Interferon versus Methotrexate in Intermediate Uveitis With Macular Edema: Results of a Randomized Controlled Clinical Trial

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• PURPOSE: To compare interferon (IFN) beta with methotrexate (MTX) in the treatment of intermediate uveitis with macular edema.

• DESIGN: Monocentric, prospective, randomized, controlled clinical trial.

• METHODS: SETTING: Specialized uveitis center at the University of Heidelberg. PATIENT OR STUDY POPULATION: Patients with either primary intermediate uveitis or uveitis associated with multiple sclerosis. MAIN INCLUSION CRITERIA: Visual acuity of 20/30 or worse (0.2 logarithm of the minimal angle of resolution) and macular edema of more than 250 μm (central 1-mm in optical coherence tomography; Stratus). Randomization into either IFN beta 44 μg subcutaneously 3 times weekly or 20 mg MTX subcutaneously once weekly. MAIN OUTCOME MEASURES: At 3 months, the primary outcome parameter of mean change in visual acuity was evaluated and efficacy was determined. Secondary parameters were macular edema by optical coherence tomography, inflammatory activity, and retinal sensitivity by microperimetry (MP-1; Nidek). In case of treatment failure, switching to the other treatment arm was possible.

• RESULTS: Nineteen patients were included. Ten were randomized to MTX, and 9 were randomized to IFN beta. At 3 months, visual acuity improved a mean 0.31 logarithm of the minimal angle of resolution (range, −0.02 to −0.96, 15.6 letters on the Early Treatment Diabetic Retinopathy Study chart) in the IFN beta group versus a mean 0.09 logarithm of the minimal angle of resolution (range, 0.12 to −0.38, 4.7 letters) in the MTX arm ($P = .0435$, Mann–Whitney U test). Macular thickness decreased by a mean of 206 μm (range, −41 to −416 μm) in the IFN arm, but increased by 47 μm (range, 108 to −28 μm) in the MTX group ($P < .0001$).

• CONCLUSIONS: Although the sample size is small, results of the trial support superiority of IFN beta over MTX in the treatment of macular edema in the setting of intermediate uveitis (Am J Ophthalmol 2013;156: 478–486. © 2013 by Elsevier Inc. All rights reserved.)

INTERMEDIATE UVEITIS IS CHARACTERIZED BY cellular infiltration of the vitreous. Approximately 25% of patients with uveitis have intermediate uveitis and approximately 10% of them have comorbid multiple sclerosis.[1] Intermediate uveitis therefore is, apart from optic neuritis, the typical manifestation of multiple sclerosis in the eye. Intermediate uveitis often is accompanied by macular edema, which is one of the main reasons for vision loss and which does not respond well to immunosuppressive therapy.[2]

In a pilot study, we tested interferon (IFN) beta in multiple sclerosis-associated intermediate uveitis. Retrospectively, 13 patients were included, and in 82%, macular edema resolved. Thirteen patients (8 female, 5 male) with proven multiple sclerosis and associated uveitis in 25 eyes from 5 uveitis centers were treated with IFN beta-1a. Visual acuity (VA) improved in 17 eyes (71%), 5 eyes did not change (21%), and 2 eyes deteriorated (8%) because of development of cataract. Cystoid macular edema resolved after or during IFN beta treatment in 82% of the eyes.[3] Although interferons are an accepted treatment for multiple sclerosis, it is not an approved treatment for uveitis. Several case series have shown efficacy for interferon alfa for ocular Behçet disease and other uveitis entities.[4–12] Deuter and associates published a retrospective case series of 24 patients and reported the effect of interferon alfa on macular edema.[13] So far, no randomized clinical trial for any of the IFNs has been published. We aimed to test the efficacy and safety of IFN beta in a prospective, randomized clinical trial comparing to methotrexate (MTX) as standard immunosuppressive therapy in patients with intermediate uveitis and inflammatory macular edema.

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METHODS

LOCAL INSTITUTIONAL REVIEW BOARDS (ETHIKKOMMISSION der medizinischen Fakultät Heidelberg, Heidelberg, Germany) and federal authorities (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany) approved the full protocol; patient information as well as written informed consent was obtained as required by German law (Arzneimittelgesetz) before study initiation (EudraCT number, 2004-004403-37). The clinical trial was registered at www.clinicaltrials.gov (NCT00344253). The research described adhered to the tenets of the Declaration of Helsinki, and Health Insurance Portability and Accountability Act rules were observed. This prospective, randomized, controlled clinical trial was performed at a specialized uveitis center at the University of Heidelberg. Regular monitoring of data by an external monitor took place. Randomization, biostatistical calculations, and evaluations were carried out in cooperation with a biostatistician (Koordinationszentrum Klinische Studien, Heidelberg, Germany).

Patients 18 years or older with intermediate uveitis of at least 1 year's duration with inflammatory macula edema either with or without associated multiple sclerosis could be included. Multiple sclerosis was diagnosed or excluded by magnetic resonance imaging, spinal fluid analysis, and neurologic examination performed by one of the authors (B.S.-H.). Other uveitis entities such as infectious or other autoimmune diseases, for example, sarcoidosis-associated uveitis, were excluded by history, physical examination, and chest radiograph as well as usual laboratory examinations.[14] There had to be macular edema present with central 1-mm measures of 250 mm or more (determined using Stratus OCT; Zeiss, Jena, Germany) and 20/30 or worse VA (0.2 logarithm of the minimal angle of resolution [logMAR]). All patients included in the study had to have insufficient response to oral prednisone (at least 0.5 mg/kg body weight over a period of 4 weeks) and acetazolamide. All patients also had to have received local injections in the past (at least 3 months before study entry). Main exclusion criteria were a diagnosis of depression or a history of suicide attempts, ocular triamcinolone injection within 3 months, current oral prednisone of more than 10 mg/day, or other associated diseases or infectious uveitis (for a complete list, see http://clinicaltrials.gov/ct2/show/NCT00344253?term=team+uveitis&rank=1).

The primary outcome criterion was mean change in best-corrected BCVA on Early Treatment Diabetic Retinopathy (EDTRS) charts at 3 months as compared with baseline. Standardized refraction was performed at each visit. A change of more than 2 lines (ie, 11 letters or more on Early Treatment Diabetic Retinopathy charts) was deemed significant. Secondary outcome criteria were improvement of macular edema (determined using Stratus OCT), intraocular inflammatory activity (anterior chamber cells and vitreous haze[15]), rate of ocular complications (eg, neovascularization and change in retinal sensitivity, assessed using 10-degree visual field testing with fundus perimetry [MP1, Nidek Technologies, Padova, Italy]). An increase of 2 dB was deemed significant. Quality of life was measured by 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) and the 36-item Short-Form Health Survey.[16,17] Questions about adverse events (AEs) were posed systematically, and answers were documented at each visit. Safety laboratory examinations took place at each visit. Patients were randomized to treatment with either IFN beta (Rebif; Merck-Serono) 22 μg subcutaneously 3 times weekly for 2 weeks, then 44 μg 3 weekly, or MTX 20 mg subcutaneously once weekly.

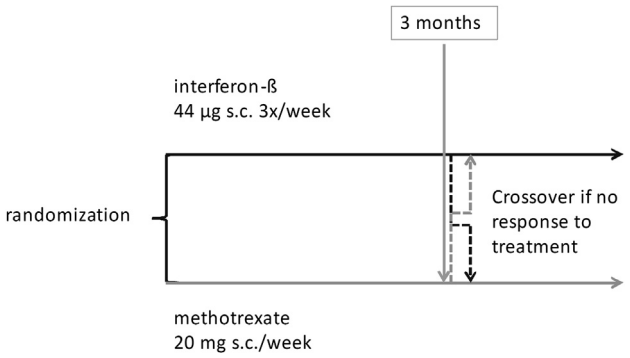

FIGURE 1. Diagram showing the study design for interferon versus methotrexate in intermediate uveitis with macular edema. Patients were randomized into either a therapy with interferon beta 44 μg subcutaneously (s.c.) 3 times weekly or 20 mg methotrexate s.c. once weekly. At the 3-month time point, efficacy was assessed, and in case of lack of improvement, switching to the other study arm was possible.

Assuming a standard deviation of VA change of 2 lines, a relevant difference of 2 lines in comparison with baseline will show a difference between groups with 80% power and a significance of $\alpha = 0.05$ when 17 patients are included in each group. On this basis of a difference of 2 lines in ETDRS visual acuity, a study sample of 34 patients was planned initially. Because during the trial the difference in VA gain between the groups was higher than expected, the protocol was recalculated in cooperation with a biostatistician, and a lower number of cases of at least 17 patients total was fixed by an amendment to the protocol.

One study eye was defined as the worse eye fulfilling inclusion and exclusion criteria. If both eyes were affected equally, the primary investigators (M.D.B. and F.M.) decided on the eye. After 3 months, outcome parameters were assessed. In case of treatment failure at the 3-month time point, switching to the other treatment arm was possible (for study design, see also Figure 1; numbers that crossed over can be seen in Figure 2, the Consolidated Standards of Reporting Trials [CONSORT] diagram). The last study visit was at 1 year after screening.

• **STATISTICAL ANALYSIS:** A linear regression model with baseline and 3 months' difference was used. For the descriptive