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BETA INTERFERONS IN CLINICALLY ISOLATED SYNDROMES

A meta-analysis

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Abstract – Beta-interferon use in definite multiple sclerosis (MS) has been proven to modify clinical and magnetic resonance imaging outcome. We review and summarize the data of published double-blind, randomized clinical trials to assess, with a meta-analysis the safety and efficacy of beta-interferon on the occurrence of relapses in patients with a first clinical event suggestive of MS. After two years of follow-up, interferon beta decreased the risk of conversion to clinically definite MS 0.51[0.39-0.65], and delayed the time to diagnosis up to 367 days. Side-effects were mild and self limited. Our findings support the efficacy of early treatment with beta-interferon in reducing conversion to clinically defined MS in patients with clinically isolated syndromes.

KEY WORDS: interferon, clinically isolated syndromes, multiple sclerosis, immunomodulating therapy.

Interferons beta nas síndromes clínicas isoladas: meta-análise

Resumo – Já é suficientemente conhecido que a utilização de interferon beta modifica o prognóstico clínico e de ressonância magnética em pacientes com esclerose múltipla (EM). Revisamos e sumarizamos os dados dos ensaios clínicos, duplo-cegos, randomizados e controlados com placebos para analisar, através de meta-análise, a segurança e eficácia dos interferons-beta sobre a ocorrência de recidivas em pacientes com um primeiro evento clínico sugestivo de EM. Após dois anos de seguimento, os interferons-beta diminuíram o risco de conversão para EM clinicamente definida 0,51[0,39-0,65] e retardaram o tempo para diagnóstico em 367 dias. Os efeitos colaterais foram leves e auto limitados. Nossos dados comprovam a eficácia e segurança do interferon-beta em reduzir a conversão para EM clinicamente definida de pacientes com síndromes clínicas isoladas.

PALAVRAS-CHAVE: interferon, síndromes clínicas isoladas, esclerose múltipla, terapia imunomoduladora.

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease characterized by relapsing-remitting episodes and progressive disability[1]. Although the diagnostic criteria of MS have been submitted to successive reviews, establishing the diagnosis continues to require evidence of two or more different lesions in the white matter of the central nervous system (CNS) and evidence of disease activity over time[2]. The use of magnetic resonance image (MRI) has made it possible to diagnose MS in patients with one clinical event of neurological disturbance and MRI findings suggestive of demyelinating lesions that are disseminated in time and space[3,4]. Over a decade of experience with beta-interferon (β-INF) therapies have shown these treatments decrease the frequency and intensity of relapses as well as the disease progression when used in the early phases of MS[5,6]. The mechanism of action of the β-IFN is thought to relate to decrease of the pathologic inflammatory process through immune modulation and decreased trafficking of T-helper type 1 (Th1) responses, which otherwise would release pro-inflammatory mediators that would contribute to oligodendrocyte and neuronal injury, and development of CNS lesions[7].

Several parameters have been described that help to predict conversion to clinically defined MS (CDMS) after an isolated clinical demyelinating event (clinically isolated syndrome, CIS). The strongest predictor is the number of T2 hyperintense lesions present at the time of CIS[8,9]. Therefore, several trials were performed to study

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the impact of β-IFN in reducing the conversion of CIS to CDMS.

In this meta-analysis we analyze if there is evidence to support the use of β-IFN in CIS.

METHOD

In a systematic review of literature, we selected all double-blind, placebo-controlled, randomized clinical trials assessing the risk of conversion to clinically definite MS. Only dichotomous data, presented as (or allowing transformation into) mean ±standard deviation, were analysed.

The searches were performed by means of MEDLINE, Cochrane Library, BIREME databases, using the words "interferon, multiple sclerosis, clinically definite multiple sclerosis, isolated clinical syndromes". In a second search, references cited in all the selected studies were checked with the purpose of identifying additional papers not found during the electronic search. The studies were selected and the quality of the randomized placebo-controlled trials evaluated by two independent reviewers using the method proposed by Jadad et al.[10]. The outcome measured was the cumulative probability of conversion from CIS into CDMS.

Data were analyzed with the statistical pack RevMan 4.0 from Cochrane Collaboration, and SPSS 9.0.

RESULTS

Three papers fulfilled the inclusion criteria[11-13]. Two of them used interferon beta-1a[11,12] and one interferon beta-1b[13]. Eligible subjects were patients between the age from 18 to 40 years in the ETOMS and BENEFIT and from 18 to 50 years in the CHAMPS. All patients were followed for at least 2 years and were allowed the use of steroid treatment at the time of the initial attack. A total of 639 patients were enrolled in the treatment groups and 520 patients in the placebo groups. The three studies were able to delay the conversion to CDMS, which ranged from 317 days in the ETOMS to 363 days in the BENEFIT study, while we could not access this result in the CHAMPS. The risk of conversion to CDMS is shown in the Figure. Side effects could not be fully evaluated in this meta-analysis. However, for side effects that were associated with the interferon therapy, the most frequent were local reactions and influenzae-like symptoms.

DISCUSSION

The results of our meta-analysis support the evidence that early beta-interferon treatment delays the time to conversion of CIS to CDMS. As we can see in previous papers, the use of beta-interferons has modified the prognosis of MS, but there are some controversies regarding their potential benefits in the primary or secondary progressive forms of disease[14,15]. In spite of not emerging as very beneficial in SPMS trials, β-IFN may nonetheless impact the neurobiology of the disease[16]. One aspect to be emphasized is related to the inflammatory process in MS, which is more active in the earlier phase of the disease[17], favoring the use of beta-interferon. Thus, although some predictors of prognosis in MS have been well identified[1], there are only few papers regarding the risk factors of CIS conversion to CDMS[18]. Brain MRI and oligoclonal IgG band (OCGB) detection are the most frequent paraclinical tests used in MS diagnosis[8,19]. According to Barkhoff et al., CIS patients with high risk of conversion to CDMS are defined

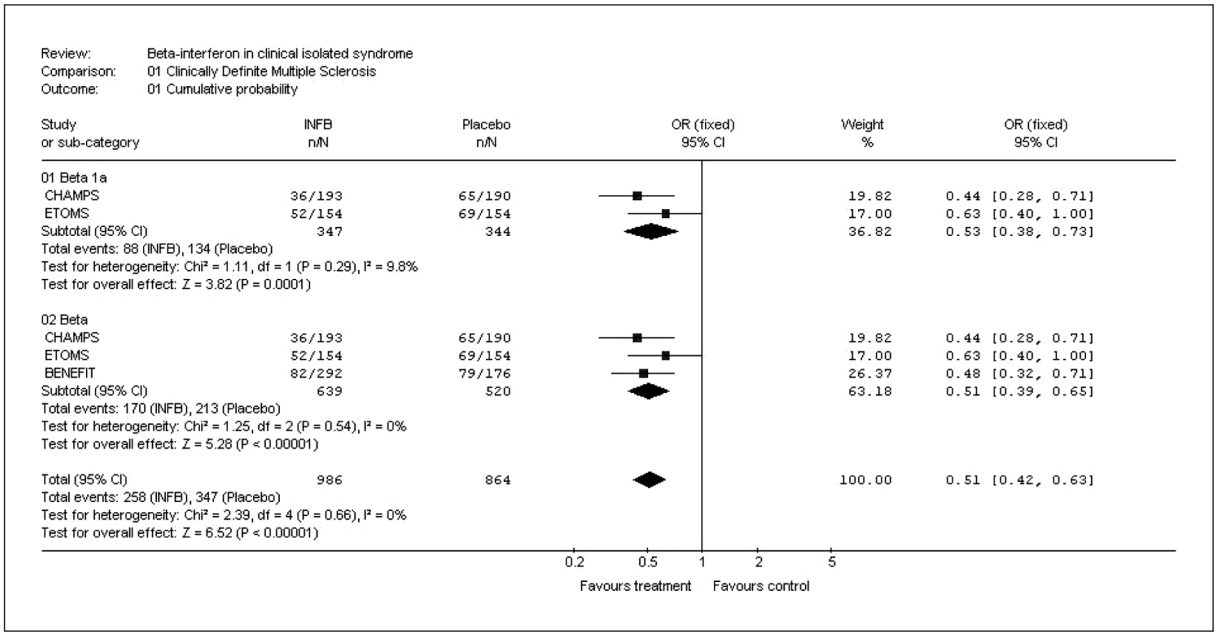

Figure. Risk of conversion from CIS to CDMS.

as those with >8 T2-weighted hyperintense lesions and at least 1 gadolinum-enhanced lesion in MRI[8]. One study reported that the presence of oligoclonal IgG bands is highly specific and sensitive for early prediction of conversion to MS[20]. In this last paper, the authors emphasized that the simultaneous use of both tests shows high sensitivity and specificity in predicting clinically isolated demyelinating syndrome conversion to clinically definite MS.

One point that needs to be clarified is the optimal dose of beta-interferon. It seems that for most patients it is necessary to use a dose greater than 22 μcg used in the ETOMS study, however, it remains important to establish the optimal dose and, if possible, define a therapeutic window to treat this group of patients. Another issue is the role of neutralizing antibodies (Nabs) that may develop in the course of treatment. The follow up of patients in the CHAMPS study showed that Nabs were present in 2% of patients[12], while in the BENEFIT study it ranged from 16.5% to 25.2%. Despite several studies pointed out that patients with Nabs have higher risk of relapse and MRI lesions, there are no studies evaluating the role of Nabs in patients with CIS and further studies will be necessary to clarify this issue.

Thus, relatively reliable tests exist, and are being used, to predict the conversion of CIS to CDMS in several regions of Europe and North America, favoring the use of beta-interferon in these patient populations. However, despite this evidence that the presence of oligoclonal IgG bands and MRI lesions disseminated in space and time are strong predictors of MS, we can not be certain the same results will be obtained in different populations.

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