REFRACTORY PULMONARY SARCOIDOSIS: PERSPECTIVES FOR THE USE OF COMBINED THERAPY WITH METHOTREXATE AND HYDROXYCHLOROQUINE

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Abstract

Refractory sarcoidosis is a variant of sarcoidosis course when glucocorticosteroids (GCS) used in maintenance dose not less than 10 mg daily (prednisolone equivalent) and methotrexate (MTX), including combined use, are not effective enough to achieve clinical remission.

Aim — to evaluate the feasibility of combination use of MTX and GCS in patients with refractory pulmonary sarcoidosis.

Materials and methods. There were enrolled 7 patients with refractory sarcoidosis: 4 females, 3 males; age – from 32 to 62 years. In 1 patient the diagnosis of refractory sarcoidosis was jastified by low effectiveness of MTX monotherapy 15 mg weekly for not less than 3 months, prescribed due to contraindications for use of GCS (history of manifest mental disturbance in response to short course of GCS, prescribed for other indication). In 5 patients the refractoriness was defined by low effectiveness of MTX, prescribed due to relative resistance to GCS (initial response to GCS followed by progression of the disease during dose tapering). In 1 patient there was a combination treatment failure (methylprednisolone 12 mg daily with MTX 15 mg weekly) used for at least 3 months. In addition to clinical evaluation all patients were examined using high resolution computed tomography (CT) of lungs using multi-slice CT scanner Aquilion TSX-101A (Toshiba). CT scans were assessed using criteria described by M. Veltkamp, J. C. Grutters (2014). Lung function was assessed using flow-volume curve analysis, whole bodypletysmography, and spirometry by means of spirometry system MasterScreen («Viasys Healthcare GmbH») equipped by appropriate modules.

For patients, who failed to respond to MTX monotherapy, combination therapy MTX 10 mg weekly with hydroxychloroquine (HCQ) 200 mg daily was prescribed. For patients, failed to respond to MTX/GCS therapy, we recommended tapering GCS dose until complete discontinuation, followed by MTX/HC combination therapy in above mentioned doses. To assess treatment tolerance before the initiation of combination treatment, 2 weeks after initiation and later on, once per month a laboratory workup including total blood count and blood chemistry (WBC, PLT, creatinine, alanineaminotransferase (ALT)) was done. Additionally, before the start of combination therapy all patients underwent ophthalmological examination.

Results are presented in form of clinical series case report. Considering limited number of cases, a level of statistical significance (p) of prior treatment and combination MTX and HCQ treatment was determined using Fisher's exact test.

Combination therapy with MTX (15 mg/week) with HCQ (200 mg daily) for at least 3 months was quite effective in 5 out of 7 patients with refractory pulmonary sarcoidosis (Fisher's exact test was 0,011, $p < 0,05$)) with overall satisfactory tolerability of treatment. Serious adverse reactions resulted in discontinuation of combination therapy were observed in 2 cases. Those patients were switched on GCS therapy.

Conclusion. Despite successful use of combination therapy (MTX+HCQ) in majority of patients with refractory pulmonary sarcoidosis, high frequency of adverse reactions (almost in 1/3 of patients) requires justified personal treatment with regular monitoring of blood cellular composition and functional liver and kidney parameters.

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

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