to our knowledge, this study is the first comprehensive and the most current meta-analysis evaluating the efficacy and safety of DARA IV for the treatment of patients with AL amyloidosis. Third, we conducted subgroup analyses to reduce heterogeneity as much as possible.

There are nonetheless several limitations. Due to the language limitation, literature not in English and Chinese were excluded. All included studies were single arm studies or cohort studies, blinding and sample size calculation methods were not reported for most studies, which may either overestimate or underestimate the efficacy of DARA IV.

In conclusion, results of this meta-analysis suggests that DARA IV-based therapies are effective in generating hematologic and organ responses in both newly diagnosed and relapsed/refractory patients with AL amyloidosis. The safety profile is consistent with that has been previously documented for DARA IV in this population.

**Abbreviations**

DARA IV: Intravenous daratumumab; AL: Amyloid light-chain; FLCs: Free light chains; ASCET: Autologous stem cell transplantation; OS: Overall survival; CyBorD: Bortezomib-Cyclophosphamide-Dexamethasone; CR: Complete remission; DARA: Daratumumab; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; INPLASY: International Platform of Registered Systematic Review and Meta-analysis Protocols; VGPR: Very good partial response; dFLC: Difference between involved and uninvolved free light chain; PR: Partial response; ORR: Overall response; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; eGFR: Estimated glomerular filtration rate; FAB: FAB classification; PFS: Progression-free survival; AE: Adverse events; IRRs: Infusion-related reactions; PICOS: Population, Intervention, Comparison, Outcome, Study design; eGFR: Estimated glomerular filtration rate; RCTs: Randomized controlled trials; NRSIs: Non-randomized studies of interventions; NHLBI: National Heart, Lung, and Blood Institute; IQR: Interquartile range; RRs: Risk ratios; CI: Confidence intervals.

**Supplementary Information**

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**Author contributions**

Draft protocol, JL and BW; study selection, RZ and XW; data extraction, LX and BW; data analysis, CS and JX; writing-review and editing, CS and JL. All authors have read and approved the final manuscript.

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Not applicable.

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**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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