Identity of Interferon-β1a Product in Multiple Sclerosis Study

Wieland W. Wolf, PhD

We extend sincere congratulations to Dr. Jacobs and colleagues for the successful conclusion of their study of recombinant interferon β1a (rIFN-β1a) in patients with multiple sclerosis (MS). The impressive results showed that 6 million international units of rIFN-β1a applied once weekly via the intramuscular route was safe and effective in patients with relapsing-remitting MS.

For all its merits, we are compelled to point out an error in the article [1]. Dr. Jacobs’ designation of the study material as Avonex is incorrect and misleading. The only IFN-β1a used in this study was not as stated in the study, i.e., the substance with the trade name Avonex, produced by Biogen Inc, in Cambridge, Massachusetts, but the Chinese hamster ovary-derived rIFN-β1a developed and produced by Bioferon Biochemische Substanzen GmbH (Bioferon) in Laupheim, Germany. Today all product rights of the clinically tested product are held by Dr. Rentschler Biotechnologie GmbH (Rentschler), which is continuing the development of its proprietary rIFN-β1a product.

According to a public statement by an FDA official, the marketed Biogen product Avonex is only “comparable” with [2] but not identical to the Bioferon product used in the trial by Dr. Jacobs. The FDA obviously decided that the clinical data derived from the use of Bioferon’s product supports licensure of Biogen’s product. However, according to our knowledge, an identity or comparability between the two molecules in terms of safety and efficacy in MS has not been proved in a pivotal trial.

Rentschler Biotechnologie, Laupheim, Germany

References

Reply

Lawrence Jacobs, MD

Dr. Wolf’s statements relate primarily to a commercial and legal dispute between Biogen, Inc, and Berlex Laboratories, the American subsidiary of Schering, AG, Schering, one of Biogen’s principal competitors, sells interferon β1b (Betaseron in the United States) and owns whatever rights Dr. Wolf’s company may have had, to manufacture interferon-β. The following brief history serves to clarify the commercial/legitimate nature of Dr. Wolf’s concerns.

The Avonex used in our clinical trial was manufactured for Biogen on a contract basis at a facility owned by Bioferon, a joint venture between Biogen and Dr. Wolf’s company, Rentschler. During the course of our study, Bioferon went into receivership, although Biogen had already produced a sufficient supply of the interferon-β to complete our study. Biogen also initiated production of Avonex at its own commercial manufacturing site in Cambridge, Massachusetts. Subsequently, Biogen performed extensive tests to demonstrate the equivalence of the clinical trial material and the material being produced for market use. Based on our clinical study results published in Annals (1996;39:285-294), the equivalency tests, and additional clinical studies performed by Biogen with the material being produced for commercial use, the FDA granted a license to Biogen to manufacture and market Avonex.

Berlex relied on Dr. Wolf’s arguments and testimony in challenging the approval of Avonex. The United States District Court dismissed Berlex’s lawsuit on October 7, 1996. The Judge in the case made two statements in his ruling that are very pertinent. (1) He noted that the FDA had found Biogen’s interferon β1a manufactured at the Bioferon facility to be “biochemically and functionally equivalent” to that manufactured at Biogen’s own manufacturing facility in Cambridge, Massachusetts. (2) He also concluded that “FDA’s determination that Avonex is safe, pure and potent is amply supported by the record.”

Thus, this issue has already been resolved by both the FDA and the United States District Court.

Department of Neurology, Buffalo General Hospital, Buffalo, NY

Central Nervous System Whipple’s Disease

Wim I. M. Verhagen, MD, PhD,*
Patrick L. M. Huygen, PhD,†
and Johanna E. Dalman, MD*

We read with interest the report by Louis and colleagues [1] on guidelines for diagnostic screening and treatment in central nervous system (CNS) Whipple’s disease (WD). Recently, we reported on a similar patient [2]. CNS involvement is reported in about 10 to 43% of the WD patients (for review, see References 1 and 2), but autopsy frequently revealed brain involvement, even in the absence of neurologic symptoms [2]. Other cranial nerves than those mentioned by Louis and colleagues [1] might also be involved. Facial paresis, hearing loss, and vestibulo-ocular reflex impairment have been described [2]; the latter two might be the result of peripheral labyrinthine or cranial nerve involvement.

Cerebrospinal fluid protein and leukocyte count are indeed often elevated [1, 2]. It is also important that oligoclonal banding and an increased IgG level in the CSF are often seen [2], as is a decrease in IgG after treatment [2, 3].

The most effective antibiotic treatment regimen for WD is still under discussion. Even clinical and jejunal histological improvement after drug treatment do not guarantee an uncomplicated clinical course [2]. Fleming and co-workers [4] mentioned relapses in 31 of 88 WD patients. Oral tetracycline alone had been the initial treatment in 9 of the 30 patients who developed CNS relapse. Tetracycline does not cross the blood–brain barrier well, unless there is meningeal inflammation [5]. Keinath and associates [6] stated that ini-
tial treatment with double-dose sulfamethoxazole-trimethoprim (ST), given twice daily for 1 year, might be the best approach. Because folate deficiency is a potential complication of such treatment, supplementation is recommended [5]. In many studies, there was no improvement in CNS involvement during treatment with tetracycline alone, or in combination with other antibiotics [2]. Gaze palsy and nystagmus were most responsive to treatment, and dementia was arrested in patients with WD confined to the nervous system (for review, see Reference 2). Remarkable improvement in the organic psychosis syndrome was noted when using ST and slight improvement when using ceftriaxone [2]. The optimum duration of antibiotic treatment is unknown. In the initial stage of WD, it appears wise to prescribe ST for a period of about 1 year [3]. Several of the CNS relapse patients had been undergoing treatment for about a year or more [2], although Fleming and co-workers [3] stated that the duration of treatment did not have any substantial effect on the outcome. We prefer long-term treatment [2]; our patient has now been treated for 32 months without having a relapse.

*Department of Neurology, Canisius-Wilhelmina Hospital; and †Department of Otolaryngology, University Hospital, Nijmegen, The Netherlands

References

Treatment Guidelines in Central Nervous System Whipple’s Disease
P. J. Schneider, MD,* E. C. Reisinger, MD,† T. Berger, MD,* G. J. Krejs, MD,* and E. Aul, MD*

We read with interest the review by Louis and colleagues [1] on the diagnostic guidelines in central nervous system Whipple’s disease (WD). The authors presented guidelines for diagnostic screening and selection for biopsy by reviewing 84 cases of cerebral WD. For antibiotic treatment the authors refer to a review by Keinath and colleagues on antibiotic treatment in WD (including only a few with cerebral WD) published in 1985 [2]. The authors stated that guidelines for treatment of cerebral WD have not been proposed so far. We recently published treatment guidelines for cerebral WD, but our results were published when Louis’ paper was already submitted for publication. We reviewed the literature and contacted all authors who had reported on cerebral WD within the past 10 years [3]. The data published by Louis support our findings and treatment guidelines.

While antibiotic therapy achieves good results in patients with gastrointestinal involvement in WD, the outcome is poor with central nervous system (CNS) involvement. On the basis of empirical observations, trimethoprim and sulfamethoxazole (TMP-SMX) have been recommended for patients with WD to prevent spread to the CNS involvement [2]. In our report some of the reviewed patients responded well to TMP-SMX, but others did not. Three of 5 patients developed CNS involvement while on TMP-SMX therapy [3]. Third-generation cephalosporins were successful in preventing CNS involvement in all 4 patients in whom it was used [3–5]. Patients initially treated with penicillin and streptomycin showed a better long-term outcome than patients treated with penicillin alone [3]. Louis and colleagues reported on 1 patient with cerebral WD who relapsed after initial improvement while on TMP-SMX. When diarrhea developed, ceftriaxone (2 g IV daily) for 1 month led to improvement. After the patient was switched to doxycycline, a second relapse occurred; the patient was again successfully treated with ceftriaxone [1]. Another patient improved after ceftriaxone (2 g IV daily), and supranuclear gaze palsy and lethargy recurred after the patient was switched to TMP-SMX therapy [1]. The outcome in these 2 patients supports our findings that TMP-SMX neither prevents nor cures CNS involvement in all patients with WD. TMP-SMX reaches high intracellular concentrations, but it is bacteriostatic and therefore cannot destroy pathogens in possibly defective macrophages [6]. Third-generation cephalosporins have been shown to be effective in the treatment of cerebral WD that did not respond to TMP-SMX [1, 3]. However a low dose of ceftriaxone (2 g IV daily) might be responsible for the CNS relapses after discontinuation of ceftriaxone [1]. Based on our own long-term follow-up study and the results of Louis and colleagues, we suggest initial treatment of WD with intravenous ceftriaxone (instead of penicillin), 2 g twice daily, plus streptomycin, 1 g once daily for 2 weeks, or alternatively intravenous TMP-SMX, 960 mg twice daily for 1 to 2 weeks. Follow-up treatment for 1 year should consist of oral TMP-SMX, 960 mg twice daily, or oral cefixime, 400 mg once daily.

*Division of Neurological Rehabilitation, Department of Neurology, University of Vienna; and †Division of Infectious Diseases, Department of Medicine, Karl Franzens University, Graz, Austria

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