The efficacy of treatment for systemic sclerosis interstitial lung disease: results from a meta-analysis

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CRD summary
The review concluded that the conservative yet significant effect of cyclophosphamide demonstrated the need for further research on patient-important outcomes such as quality of life and dyspnoea. The review had some methodological problems and more details about the characteristics of included studies would have aided interpretation. However, the authors’ conclusions were suitably cautious and appear appropriate.

Authors’ objectives
The review appeared to aim to determine the efficacy and safety of drug treatment for systemic sclerosis interstitial lung disease (SSc-ILD).

Searching
EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles published in any language. Search terms were reported. Reference lists of retrieved articles were searched. Experts in the field were contacted. ControlledTrials.com was searched for unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared any drug against any drug or placebo in patients with SSc-ILD were eligible for inclusion. Primary outcomes were forced vital capacity and quality of life. Secondary outcomes were total lung capacity, diffusing capacity of lung for carbon monoxide (DLCO), dyspnoea, skin thickness and adverse events. Trials had to have scleroderma lung function as a primary outcome measure. Trials of systemic sclerosis were included if a subgroup of more than 20 patients of SSc-ILD could be identified in the trials.

The included trials studied cyclophosphamide or bosentan with placebo in patients with limited or diffuse systemic sclerosis. All studies reported forced vital capacity and DLCO. Other outcomes, such as total lung capacity and adverse events, were reported.

Two reviewers performed study selection. Disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed using the five-point Jadad scale of appraised randomisation, blinding, withdrawals and dropouts. A score of 5 represented high quality and zero was low quality.

The authors did not state how many reviewers performed quality assessment.

Data extraction
Data were extracted on forced vital capacity, DLCO, total lung capacity, dyspnoea and adverse events and used the data to calculate mean differences and odds ratios, together with 95% confidence intervals (CIs). Trial authors were contacted for missing data.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
A random-effects meta-analysis was undertaken to calculate mean differences and odds ratios, together with 95% CIs. Statistical heterogeneity was assessed using the $I^2$ statistic. Subgroup analysis was performed on cyclophosphamide trials.
Results of the review

Three RCTs (366 participants) were included in the review: two trials of cyclophosphamide and one trial of bosentan. The quality of the cyclophosphamide trials was high (5 on the Jadad scale). The quality of the bosentan trial was suboptimal (2 on the Jadad scale).

There was a statistically significantly greater effect on forced vital capacity with cyclophosphamide compared with placebo (mean difference 3.30%, 95% CI 0.06 to 6.54, $I^2=0\%$; two RCTs). There was no statistically significant difference with cyclophosphamide compared with placebo in terms of DLCO or total lung capacity scores between baseline and 12 months. There was no statistically significant difference with cyclophosphamide and bosentan compared with placebo in terms of forced vital capacity or DLCO scores between baseline and 12 months. Compared with placebo, there was no statistically significant difference in the incidence of haematuria, respiratory tract infections and serious adverse events with cyclophosphamide.

Authors’ conclusions

The conservative yet significant effect of cyclophosphamide demonstrated the need for further research on patient-important outcomes such as quality of life and dyspnoea.

CRD commentary

Inclusion criteria for the review were clearly defined. Several relevant data sources were searched for articles in any language. Unpublished data were sourced. Search dates were not reported. Attempts were made to reduce reviewer error and bias during study selection; it was unclear whether similar attempts were made for quality assessment and data extraction. Limited trial details were provided, which made determining the robustness of results difficult. Quality assessment was undertaken using a standard tool, which indicated the good quality of the included cyclophosphamide trials and suboptimal quality of the bosentan trial. Trials were pooled using random-effects meta-analysis. Statistical heterogeneity was assessed.

Overall, the review had some methodological problems and more details about the characteristics of the included studies would have aided interpretation. However, the authors’ conclusions were suitably cautious and appear appropriate.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further investigation of cyclophosphamide on patient-important outcomes such as dyspnoea and quality of life was needed. Future trials may require outcomes that are more sensitive to change, such as dyspnoea.

Funding

Self funded.

Bibliographic details


PubMedID

20802426

Original Paper URL


Indexing Status

Subject indexing assigned by NLM
MeSH
Cyclophosphamide /therapeutic use; Humans; Lung Diseases, Interstitial /complications /drug therapy /physiopathology; Randomized Controlled Trials as Topic; Scleroderma, Systemic /complications /drug therapy /physiopathology; Treatment Outcome; Vital Capacity /physiology

AccessionNumber
12010007102

Date bibliographic record published
26/01/2011

Date abstract record published
29/06/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.