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### **Randomized Controlled Trial in limited Cutaneous Systemic Sclerosis: A Systematic Literature Review.**

Limited cutaneous systemic sclerosis (lcSSc) is characterized by distal skin fibrosis, vasculopathy, variable extent of inflammation and fibrosis of internal organs. Given the better prognosis associated with lcSSc compared to the diffuse subtype (dcSSc), most interventional trials have focused on the latter. In contrast with dcSSc, current treatment in lcSSc is mostly aimed at alleviating symptoms, while immunosuppressive drugs are initiated only if significant complications develop. The objective of this study is to review the literature on the efficacy of drug interventions, including immunosuppressive drugs, in patients with lcSSc for the prevention of new or progressive scleroderma complications.

The electronic databases MEDLINE, EMBASE and EBM Reviews were searched from cohort inception to August 2024, using terms related to scleroderma, pharmacological interventions and randomized controlled trials. Titles, abstracts, as well as full-texts were screened by two independent reviewers. We included randomized controlled trials (RCTs) or meta-analyses of RCTs that evaluated the efficacy of pharmacological interventions on clinical outcomes in at least 20 SSc patients, including lcSSc.

Out of a total of 759 articles identified from the initial database search, 141 studies met the inclusion criteria. Notably, 110 papers were excluded because they focused exclusively on dcSSc patients. Of the remaining studies, the majority reported minimal (77%) or few (18%) details in regard to the lcSSc population, with data limited to the number of patients, baseline characteristics and/or general comments in the discussion. Only 6 studies performed subgroup analyses specific to lcSSc. Among these, two studies looked at the effect of treatments for lung fibrosis in lcSSc. Specifically, subanalyses of the Scleroderma Lung Study and of the SENSICIS trials, which included patients with lung fibrosis, reported significant effects of the immunosuppressive drug cyclophosphamide and the anti-fibrotic drug nintedanib, respectively, in slowing lung function decline in both lcSSc and dcSSc subsets. However, the former study found that the impact of cyclophosphamide on skin fibrosis was less important in lcSSc compared to dcSSc. In addition, four studies reported on the benefit of vasodilator drugs, including bosentan and sildenafil, and other therapies, like interferon-gamma and antioxidants, on peripheral vascular disease in lcSSc.

In conclusion, despite lcSSc representing most patients with scleroderma, very few RCTs have yet been done to study the effect of immunosuppressive drugs in preventing complications in this subgroup. High-quality research is needed to answer this critical question.