EFFECTIVENESS AND TOLERABILITY OF FIRST AND SECOND-LINE DRUGS COMBINATION THERAPY IN PATIENTS WITH REFRACTORY PULMONARY SARCOIDOSIS

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Abstract

Refractory pulmonary sarcoidosis is a variant of sarcoidosis that has failed to reach a clinical remission despite the use of glucocorticosteroids (GCS) at maintenance dose (10 mg daily, prednisolone equivalent) and methotrexate (MTX), alone or in combination.

A huge experience with MTX and hydroxychloroquine (HQ), accumulated in rheumatology for treatment of rheumatoid arthritis patients, confirms an improvement of treatment outcomes. Currently, the literature presents the evidence of the effectiveness of TNF-alfa inhibitor pentoxifylline (PF) in both newly diagnosed and GCS-refractory sarcoidosis patients. These medications are different by mechanism of pharmacodynamic effect and safety profile, which encourages to expect a cumulative and mutually potentiated effect of their combibation along with uncompromised tolerability in treatment of refractory sarcoidosis patients.

Aim: to study the effectiveness and tolerability of combination therapy using the first (methylprednisolone — MP, HQ, PF) and second-line (MTX) drugs in patients with refractory pulmonary sarcoidosis.

Material and methods. 31 patients with radiological stage 2 sarcoidosis were enrolled in the study: 17 women and 14 men, age 35-60 years. 8 patients received PF+MTX, 7 — PF+MP, 16 — HQ+MTX. All patients failed to improve on previous initial MT monotherapy (GCS were contraindicated or adverse reactions on GCS occurred) or MTX+GCS combination (GCS resistance). PF was prescribed in dose 800 mg daily (200 mg every 6 h), MTX — 10 mg weekly, MP — 12 mg daily, HQ 200 mg daily. All patients were examined using Aquilion TSX-101A CT-scanner (Toshiba). Pulmonary function test was done using MasterScreen system equipped with appropriate modules («Viasys Healthcare GmbH»). For statistical analysis the data were processed using exact Fisher's test and two-tail p-value.

Results. PF+MP treatment arm showed higher effectiveness compared to PF+MTX: the rate of initial regression at first treatment period (3 months) was 85,7 % and 12,5 %, respectively ($p < 0,05$), although the final outcomes assessment demonstrated no significant difference of complete clinical remission rates between the two groups (28,6 % and 12,5 %, respectively). The rate of clinical regression at 6 months in HQ+MTX combination arm was higher than in PF+MP (28,6 %). Serious side effects, which caused discontinuation of further treatment, were observed in only 4 cases (12,9 %): gastro-intestinal bleeding in PF+MTX arm, significant dizziness in PF + MP arm, hemopoiesis inhibition (unacceptable decreased of WBC, PLT counts and severe skin allergic reaction to HQ) in HQ+MTX arm. Typical for PF, MTX and MP side effects, managed by symptom-relief medications or regimen modification, were observed in majority of patients (58 %).

Conclusion. Despite a successful use of combination therapy (HQ+MTX and PF+MTX) in a majority of refractory sarcoidosis patients, a significant rate of adverse reactions requires strictly individualized treatment with blood count and chemistry (liver and kidney function tests) control.

Key words: refractory pulmonary sarcoidosis, methylprednisolone, methotrexate, pentoxifylline, hydroxychloroquine, combination therapy, effectiveness, tolerability.

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