# First-line treatment of pulmonary sarcoidosis with prednisone or methotrexate

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Sarcoidosis is multisystem inflammatory disease of unknown origin, characterised by the development of granulomas and often involving the lungs. The Sarcoidosis Corticosteroid (SARCORT) trial demonstrated that up to 45% of patients undergoing a 6-month course of prednisone for pulmonary sarcoidosis experienced disease relapse between 12 and 18 months after discontinuation of therapy.[1] Long-term sarcoidosis treatment is often necessary to control granulomatous inflammation, so considering side-effects and patient preferences is essential for adherence.

A recent multicentre, open-label, non-inferiority randomised trial compared methotrexate and prednisone as first-line treatments for pulmonary sarcoidosis.[2] The trial addresses a significant clinical gap due to the lack of robust evidence supporting the current guideline preference for prednisone, despite its known adverse effect profile.

The main outcome measured was the mean change in the percentage predicted forced vital capacity (FVC) at week 24 compared with baseline. The non-inferiority margin was set to 5 percentage points. Among 138 randomised patients (70 prednisone, 68 methotrexate), the unadjusted mean change in percentage predicted FVC was 6.75 percentage points (95% confidence interval (CI) 4.50 - 8.99) for prednisone and 6.11 percentage points (95% CI 3.72 - 8.50) in the methotrexate group, with the latter having a much slower effect. Methotrexate proved non-inferior to prednisone, with an adjusted between-group difference of −1.17 percentage points (95% CI −4.27 - 1.93).[2]

Secondary outcomes, including FVC in diffusing capacity for carbon monoxide, patient-reported outcomes (King's Sarcoidosis Questionnaire, Fatigue Assessment Scale, EQ-5D-5L), and biomarker levels (soluble interleukin-2 receptor), supported the primary findings, revealing comparable clinical improvements in both groups.[2]

The profiles of adverse events showed clear distinctions between the two treatment groups. The most common side-effects seen among the participants in the prednisone group included weight gain (mean 5.0 (standard deviation 5.1) kg), insomnia and increased appetite. In contrast, participants treated with methotrexate had symptoms including nausea, fatigue and elevated liver enzyme levels. Notably, the side-effects associated with methotrexate were temporary in nature and could be managed effectively through adjustments in dosage or by altering the method of administration.[2]

Strengths of the study include its randomised controlled design, addressing a clear clinical question with substantial relevance. However, limitations include small number of participants, potential biases due to crossover between groups, and the single-country context and lack of ethnic diversity, potentially limiting generalisability. Future research should investigate optimal dosing strategies and longer-term outcomes, particularly focusing on methotrexate's sustained efficacy and safety profile.[2]

This trial suggests methotrexate as a viable first-line treatment option for pulmonary sarcoidosis, highlighting a more favourable adverse event profile compared with prednisone. However, prednisone is preferred for rapid symptom relief and, perhaps, could be tapered and stopped earlier and the patient thereafter observed on methotrexate alone. These options are crucial for patient-centred clinical decision-making, emphasising patient preference and tolerability in managing chronic pulmonary sarcoidosis.

The cumulative corticosteroid exposure and adverse-effect profile of long-term use therefore need to be taken into account when considering treatment modalities. Another aspect to consider is the risk of reactivation of tuberculosis (TB) infections associated with the use of immunosuppressants, especially corticosteroids.[3] This is of particular relevance in areas with high TB prevalence, where having an alternative immunomodulating drug may be of value. More studies in the South African context would be helpful to better delineate the infectious risks and thus guide treatment.

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