INPLASY PROTOCOL

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Review Stage at time of this submission: **Data analysis.**

A systematic literature review - Calcineurin inhibitors treatment in systemic sclerosis

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Review question / Objective: **To systematically review treatment effectiveness and adverse events of calcineurin inhibitors (CNIs) such as cyclosporine A (CsA) and tacrolimus in patients with systemic sclerosis (SSc).**
Condition being studied: **Systemic sclerosis.**
Eligibility criteria: **• Publications with SSc patients treated with CNIs and available information on the outcome of CNI therapy on SSc disease manifestation will be analysed.• Article types: case reports, clinical study, clinical trial, controlled clinical trial, historical article, randomized controlled trial.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 October 2021 and was last updated on 25 October 2021 (registration number INPLASY2021100095).

INTRODUCTION

Review question / Objective: **To systematically review treatment effectiveness and adverse events of calcineurin inhibitors (CNIs) such as cyclosporine A (CsA) and tacrolimus in patients with systemic sclerosis (SSc).**

Rationale: **Systemic sclerosis (SSc) is a rare, potentially lethal autoimmune connective tissue disease, characterised by vasculopathy and fibrosis affecting the skin and a variety of internal organs. Cyclosporin A (CsA) and tacrolimus (Tac), are group of immunosuppressive agents referred to as calcineurin inhibitors (CNIs). By forming a complex with cyclophilin or FK506 binding protein (FKBP), respectively, they competitively bind to calcineurin, inhibiting translocation of the nuclear (transcription) factor of activated T-cells (NF-AT). This leads to reduced transcription of cytokines and inhibition of T cell**

activation. Effects of CsA on skin fibrosis of SSc patients are already published. However, its potential renal toxicity and reports of occurrence of scleroderma renal crisis (SRC) in patients treated with CsA complicate its use in clinical practice and performance of large prospective randomized controlled clinical trials.

Condition being studied: Systemic sclerosis.

METHODS

Search strategy: A systematic literature search on PubMed was performed using the following two terms: 1) «systemic sclerosis» OR scleroderma, 2) cyclosporine* OR tacrolimus. Using the advanced search method, one query was added to the other by the word «AND». Filters were applied for language (English, German) and article type (case reports, clinical study, clinical trial, controlled clinical trial, historical article, randomized controlled trial). All articles were included up to 31.12.2019. PRISMA guidelines were followed.

Participant or population: Systemic sclerosis patients.

Intervention: Calcineurin inhibitors.

Comparator: Without CNI, but low number of patients.

Study designs to be included: Excusion criteria: • Duplicates• Studies of SSc patients receiving CNI therapy for reasons other than systemic sclerosis (e.g. organ transplantation) • if the effect on SSc was not specified • if studies reported on other forms of scleroderma (e.g. morphea/ localized scleroderma).

Eligibility criteria: • Publications with SSc patients treated with CNIs and available information on the outcome of CNI therapy on SSc disease manifestation will be analysed.• Article types: case reports, clinical study, clinical trial, controlled clinical trial, historical article, randomized controlled trial.

Information sources: PubMed.

Main outcome(s): Effectiveness of CNI on skin and lung fibrosis • Skin fibrosis: improvement, stabile and worsening • Lung fibrosis outcome: improvement, stability and worsening.

Additional outcome(s): Side effects of CNI in SSc patients

Data management: Publications (data) from the search, applying the mentioned search criteria, will be collected in the summary table. They will be selected according to the inclusion and the exclusion criteria stated above. Selected case reports, clinical studies, clinical trials, controlled clinical trials, historical articles, randomized controlled trials will be summarized in the specific tables for analysis of the baseline characteristics, skin and lung fibrosis outcome and for the analysis of the adverse events (safety) Data will be analyzed by descriptive statistics.

Quality assessment / Risk of bias analysis: Publication bias- data were searched only in PubMed in English and German and maybe some publications were missed Heterogeneity bias- in the outcome, inclusion and classification criteria, in treatment and dosage, in the measurement of the outcomes, in the number of patients.

Strategy of data synthesis: Publications will be summarized by: • making table with summary of findings • making baseline characteristic summary of the publications (with number of patients, disease, duration, disease subtype and organ involvement summary • assessment of skin fibrosis outcome (improvement, stabilization, worsening) through all the publications under CNI treatment • assessment of the lung fibrosis outcome (improvement, stabilization or worsening) through all the publications under CNI treatment • assessment of the kidney function under CNI treatment.

Subgroup analysis: Not planned.

Sensitivity analysis: Not planned.

Language: English and German.

Country(ies) involved: Switzerland.

Keywords: Systemic sclerosis, scleroderma, calcineurin inhibitors, cyclosporine, tacrolimus.

Dissemination plans: After analysis we plan to submit the manuscript to peer -reviewed journal.

Contributions of each author:

Author 1 - Nina Hofmann - Acquisition of the data, analysis of the data, will write the manuscript.
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Conflicts of interest: Oliver Distler-O. Distler has received consultancies, honoraria, speakers bureau and/or grants/ research support from Abbvie, Acceleron, Amgen, AnaMar, Arxx, Baecon, Blade, Bayer, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Galapagos NV, Glenmark, GSK, Horizon (Curzion), Inventiva, iQvia, Italfarmaco, Kymera, Lupin, Med-scape, Mitsubishi Tanabe, MSD, Novartis, Pfizer, Roche, Roivant, Sanofi, Ser-odapharm, Topadur, Target Bioscience and UCB. The other co-authors have declared no competing interests.