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A Systematic Review on the Efficacy of Interferon Beta in Relapsing Remitting Multiple Sclerosis; Comparison of Different Formulations

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Abstract: Interferon beta (IFNβ) an immunomodulatory agent has been approved for Multiple Sclerosis (MS) patients with a relapsing course. The aim of this meta-analysis was to compare three different formulations of IFNβ including intramuscular IFNβ-1a (Avonex®), subcutaneous IFNβ-1a (Rebif®) and subcutaneous IFNβ-1b (Betaseron or Betaferon) in Relapsing Remitting MS (RRMS). Pubmed, Scopus and Cochrane Central Register of controlled trials were searched for studies comparing efficacy of different formulations of IFNβ in RRMS. Data were collected from 1966 to 2009 (up to July). Mean change in Expanded Disability Status Scale (EDSS) and number of patients with at least one relapse were the key outcomes of interest for assessment of efficacy. Six studies met our criteria and were included. Comparison of Avonex with Rebif yielded a non-significant Relative Risk (RR) of 0.85 (95% CI of 0.57-1.25, p = 0.3954). A non-significant RR of 0.91 (95% CI of 0.75-1.10, p = 0.3378) was obtained when Avonex compared with Betaferon. Comparison of Rebif with Betaferon yielded a significant RR of 0.9 (95% CI of 0.82-1, p = 0.0481). Although, not statistically significant, Rebif or Betaferon work better than Avonex whereas Betaferon was even better than Rebif in management of RRMS.

Key words: Interferon beta, relapsing remitting multiple sclerosis, Avonex, Rebif, Betaferon, Betaseron, meta-analysis, systematic review

INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune and inflammatory disease that courses with a demyelination process, which finally produces axonal degeneration and neuronal death. The international panel of neurologists has outlined four distinct clinical disease patterns in MS including relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS) and progressive relapsing (PRMS). At onset, over 80% of MS patients have a RRMS disease course which mostly will develop SPMS after 10-15 years. RRMS, which is the most common phenotype, starts with a single mono- or multi-focal demyelinating episode with partial or full recovery. The relapse stage of disease is dominated by overt inflammation and demyelination, manifesting as clinical attacks and the formation of new MRI lesions; though subclinically damage to neurons and axons is slowly amassing, gradually diminishing the ability to sustain further events without acquiring disability (Lublin and Reingold, 1996). First-line agents approved for the treatment of MS are interferon-beta (IFNβ) and glatiramer acetate. Second-line drugs for MS therapy include mitoxantrone and natalizumab. There are four different formulations of IFNβ, which are already approved for the treatment of RRMS including intramuscular IFNβ-1a (Avonex), subcutaneous IFNβ-1a (Rebif) and subcutaneous IFNβ-1b (Betaseron or Betaferon) (Vosoughi and Freedman, 2010). Recently a new branded version of IFNβ-1b, Extavia, has been approved by FDA for treatment of MS and it is the same as Betaferon. However, there is no published studies on the efficacy of this new brand. In fact, the precise mechanisms by which IFNβ exerts uncertain beneficial

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effects in MS remain unresolved. Immunomodulatory effects of IFNβ include dendritic cell activation, enhanced natural killer cell activity, stimulation of macrophage development and activation and stimulation of inducible nitric oxide synthase expression by macrophages, enhanced T-cell proliferation via a direct mechanism or via IL-15 induction by antigen-presenting cells, pro-apoptotic and anti-proliferating effects on T cells, enhanced B-cell proliferation, enhanced immunoglobulin class switching and anti-angiogenic and anti-proliferating (Meyer, 2009). There are various studies comparing the efficacy of three different formulations of IFNβ. Limmroth *et al.* (2007) showed similar effectiveness among IFNβ products. Etemadifar *et al.* (2006) demonstrated superiority of Betaseron to Rebif and Rebif to Avonex in decreasing relapse rate and Expanded Disability Status Scale (EDSS) (Etemadifar *et al.*, 2006). Panitch *et al.* (2002) also showed Rebif was more effective than Avonex. Another study by Koch-Henriksen did not prove superiority of Betaseron to Rebif (Koch-Henriksen *et al.*, 2006). Khan *et al.* (2001) reported more efficacy of Betaseron to Avonex in reducing relapse rate (Khan *et al.*, 2001). However, Patti *et al.* (2006) demonstrated that the efficacy of Betaseron and Avonex in decreasing relapse rate and EDSS is similar. Because of these conflicting results we decided to do the first meta-analysis for comparing the efficacy of three different formulations of IFNβ.

MATERIALS AND METHODS

Data sources: Pubmed, Scopus, Web of Science and Cochrane Central Register of Controlled Trials were searched for studies comparing efficacy of three different formulations of IFNβ including intramuscular IFNβ-1a (Avonex), subcutaneous IFNβ-1a (Rebif) and subcutaneous IFNβ-1b (Betaseron) in MS. Data were collected from 1966 to 2009 (up to July). The search terms were multiple sclerosis or MS and interferon beta. The language was restricted to English. The reference list from retrieved articles was also reviewed for additional applicable studies.

Study selection: Studies comparing the efficacy of three different formulations of IFNββ including intramuscular IFNβ-1a (Avonex), subcutaneous IFNβ-1a (Rebif) and subcutaneous IFNβ-1b (Betaseron) in patients with MS were considered. Mean change in Expanded Disability Status Scale (EDSS) and number of patients with at least one relapse were the key outcomes of interest for assessment of efficacy. We evaluated all published studies as well as abstracts presented at meetings. Three reviewers independently examined the title and abstract of each article to eliminate duplicates, reviews, case studies and uncontrolled studies. Studies were disqualified if they compared any formulations of IFNβ with only placebo or their outcomes did not consider relapse or EDSS. The reviewers independently extracted data on patients' characteristics, type of MS, EDSS at the beginning of study, type and dosage of IFNβ, study duration and outcome measures. Disagreements, if any, were resolved by consensus.

Assessment of trial quality: Jadad score, which evaluates studies based on their description of randomization, blinding and dropouts (withdrawals), was used to assess the methodological quality of the trials (Jadad, 1998). The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

Statistical analysis: Data from selected studies were extracted in the form of 2×2 tables. Included studies were weighted and pooled. The data were analyzed using Stats direct software version 2.7.7. Relative Risk (RR) and 95% confidence intervals (95% CI) were calculated using the Der Simonian-Laird method. The Cochran Q test was used to test heterogeneity. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L'Abbe plot as an aid to explore the heterogeneity of effect estimates. Funnel plot analysis was used as publication bias indicator.

Findings: The electronic searches yielded 3147 items; 518 from PubMed, 417 from Cochrane Central Register of Controlled Trials and 2212 from Scopus. Of those, 11 studies were scrutinized in full text. Five reports were considered ineligible while 6 studies (Limmroth *et al.*, 2007; Etemadifar *et al.*, 2006; Panitch *et al.*, 2002; Koch-Henriksen *et al.*, 2006; Khan *et al.*, 2001; Patti *et al.*, 2006) were included in the analysis (Fig. 1). Among 6 studies, 4 of them (Etemadifar *et al.*, 2006; Panitch *et al.*, 2002; Koch-Henriksen *et al.*, 2006; Khan *et al.*, 2001) were clinical trials but only one of them (Panitch *et al.*, 2002) obtained Jadad score of more than 3 (Table 1). Other two included studies (Limmroth *et al.*, 2007; Etemadifar *et al.*,

Table 1: Jadad quality score of clinical trials included in the meta-analysis

	Factors and Jadad score			
Study	Randomization	Blinding	Withdrawals and dropouts	TotalJadad score
Etemadifar *et al.* (2006)	1	0	0	1
Koch-Henriksen *et al.* (2006)	1	0	1	2
Panitch *et al.* (2002)	1	2	1	4
Khan *et al.* (2001)	0	0	0	0

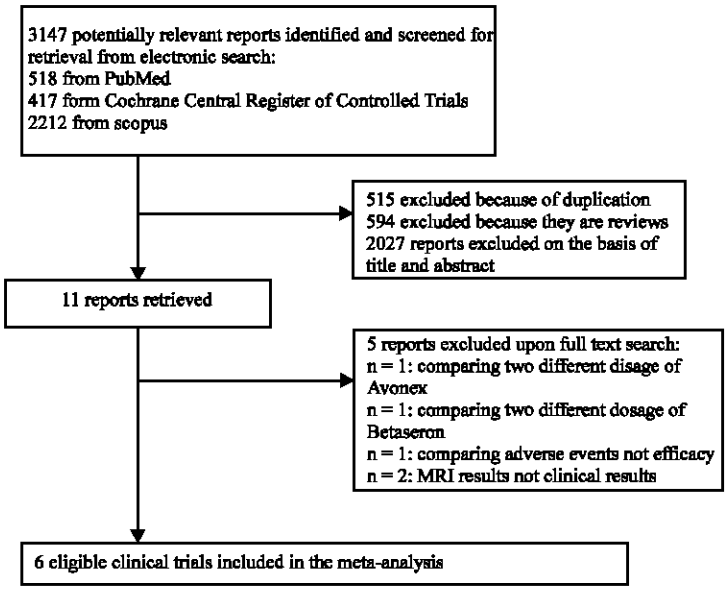

Fig. 1: Flow diagram of the study selection process

Table 2a: Characteristics of papers included in the meta-analysis for comparing Avonex and Rebif

Study	Mean age	Sex		Type of MS	EDSS		Dosage		Duration of treatment
		Female	Male		Avonex	Rebif	Avonex	Rebif	
Limmroth *et al.* (2007)	35.75	1787	720	RRMS	2.5±1.3	22 μg: 2.4±1.4 44 μg: 2.7±1.5	30 μg/week	22 or 44 μg, 3 times a week	2 years
Etemadifar *et al.* (2006)	27.75	47	13	RRMS	1.9±1.1	1.9±0.7	30 μg/week	44 μg, 3 times a week	2 years
Panitch *et al.* (2002)	37.85	506	171	RRMS	2.0±2.3	2.0±2.3	30 μg/week	44 μg, 3 times a week	48 weeks

MS: Multiple sclerosis, EDSS: Expanded disability status scale, RRMS: Relapsing remitting multiple sclerosis

Table 2b: Characteristics of papers included in the meta-analysis for comparing Avonex and Betaseron

Study	Mean age	Sex		Type of MS	EDSS		Dosage		Duration of treatment
		Female	Male		Avonex	Betaseron	Avonex	Betaseron	
Limmroth *et al.* (2007)	36.90	2077	876	RRMS	2.50±1.3	2.90±1.6	6 MIU/week	8 MIU alternate days	2 years
Etemadifar *et al.* (2006)	29.00	45	15	RRMS	1.90±1.1	1.90±0.7	6 MIU/week	8 MIU alternate days	2 years
Patti *et al.* (2006)	36.70	74	52	RRMS	2.21±0.87	2.37±1.00	6 MIU/week	8 MIU alternate days	2 years
Khan *et al.* (2001)	32.25	52	29	RRMS	2.69±0.1	2.56±0.1	6 MIU/week	8 MIU alternate days	18 months

MS: Multiple sclerosis, EDSS: Expanded disability status scale, RRMS: Relapsing remitting multiple sclerosis

Table 2c: Characteristics of papers included in the meta-analysis for comparing Rebif and Betaseron

Study	Mean age	Sex		Type of MS	EDSS		Dosage		Duration of treatment
		Female	Male		Rebif	Betaseron	Rebif	Betaseron	
Limmroth *et al.* (2007)	36.45	1744	778	RRMS	22 μg: 2.4±1.4 44 μg: 2.7±1.5	2.9±1.6	22 or 44 μg, 3 times a week	250 μg alternate days	2 years
Etemadifar *et al.* (2006)	28.65	44	16	RRMS	1.9±0.7	2.1±0.1	44 μg, 3 times a week	250 μg alternate days	2 years
Koch-Henrison *et al.* (2006)	37.50	194	107	RRMS	-	-	22 μg/week	250 μg alternate days	2 years

MS: Multiple sclerosis, EDSS: Expanded disability status Scale, RRMS: Relapsing remitting multiple sclerosis

2006; Panitch *et al.*, 2002; Koch-Henriksen *et al.*, 2006; Khan *et al.*, 2001; Patti *et al.*, 2006) were observational cohort studies. Patients' characteristics, type of MS, EDSS at the beginning of study, type and dosage of IFNβ, study duration for each trial are shown in Table 2a-c. All patients in included studies had RRMS. This meta-analysis included 5266 patients with RRMS randomized to receive either IFNβ or placebo. Of those 1940 received IM IFNβ-1a (Avonex), 1613 SC IFNβ-1a (Rebif) and 1713 IFNβ-1b (Betaseron). There was no enough data to evaluate mean change in EDSS, thus only relapse rate was compared between these three formulations (Table 3a-c).

Table 3a: Outcomes for studies comparing Avonex and Rebif

	Mean change in EDSS (No. of patients)		No. of patients with at least one relapse	
Study	Avonex	Rebif	Avonex	Rebif
Limmroth *et al.* (2007)	0.17±0.99 (790)	22 μg: 0.20±0.81 (394) 44 μg: 0.35±0.95 (134)	564/1094	22 μg: 334/555 44 μg: 121/185
Etemadifar *et al.* (2006)	-0.1 (30)	-0.3 (30)	24/30	13/30
Panitch *et al.* (2002)	-	-	161/338	130/339

Table 3b: Outcomes for studies comparing Avonex and Betaseron

	Mean change in EDSS (No. of patients)		No. of patients with at least one relapse	
Study	Avonex	Betaseron	Avonex	Betaseron
Limmroth *et al.* (2007)	0.17±0.99 (790)	0.25±0.99 (738)	564/1094	562/1034
Etemadifar *et al.* (2006)	-0.1 (30)	-0.7 (30)	24/30	17/30
Patti *et al.* (2006)	ND	ND	40/62	42/64
Khan *et al.* (2001)	+0.19 (34)	-0.25 (34)	30/34	23/34

Table 3c: Outcomes for studies comparing Rebif and Betaseron

	Mean change in EDSS (No. of patients)		No. of patients with at least one relapse	
Study	Rebif	Betaseron	Rebif	Betaseron
Limmroth *et al.* (2007)	22 μg: 0.20±0.81 (394) 44 μg: 0.35±0.95 (134)	2.9±1.6	22 μg: 334/555 44 μg: 121/185	562/1034
Etemadifar *et al.* (2006)	-0.3 (30)	-0.7 (30)	13/30	17/30
Koch-Henrison *et al.* (2006)	-	-	79/143	81/158

ND: Not determined

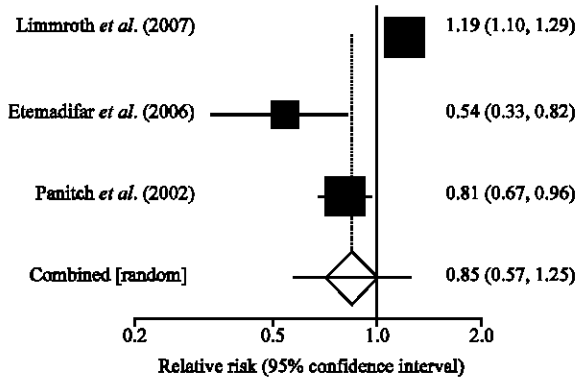

Fig. 2a: Individual and pooled relative risk for the outcome of at least one relapse in the studies considering comparing two types of IFNβ-1a (Avonex and Rebif) in RRMS

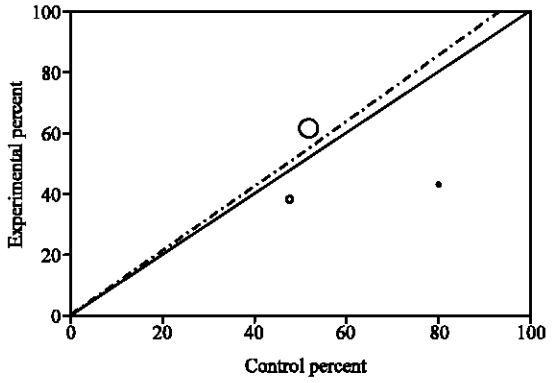

Fig. 2b: Heterogeneity indicators for the outcome of at least one relapse in the studies considering comparing two types of IFNβ-1a (Avonex and Rebif) in RRMS

Comparative efficacy of 2 types of IFNβ-1a (Avonex and Rebif) in RRMS: The summary RR for at least one relapse in three studies (Limmroth *et al.*, 2007; Etemadifar *et al.*, 2006; Panitch *et al.*, 2002) was 0.85 with a 95% CI of 0.57-1.25 and a non-significant RR (p = 0.3954, Fig. 2a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p<0.0001, Fig. 2b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect versus precision for studies comparing at least one relapse between two types of IFNβ-1a therapy in RRMS could not be calculated because of too few strata.

Comparative efficacy of types of IFNβ-1a (Avonex) and IFNβ-1b (Betaseron) in RRMS: Summary RR for at least one relapse in four studies (Limmroth *et al.*, 2007; Etemadifar *et al.*, 2006; Khan *et al.*, 2001; Patti *et al.*, 2006) was 0.91 with a 95% CI of 0.75-1.10 and a non significant RR (p= 0.3378, Fig. 3a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p = 0.0266, Fig. 3b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect versus precision for studies comparing at least one relapse among IFNβ-1a (Avonex) and IFNβ-1b

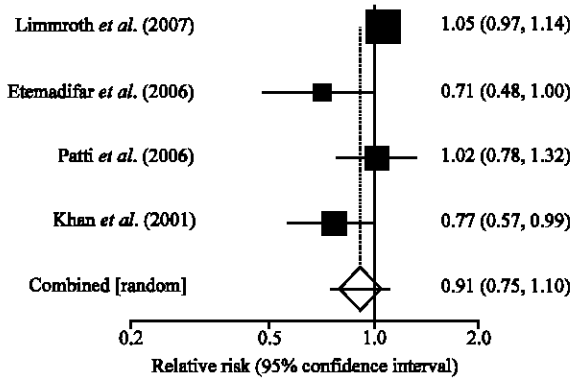

Fig. 3a: Individual and pooled relative risk for the outcome of at least one relapse in the studies considering IFNβ-1a (Avonex) and IFNβ-1b (Betaseron) therapy in RRMS

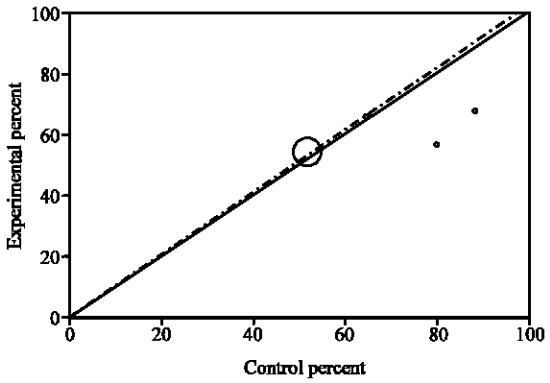

Fig. 3b: Heterogeneity indicators for the outcome of at least one relapse in the studies considering IFNβ-1a (Avonex) and IFNβ-1b (Betaseron) therapy in RRMS

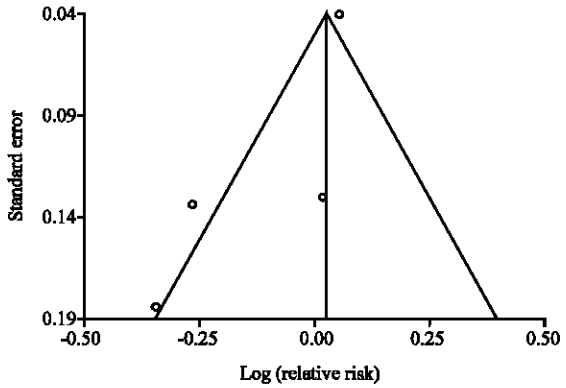

Fig. 3c: Publication bias indicators for the outcome of at least one relapse in the studies considering IFNβ-1a (Avonex) and IFNβ-1b (Betaseron) therapy in RRMS

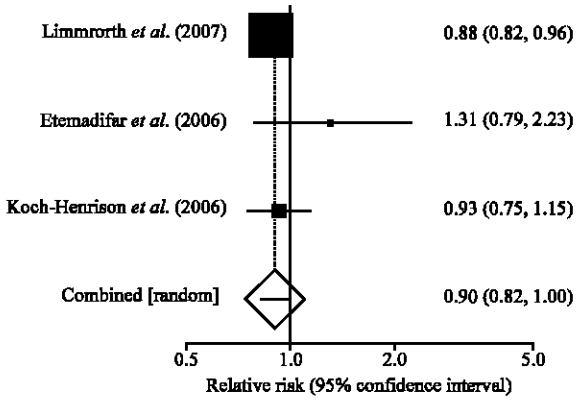

Fig. 4a: Individual and pooled relative risk for the outcome of at least one relapse in the studies considering IFNβ-1a (Rebif) and IFNβ-1b (Betaseron) therapy in RRMS

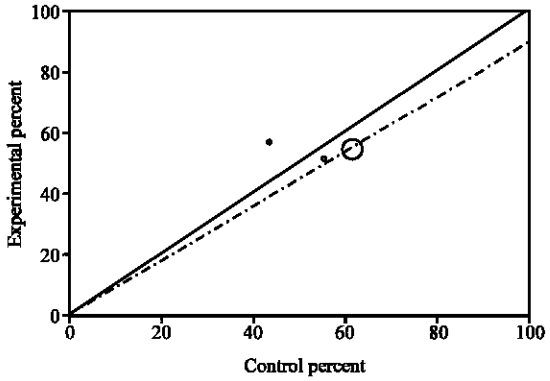

Fig. 4b: Heterogeneity indicators for the outcome of at least one relapse in the studies considering IFNβ-1a (Rebif) and IFNβ-1b (Betaseron) therapy in RRMS

(Betaseron) therapy in RRMS was -2.281311 (95% CI = -6.498821 to 1.936199, p = 0.1454) and Kendall's test on standardized effect versus variance indicated tau = -0.666667, p = 0.0833 (Fig. 3c).

Comparative efficacy of types of IFNβ-1a (Rebif®) and IFNβ-1b (Betaseron®) in RRMS: Summary RR for at least one relapse in three studies (Limmroth *et al.*, 2007; Etemadifar *et al.*, 2006; Koch-Henriksen *et al.*, 2006) was 0.9 with a 95% CI of 0.82-1 and a significant RR (p = 0.0481, Fig. 4a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.3184, Fig. 4b) and could be combined but because of few included studies, the random effects for individual and summary of RR was applied. Regression of normalized effect versus precision for studies comparing at least one relapse among IFNβ-1a

(Rebif) and IFNβ-1b (Betaseron) therapy in RRMS could not be calculated because of too few strata.

DISCUSSION

In the present study, the efficacy of three different formulations of INFβ including two types of 1a (Avanex and Rebif) and 1b (Betaseron) were compared to each other in patients with RRMS for the first time by meta-analysis technique. The results demonstrated almost equal effectiveness of these three formulations in preventing relapse (Fig. 2a, 3a, 4a).

In the previous meta-analysis, we demonstrated that administration of various types of IFNβ in different types of MS may change the effectiveness of IFNβ (unpublished data). This meta-analysis has been designed to compare effectiveness of various formulation of IFNβ in controlling relapse only in on one kind of MS (RRMS). Related to epidemiologic data, RRMS is the most common subtype of MS (Lublin and Reingold, 1996).

Among 6 studies included in this meta-analysis, 4 were clinical trials (Etemadifar *et al*., 2006; Panitch *et al*., 2002; Koch-Henriksen *et al*., 2006; Khan *et al*., 2001) and among these four clinical trials, only one has got appropriate quality score (Panitch *et al*., 2002). The other two included studies were observational cohort with mixed retrospective and prospective data (Patti *et al*., 2006) and retrospective (Limmroth *et al*., 2007) data. Notably, although there was heterogeneity in meta-analysis that cannot be ignored but this is the first meta-analysis in this subject and thus valuable to evaluate the impact of different IFNβ in MS, which is an illness with high burden of disease and mortality and morbidity affecting quality of life (Murray and Lopez, 1997; Nortvedt *et al*., 1999; Jacobson *et al*., 1997). Although, not statistically significant but overall results indicate that IFNβ-1b (Betaseron) is slightly more effective than IFNβ-1a (both formulations including Avonex and Rebif). Regarding our previous meta-analyses specially on bowel disease, we had the same experience in observing both statistically significant (Rahimi *et al*., 2007a, b; Elahi *et al*., 2008; Nikfar *et al*., 2008) and statistically non-significant results (Rahimi *et al*., 2007b, 2008a-c; Darvish-Damavandi *et al*., 2010), but clinically much remarkable. In fact, other factors like clinical significance, presence of publication bias and methodological variability can affect judgment in meta-analysis in different ways. Although, statistically significance or non significance is important in our decision making but usually studies which are non significant because of their less included studies in meta- analysis, in most of the time change to significant results when sample size and included studies are increased. So, regarding the extent of the population suffering from this rare disease and cost of therapy, conclusion should be considered cautiously to find appropriate type of administration. The Independent Comparison of Interferon (INCOMIN) (Durelli *et al*., 2002) also mentioned the superiority of IFNβ-1b comparing to IFNβ-1a in MS. On the other hand, result of this meta-analysis demonstrate more effectiveness but not statistically significant of Rebif in comparison to Avonex.

Interestingly, comparison of Betaseron, Avonex and Rebif in treatment of RRMS by another study showed the same result (Etemadifar *et al*., 2006). There are some differences between two IFNβ-1a including the way of delivery. Avonex is injected directly into the muscle on a belief that IM injection allows the medication to be released slowly into the bloodstream. Because effective amounts of Avonex stay longer in the body, then injection does not have to be repeated. Rebif and Betaseron are injected under the skin, not into the muscle on belief that they remain in the body for shorter period but they must be given three times a week or every other day. The three drugs show markedly different side effects. Obviously, patients using Rebif and Betaseron experience more injection site reactions (redness, pain or swelling) versus patients using Avonex. The possibility of conducting meta-analysis to compare all side effects of IFNβ regarding effectiveness, compliance and cost may clarify the best IFNβ choice for management of disease, as Guo *et al*. (2009) predicted reasonable cost trade-off for greater benefits of Rebif over Avonex. In this respect, the same evaluation should be considered for other new approved but expensive medications like Natalizumab which its effectiveness and safety in preventing relapse and occurrence of new gadolinium-enhancing lesions has been proved in a recent meta-analysis (Nikfar *et al*., 2010).

Conclusively, it seems that administration of appropriate type of IFNβ is the best method of utilization of IFNβ in patients with RRMS. The current data on the efficacy and safety of IFNβ is not enough and further clinical trials are needed to obtain more conclusive results.

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REFERENCES

Darvish-Damavandi, M., S. Nikfar and M. Abdollahi, 2010. A systematic review of efficacy and tolerability of mebeverine in irritable bowel syndrome. World J. Gastroenterol., 16: 547-553.

Durelli, L., E. Verdun, P. Barbero, M. Bergui and E. Versino *et al*., 2002. Independent Comparison of Interferon (INCOMIN) Trial Study Group. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet, 359: 1453-1460.

Elahi, B., S. Nikfar, S. Derakhshani, M. Vafaie and M. Abdollahi, 2008. On the benefit of probiotics in the management of pouchitis in patients underwent ileal pouch anal anastomosis: A meta-analysis of controlled clinical trials. Dig. Dis. Sci., 53: 1278-1284.

Etemadifar, M., M. Janghorbani and V. Shaygannejad, 2006. Comparison of Betaferon, Avonex and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol. Scand., 113: 283-287.

Guo, S., D. Bozkaya, A. Ward, J.A. O'Brien and K. Ishak, 2009. Treating relapsing multiple sclerosis with subcutaneous versus intramuscular interferon-beta-1a: Modelling the clinical and economic implications. Pharmacoeconomics, 27: 39-53.

Jacobson, D.L., S.J. Gange, N.R. Rose and N.M. Graham, 1997. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin. Immunol. Immunopathol., 84: 223-243.

Jadad, A.R., 1998. Randomised Controlled Trials: A Users Guide. BMJ Books, London.

Khan, O.A., A.C. Tselis, J.A. Kamholz, J.Y. Garbern, R.A. Lewis and R.P. Lisak, 2001. A prospective, open-label treatment trial to compare the effect of IFNbeta-1a (Avonex), IFNbeta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis: Results after 18 months of therapy. Mult. Scler., 7: 349-353.

Koch-Henriksen, N., P.S. Sorensen, T. Christensen, J. Frederiksen and Danish Multiple Sclerosis Group *et al*., 2006. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology, 66: 1056-1060.

Limmroth, V., R. Malessa, U.K. Zettl, J. Koehler and QUASIMS Study Group *et al*., 2007. Quality assessment in multiple sclerosis therapy (QUASIMS): A comparison of interferon beta therapies for relapsing-remitting multiple sclerosis. J. Neurol., 254: 67-77.

Lublin, F.D. and S.C. Reingold, 1996. Defining the clinical course of multiple sclerosis: Results of an international survey. National multiple sclerosis society (USA) advisory committee on clinical trials of new agents in multiple sclerosis. Neurology, 46: 907-911.

Meyer, O., 2009. Interferons and autoimmune disorders. Joint Bone Spine, 76: 464-473.

Murray, C.J. and A.D. Lopez, 1997. Alternative projections of mortality and disability by cause 1999-2020: Golden burden of disease study. Lancet, 349: 1498-1504.

Nikfar, S., R. Rahimi, F. Rahimi, S. Derakhshani and M. Abdollahi, 2008. Efficacy of probiotics in irritable bowel syndrome: a meta-analysis of randomized, controlled trials. Dis. Colon Rectum., 51: 1775-1780.

Nikfar, S., R. Rahimi, A. Rezaie and M. Abdollahi, 2010. A meta-analysis on the efficacy and tolerability of natalizumab in relapsing multiple sclerosis. Arch. Med. Sci., 6: 236-244.

Nortvedt, M.W., T. Riise, K.M. Myhr and H.I. Nyland, 1999. Quality of life in multiple sclerosis measuring the disease effects more broadly. Neurology, 53: 1098-1103.

Panitch, H., D.S. Goodin, G. Francis, P. Chang and P.K. Coyle *et al*., 2002. Evidence of interferon dose-response: European North American comparative efficacy; university of British Columbia MS/MRI research group. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology, 59: 1496-1506.

Patti, F., A. Pappalardo, C. Florio, G. Politi, T. Fiorilla, E. Reggio and A. Reggio, 2006. Effects of interferon beta-1a and -1b over time: 6-year results of an observational head-to-head study. Acta Neurol. Scand., 113: 241-247.

Rahimi, R., S. Nikfar and M. Abdollahi, 2007a. Meta-analysis technique confirms the effectiveness of anti-TNF-α in the management of active ulcerative colitis when administered in combination with corticosteroids. Med. Sci. Monit., 13: 13-18.

Rahimi, R., S. Nikfar and M. Abdollahi, 2007b. Do anti-tumor necrosis factors induce response and remission in patients with acute refractory Crohns disease? A systematic meta-analysis of controlled clinical trials. Biomed. Pharmacother., 61: 75-80.

Rahimi, R., S. Nikfar and M. Abdollahi, 2008a. Efficacy and tolerability of alosetron for the treatment of irritable bowel syndrome in women and men: A meta-analysis of eight randomized, placebo-controlled, 12 week trials. Clin. Thera., 30: 884-901.

Rahimi, R., S. Nikfar, F. Rahimi, B. Elahi, S. Derakhshani, M. Vafaie and M. Abdollahi, 2008b. A meta-analysis on the efficacy of probiotics for maintenance of remission and prevention of clinical and endoscopic relapse in Crohns disease. Dig. Dis. Sci., 53: 2524-2531.

Rahimi, R., S. Nikfar and M. Abdollahi, 2008c. Selective serotonin reuptake inhibitors for the managementof irritable bowel syndrome: A meta- analysis of randomized controlled trials. Arch. Med. Sci., 4: 71-76.

Vosoughi, R. and M.S. Freedman, 2010. Therapy of MS. Clin. Neurol. Neurosurg., 112: 365-385.