Interleukin 1 inhibition with anakinra in adult-onset Still disease: a meta-analysis of its efficacy and safety

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Background: Anakinra is the first interleukin-1 inhibitor to be used in clinical practice, and recent evidence showed that interleukin-1 plays a pivotal role in the pathogenesis of adult-onset Still disease (AoSD). However, data concerning efficacy with anakinra use in different clinical trials has not been evaluated, and the overall remission of AoSD with anakinra treatment has not been well defined.

Methods: We conducted a search on Embase, PubMed, and the Cochrane Library for relevant trials. Statistical analyses were conducted to calculate the overall remission rates, odds ratios (OR), and 95% confidence intervals (CI), by using either random effects or fixed effect models according to the heterogeneity.

Results: Of the 273 articles that were identified, 265 were excluded. Eight studies were eligible for inclusion. The overall remission rate and complete remission rate of anakinra in AoSD patients were 81.66% (95% CI: 69.51%–89.69%) and 66.75% (95% CI: 59.94%–75.3%), respectively. Compared with the controls, the use of anakinra was associated with a significant remission in AoSD, with an OR of 0.16 (95% CI: 0.06–0.44, P=0.0005). There were also significant reductions of the dosage of corticosteroid (mean difference =21.19 (95% CI: 13.2–29.18, P<0.0001) from anakinra onset to the latest follow up time. Clinical and laboratory parameters were all improved, and anakinra was well tolerated in patients with AoSD. No evidence of publication bias was observed.

Conclusion: Our study has shown that anakinra is effective in remitting the manifestations of AoSD, with reduction of the dose of corticosteroid in patients with AoSD. Further, anakinra therapy was not associated with increased risk of adverse events, and it was well tolerated in patients with AoSD. Further research is still recommended to investigate these findings.

Keywords: interleukin-1 inhibitor, AoSD, anakinra, adverse events, clinical and laboratory parameters, efficacy

Introduction

Adult-onset Still disease (AoSD) is a rare multisystemic inflammatory disorder manifested by a variety of clinical features, including high, spiking fever, evanescent skin rash, hepatosplenomegaly, lymphadenopathy, polyarthritis, and other systemic symptoms. The pathogenesis of AoSD is currently unclear, and the therapeutic strategies of AoSD can be varied according to its clinical presentation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are commonly used as first-line agents for AoSD, and if first-line treatment is ineffective, disease-modifying antirheumatic drugs (DMARDs), such as methotrexate are added. Corticosteroids can control the manifestations of AoSD in about 65% of patients, and the response to corticosteroids is often quick, within a few hours. However, corticosteroids easily induce dependence – steroid dependence occurred in 42% of the cases in one study.

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Drug Design, Development and Therapy 2014:8 2345–2357

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Long-term steroid exposure in patients carries the potential for serious side effects, such as infection.\(^6\) Currently, many patients need other options to control the clinical presentation of the disease or to reduce corticosteroid dependence.

Hence, in clinical practice, physicians are often prone to adopt other therapeutic strategies, even in the absence of large-scale clinical trials data. The blockade of the interleukin-1 (IL-1) pathway has emerged as a new therapeutic strategy since recent evidence showed that IL-1 could play a pivotal role in the pathogenesis of AoSD.\(^{14-16}\) Anakinra is the first IL-1 inhibitor to be used in clinical practice.\(^{17}\) Rudinskaya and Trock\(^{18}\) reported the first case of the treatment of AoSD with anakinra in 2003, including just one patient, and it was shown to rapidly improve the clinical symptoms and laboratory disease activity markers of AoSD.

To date, there is little information on treatment efficacy of anakinra in AoSD, with a paucity of prospective double-blinded randomized trials, but one important randomized controlled trial (RCT) has demonstrated its rapid efficacy in patients with rheumatoid arthritis.\(^{19}\) Indeed, anakinra is the most commonly described anti-IL-1 agent. In 2007, two case series including eight subjects described a good efficacy of anakinra in steroid- and DMARD-refractory AoSD with systemic symptoms;\(^{14,20}\) however, the data concerning efficacy with anakinra treatment has not been evaluated in different clinical trials, and the overall remission of AoSD with anakinra treatment has not been well defined. AoSD is a rare multisystemic disorder, which if not accurately treated in time, can progress to death. The treatment strategies are poor currently, therefore, we conducted this systematic review and meta-analysis to summarize the results of studies and evaluate the evidence for efficacy and safety of anakinra in AoSD.

**Methods**

**Search strategy and study selection**

We searched Embase, PubMed, and the Cochrane Library database from onset to August 15, 2014, using the following search terms treated as Medical Subject Headings (MeSH) terms or free text: (“adult onset Still’s disease” or “adult onset stills disease” or “adult onset Still disease” or “Still’s disease” or “stills disease” or “still disease” or “Still’s Disease, Adult-Onset”) and (“Interleukin 1 Receptor Antagonist Protein” or “anakinra”). Additionally, we searched the clinical trials registry (ClinicalTrials.gov) to obtain information on the registered clinical trials. The detailed search strategy is given in Figure S1.

The following criteria were used for inclusion for study selection: (1) patients were diagnosed with AoSD according to the preliminary classification by Cush et al,\(^{21}\) Yamaguchi et al,\(^{22}\) or Faurel et al;\(^{23}\) (2) studies that reported the efficacy of anakinra in AoSD patients; and (3) prospective or retrospective studies with or without a control group. Studies were excluded if they did not show sufficient data, such as number of patients with partial response or complete response, results of clinical and laboratory parameters, the dose of corticosteroid in the treatment, or the adverse events for anakinra in AoSD patients.

**Data extraction and quality assessment**

Data extraction was conducted by two independent investigators (DSH and ZHY), and discrepancies were identified and resolved by consensus. For each study, the following information was extracted: year of publication, first author’s name, treatment arm, mean duration of follow up, number of patients in the treatment and control groups, number of patients with partial response or complete response in the treatment, number of patients with adverse events in the treatment, measurements of clinical and laboratory parameters (including C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and arthritis symptoms) in the treatment.

A quality score for each study was determined according the earlier reports, using consequential binomial parameters (Table S1).\(^{24,25}\) Each parameter was given a numerical score of 0 or 1, with an overall quality score ranging from 0 to 10. Studies with a quality score of <5 were rated as poor, while those ≥5 were rated as high.

**Data synthesis and statistical analysis**

For the calculation of remission rate, the number of patients with partial response or complete response in the anakinra group, and the total number of patients receiving anakinra were extracted from the selected clinical trials; for each study, the proportion of patients with remission rates and the 95% confidence interval (CI) were derived. The remission rate of anakinra therapy versus controls was expressed as odds ratio (OR) with 95% CI. Heterogeneity was assessed by using the \(Q\) statistic and \(F\) tests among trials.\(^{26}\) Heterogeneity was considered statistically significant when \(P < 0.1\) (for heterogeneity) or \(F > 40\%.\(^{27}\) If heterogeneity existed, the data was analyzed using a random effects model; if heterogeneity did not exist, a fixed effect model was used. A statistical test with a \(P\)-value less than 0.05 was considered significant. The presence of publication bias was evaluated by using funnel plots.\(^{27}\) All statistical analysis was performed by using R software, version 3.0.3 (The R Core Team, Vienna, Austria) (http://www.r-project.org).
Results
Description of studies
A total of 273 potentially studies were reviewed, and 265 were excluded (Figure 1). The remaining eight studies,\textsuperscript{13,28–34} with 134 subjects, that met our inclusion criteria were included in our analyses. The major baseline characteristics of the eight studies are listed in Table 1. The studies included one RCT\textsuperscript{29} and seven observational studies.\textsuperscript{13,28,30–34} The geographical distribution of these studies was over various countries, with four studies from France,\textsuperscript{13,28,31,34} two from Greece,\textsuperscript{32,33} and one from Italy.\textsuperscript{30} One RCT included 22 patients from ten centers in Finland, Norway, and Sweden.\textsuperscript{29} These studies were all published between 2010 and 2014, and the dose of anakinra was 100 mg/day. The sample size of each study ranged from six to 28 treated patients. The majority of the studies were of good quality (mean quality score =6), as shown in the detailed information given in Table S1.

We performed this meta-analysis in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Table S2).\textsuperscript{35}

Efficacy of anakinra in AoSD patients
Eight studies,\textsuperscript{13,28–34} with a total of 134 subjects, investigated the effect of anakinra in AoSD remission. The remission rate at latest follow up was significantly increased in all studies, ranging from 50% to 100%. The highest remission rate was seen in the study by Iliou et al\textsuperscript{33} in which ten out of 44 patients (22.7%) were treated with anakinra, and a response was achieved in all of them. The complete remission rate ranged from 57% to 84%, and the highest complete remission rate was reported by Laskari et al\textsuperscript{32} who found a complete response for all disease-related symptoms (clinical and laboratory) within a median 3 months, in 80% of patients. Based on the data from these studies, the overall remission rate and
complete remission rate of anakinra in AoSD patients were 81.66% (95% CI: 69.51%–89.69%) and 66.75% (95% CI: 56.94%–75.3%), respectively (Figure 2).

Of note, to investigate the specific contribution of anakinra to the AoSD and exclude the influence of confounding factors, we determined the OR of anakinra in AoSD patients. Figure 2 shows the forest plot for the four controlled studies[^12,30,33] that investigated the remission effect of anakinra in AoSD patients. As can be seen from this figure, the meta-analysis of these studies suggests that anakinra was associated with significant remission in AoSD when compared with controls (OR=0.16, 95% CI: 0.06–0.44, P=0.0005) (Figure 2), according to the fixed effects model.

### Efficacy of anakinra as a steroid-sparing agent

Six studies[^28-32,34] with a total of 105 subjects, showed the effect of anakinra as a steroid-sparing agent. The average dose of corticosteroid was reduced in the anakinra-treated patients of all six studies, although the exact values for the change between baseline and latest follow up were described just in two studies.

Two studies[^28,31] showed the definite changes of corticosteroid dose from anakinra onset to latest follow up time, and the pooled analysis showed a significant reduction of the dosage of corticosteroid (mean difference =21.19 mg/day) (95% CI: 13.2–29.18, P<0.0001) (Figure 3). The cases of discontinued use of steroid was reported in three studies[^28,29,32] and the overall frequency of discontinuance of oral corticosteroids was 36.9% (95% CI: 24.01%–51.98%) (Figure 3). The controlled trial by Nordström et al[^29] also showed that three patients on anakinra, but none on DMARD, were able to discontinue oral corticosteroids.

### Efficacy of anakinra on clinical and laboratory parameters

Four studies[^28,29,31,32] investigated the changes of CRP, and the conclusion was consistent. The values of CRP were markedly declined over long duration of follow up in patients treated with anakinra (Table 2).

Three studies[^28,31,32] have clear descriptions of the change in ESR in patients treated with anakinra. All three studies reported a diminution in the average value of ESR, from anakinra onset to latest follow up, and the greatest change was seen in an uncontrolled study in which the mean level of ESR was 75 mm/h at anakinra onset was decreased to 4 mm/h at the last visit (Table 2).

Three studies[^28,31,32] observed the effect of anakinra on arthritis symptoms (tender joint count [TJC] and swollen joint count [SJC]). Of these, three studies[^28,31,32] with uncontrolled and open design, were able to demonstrate marked improvement in these parameters with anakinra for AoSD when values for the last visit were compared with those at anakinra onset. Compared with baseline, in a study by Lequerré et al[^28] the patients in the anakinra arm had statistically lower parameters of arthritis symptoms (P=0.0002 for TJC and P=0.0005 for SJC) (Table 2).

### Safety of anakinra in AoSD patients

Five studies[^28,29,31,32,34] reported the adverse events related to anakinra use in AoSD patients, and showed it was well tolerated in all study populations. The mainly adverse event was skin rash in five subjects in three studies[^28,31,34] which led to the withdrawal of anakinra. Three patients developed a severe urticarial reaction after the first treatment (one patient at 1.5 months and two patients at 3 months), leading to discontinued therapy.[^27] One open, randomized, and multicenter study[^29] noted that three patients had serious adverse events,
the state of patients with AoSD worsened in two out of ten patients in the control (DMARD) group and only one out of 12 patients on anakinra.

The incidence of adverse events ranged from 5.26% to 13.33%, and the overall incidence was 9.54% (95% CI: 5.03%–17.36%) (Figure 4) according to pooled analysis.28,29,31,32,34 Further, we performed the pooled analysis to acquire the incidence of rash with anakinra in AoSD patients (proportion =8.56%) (95% CI: 3.60%–19.03%) (Figure 4).28,31,34

**Publication bias**

No significant evidence of publication bias was observed for the remission rates with anakinra in AoSD patients, in the analysis by funnel plot (Figure 5).

**Discussion**

The main objective of this meta-analysis was to evaluate the evidence for the use of anakinra in AoSD. The highest strength of clinical evidence comes from RCTs, but there is a lack of such high-strength trials explaining the effects of anakinra in AoSD. The reason for the absence of RCTs among patients with AoSD are challenges related to the disease, such as (1) the difficulty of identification and initial diagnosis of AoSD, which makes it difficult to conduct planned treatments; (2) the prevalence of the disease is rare, with an annual incidence of 0.16 cases per 100,000 people,36 leading to difficulty in recruiting sufficient numbers of patients; and (3) the heterogeneity of clinical symptoms. Hence, we strictly applied inclusion criteria to collect the

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**Figure 2** Remission rate for anakinra in adult-onset Still disease.

Notes: (A) Remission rate; (B) complete remission rate; (C) odds risk of remission rate.

Abbreviations: CI, confidence interval; OR, odds ratio; W, weight.
The changes of dosage of corticosteroid

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Initial to anakinra</th>
<th>Lastest follow up</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>W (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lequerré et al</td>
<td>2</td>
<td>8.6 (7.6)</td>
<td>26.8 (20.1)</td>
<td>-18.200</td>
<td>(-29.0747; -7.3253)</td>
<td>54%</td>
</tr>
<tr>
<td>Giampietro et al</td>
<td>3</td>
<td>9.7 (7.9)</td>
<td>34.4 (21.9)</td>
<td>-24.700</td>
<td>(-36.4818; -12.9182)</td>
<td>46%</td>
</tr>
</tbody>
</table>

Fixed effect model

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = 0.4269$

The frequency of discontinue oral corticosteroids

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Initial to anakinra</th>
<th>Lastest follow up</th>
<th>Proportion</th>
<th>95% CI</th>
<th>W (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lequerré et al</td>
<td>2</td>
<td>11</td>
<td></td>
<td>0.1818</td>
<td>(0.0228; 0.5178)</td>
<td>16.2%</td>
</tr>
<tr>
<td>Nordström et al</td>
<td>3</td>
<td>12</td>
<td></td>
<td>0.2500</td>
<td>(0.0549; 0.5719)</td>
<td>22.2%</td>
</tr>
<tr>
<td>Laskari et al</td>
<td>12</td>
<td>25</td>
<td></td>
<td>0.4800</td>
<td>(0.2780; 0.6869)</td>
<td>61.6%</td>
</tr>
</tbody>
</table>

Fixed effect model

Heterogeneity: $I^2 = 43.6\%$, $\tau^2 = 0.2797$, $P = 0.1701$

The pathophysiological processes underlying AoSD are not completely understood. The role of proinflammatory cytokines has been mentioned because high levels of IL-1, IL-6, and tumor necrosis factor (TNF)-α have been observed in patients with AoSD. \(^{37,38}\) In patients with AoSD, serum levels of IL-6 are raised and correlate with systemic symptoms, such as fever, hepatic dysfunction, and raised serum CRP levels. \(^{39,40}\) Tocilizumab, an IL-6 inhibiting agent, was found to control the disease activity in some patients with AoSD. \(^{41}\)

Table 2  Clinical and laboratory parameters in patients undergoing anakinra treatment in the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>At anakinra onset</th>
<th>At last follow up</th>
<th>P-value*</th>
</tr>
</thead>
</table>
| C-reactive protein level
| Lequerré et al      | 2008 | 91.9 (71.8) mg/L  | 16.6 (20.6) mg/L  | 0.001    |
| Nordström et al     | 2012 | 25.1 mg/L         | 2.56 mg/L         | –        |
| Giampietro et al    | 2013 | 82.9 (95.7) mg/dL | 15.19 (15.9) mg/dL| –        |
| Laskari et al       | 2011 | 111 (19–318) mg/dL| 3.5 (0.4–9) mg/dL | <0.001   |
| Erythrocyte sedimentation rate
| Lequerré et al      | 2008 | 74 (33.5) mm/hour | 22.1 (24.6) mm/hour | –        |
| Giampietro et al    | 2013 | 57.9 (25.3) mm/hour| 14.6 (13.1) mm/hour| –        |
| Laskari et al       | 2011 | 75 (26–120) mm/hour| 4 (1–15) mm/hour   | –        |
| Tender joint count
| Lequerré et al      | 2008 | 8.5 (5.9)         | 1.5 (2.7)         | 0.0002   |
| Giampietro et al    | 2013 | 3.6 (3.2)         | 1.4 (2.9)         | –        |
| Laskari et al       | 2011 | 12 (0–38)         | NA                | –        |
| Swollen joint count
| Lequerré et al      | 2008 | 5.9 (5.8)         | 0.9 (1.5)         | 0.0005   |
| Giampietro et al    | 2013 | 4.2 (4.5)         | 1.53 (4.1)        | –        |
| Laskari et al       | 2011 | 1 (0–15)          | NA                | –        |

Notes: *Significant comparisons of clinical and laboratory parameters at last follow up versus at anakinra onset. †Values indicated are expressed as mean (SD). ‡Values indicated are expressed as mean (range).

Abbreviations: SD, standard deviation; NA, not applicable.
IL-1, a cytokine inducing release of IL-6 and upstream molecules in the inflammatory cascade, may represent a suitable target for the treatment of AoSD.

The results of this pooled analysis suggest significant increases in remission rates among anakinra-treated patients. The remission rates included partial or complete remission. Partial remission was mainly defined as improvement in some related clinical or laboratory manifestations of AoSD, and complete remission was defined as the resolution of all clinical and biologic AoSD symptoms, under anakinra treatment.43,44 The remission rate is widely used in AoSD clinical trials owing to its importance to the prognostic evaluation of AoSD.9,45,46 A significant increase in the remission rate was reported by all the included studies, and we also found that anakinra significantly increased remission in AoSD when compared with controls. Some of the included studies31 also reported that patients who had previously failed to respond to conventional therapy with corticosteroids, NSAIDs, and DMARDs had a long-lasting remission of AoSD under anakinra treatment.

The steroid-sparing effect of anakinra was demonstrated in six of the included studies, and significant reduction was reached from anakinra onset to the latest follow up in two of them.28,31 Steroid is effective in controlling AoSD, and the response to steroid is often quick, within a couple of hours or a few days.47,48 However, steroid dependence easily occurs and can induce adverse events. According to Gerfaud-Valentin et al13 of 51 patients treated with steroids, 49 received them as a first- or second-line treatment, and 75% of patients developed various adverse events, such as Cushing syndrome (n=19), osteoporosis (n=8), aseptic osteonecrosis (n=5), corticosteroid-induced diabetes (n=4), high blood pressure (n=4), cataracts (n=3), psychiatric disorders (n=3), and infectious diseases (n=2). Furthermore, the steroid used in AoSD would increase the risk of infectious complications and of serious harm associated with long-term steroid treatment.49–51 Hence, reducing the dose of steroids used is beneficial for patient with AoSD.
Among the clinical and laboratory parameters, reduced CRP and ESR levels, and improved arthritis symptoms (TJC and SJC) have all been shown to relate with activity of disease, and these parameters are routinely used in clinical practice to monitor patients with AoSD. Patients with AoSD tend to have higher CRP and ESR levels, and arthritis damage symptoms, with higher TJC and SJC, compared with those without AoSD. Three of the included studies showed that anakinra could normalize the level of ESR and improve arthritis symptom parameters; four of the included studies showed that anakinra could normalize the level of CRP. Hence, on the base of available data, it is possible to conclude that anakinra is beneficial in improving clinical and laboratory parameters among patients with AoSD.

AoSD is associated with a higher risk of infection, and some AoSD treatment agents, such as corticosteroid, may be associated with an increased risk of infection, rather than a decreased risk of infection. In one recent study, 9.8% AoSD patients in the long-term prednisone-treated group died because of pulmonary infection, and the mortality rate in this study was higher than that in other reports. Deaths in AoSD patients owing to infections were also reported by other studies. In all of the included studies, the adverse event of infection was not reported in any of patients treated with anakinra, and anakinra as initial therapy was not associated with increased the risk of infection in patients of AoSD. This meta-analysis showed that the main adverse event was skin rash, and according to Nordström et al anakinra-treated patients had a lower risk of infection than the control (DMARD) group. Hence, based on the existing data, anakinra was well tolerated in patients with AoSD.

Compared with other biologics, anakinra had higher remission rates with patients of AoSD. In study by Gerfaud-Valentin et al of 17 patients on other biologics, only eight (47%) had successful control of the disease; however, anakinra led to remission in five of six (83%) patients after a mean follow up of 27.8 months. In another study by Cavalli et al 15 of 19 patients with AoSD responded to anakinra (79%), and only four of eleven patients responded to other biologics, including tocilizumab, etanercept, and adalimumab (36%).

Our meta-analysis strictly applied inclusion criteria to collect the relevant literature of AoSD patients treated with anakinra, and significant heterogeneity was not observed. However, some limitations did exist. First, as pointed out earlier, there was paucity of well-designed trials on the use of anakinra in patients with AoSD. The quality assessment of studies was indeed high, but the sample sizes in all included studies were small. Although some of included studies showed statistically significant results, these may not translate to clinical practice directly. Second, there were many case reports that described the effect of anakinra in patients with AoSD, and analysis of those report might have obtained other useful information, but we choose to exclude case reports due to their low strength of evidence. Third, the included studies were performed at various international institutions by different investigators and may have had some bias in reporting the types of result, suggesting publication and language bias may have existed. Finally, all eight studies included in the analysis were from Europe, and limitations related to environment and race may have existed.

Finally, despite these limitations, the present meta-analysis provides some clinical reference for the treatment of AoSD. Corticosteroids are the first-line treatment for rapid remission of relevant symptoms of AoSD; then, if manifestations of AoSD are improved, the dose of corticosteroid could be reduced, and anakinra, as second-line agent, could be introduced.

Conclusion
Our study has shown that anakinra is effective in remission of the manifestations of AoSD, with reduction of the dose of corticosteroid in patients with AoSD. Further, anakinra therapy was not associated with increased risk of adverse events in patients of AoSD and was well tolerated in patients with AoSD. Further research is still recommended to investigate these findings.

Acknowledgments
This work was supported by the National Natural Science Foundation of China (grant number 81100277), Zhejiang TCM KEY research fund projects (grant number 2013ZZ009 and 2013ZA078), and the Zhejiang Provincial Education Department Research Fund Project (grant number Y201225107).

Disclosure
The authors report no conflicts of interest in this work.

References


Supplementary materials

**Table S1** Quality scores of the studies included in this systematic review

<table>
<thead>
<tr>
<th>Year</th>
<th>Randomized</th>
<th>Blinded</th>
<th>Prospective study</th>
<th>Control group</th>
<th>Inclusion criteria defined</th>
<th>Intervention defined</th>
<th>Outcome defined</th>
<th>Baseline characteristic similarity*</th>
<th>Intention-to-treat analysis</th>
<th>Details of drop out/deaths</th>
<th>Total score</th>
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<tr>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
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<td>N</td>
<td>Y</td>
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<td>N</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Mean score 6

**Note:** *Baseline characteristic similarity included age, sex, and the progress of the disease.
Table S2 PRISMA 2009 checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>Number</th>
<th>Checklist item</th>
<th>Reported on page number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both</td>
<td>1</td>
</tr>
<tr>
<td><strong>Abstract</strong></td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number</td>
<td>2–3</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known</td>
<td>4–5</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (picos)</td>
<td>4–5</td>
</tr>
<tr>
<td><strong>Protocol and registration</strong></td>
<td>5</td>
<td>Indicate if a review protocol exists, and if where it can be accessed (eg, web address), and, if available, provide registration information including registration number</td>
<td>–</td>
</tr>
<tr>
<td><strong>Eligibility criteria</strong></td>
<td>6</td>
<td>Specify study characteristics (eg, picos, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale</td>
<td>6</td>
</tr>
<tr>
<td><strong>Information sources</strong></td>
<td>7</td>
<td>Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched</td>
<td>5–6</td>
</tr>
<tr>
<td><strong>Search</strong></td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated</td>
<td>5</td>
</tr>
<tr>
<td><strong>Study selection</strong></td>
<td>9</td>
<td>State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)</td>
<td>6</td>
</tr>
<tr>
<td><strong>Data collection process</strong></td>
<td>10</td>
<td>Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators</td>
<td>6</td>
</tr>
<tr>
<td><strong>Data items</strong></td>
<td>11</td>
<td>List and define all variables for which data were sought (eg, picos, funding sources) and any assumptions and simplifications made</td>
<td>6–7</td>
</tr>
<tr>
<td><strong>Risk of bias in individual studies</strong></td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis</td>
<td>7</td>
</tr>
<tr>
<td><strong>Summary measures</strong></td>
<td>13</td>
<td>State the principal summary measures (eg, risk ratio, difference in means)</td>
<td>6–7</td>
</tr>
<tr>
<td><strong>Synthesis of results</strong></td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, for each meta-analysis)</td>
<td>6–7</td>
</tr>
<tr>
<td><strong>Risk of bias across studies</strong></td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies)</td>
<td>7</td>
</tr>
<tr>
<td><strong>Additional analyses</strong></td>
<td>16</td>
<td>Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified</td>
<td>6–7</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>17</td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram</td>
<td>7–8</td>
</tr>
<tr>
<td><strong>Study selection</strong></td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (eg, study size, picos, follow-up period) and provide the citations</td>
<td>7–8</td>
</tr>
<tr>
<td><strong>Risk of bias within studies</strong></td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)</td>
<td>11</td>
</tr>
<tr>
<td><strong>Results of individual studies</strong></td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot</td>
<td>7–11</td>
</tr>
<tr>
<td><strong>Synthesis of results</strong></td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency</td>
<td>7–11</td>
</tr>
<tr>
<td><strong>Risk of bias across studies</strong></td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see item 15)</td>
<td>11</td>
</tr>
<tr>
<td><strong>Additional analysis</strong></td>
<td>23</td>
<td>Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16])</td>
<td>7–11</td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers)</td>
<td>11–14</td>
</tr>
</tbody>
</table>

(Continued)
Table S2 (Continued)

| Limitations | 25 | Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias) |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research |
| Discussion |  | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review |


**Abbreviation:** picos, patient, intervention, comparison, outcome and study; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**References**


