

## Safety and effectiveness assessment of intravenous immunoglobulin in the treatment of relapsing-remitting multiple sclerosis: A meta-analysis

Alireza Olyaeemanesh<sup>1</sup>, Mahbobeh Rahmani\*<sup>2</sup>, Reza Goudarzi<sup>3</sup>  
Abulghasem Rahimdel<sup>4</sup>

Received: 14 September 2015

Accepted: 14 November 2015

Published: 23 February 2016

### Abstract

**Background:** Intravenous immunoglobulin (IVIG) is an established treatment of immune mediated demyelinating neuropathy including Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Recent trials suggest its efficacy in treating relapsing-remitting multiple sclerosis. IVIG exerts a number of effects, which may be beneficial in treating multiple sclerosis (MS): Reduction of inflammation, inhibition of macrophages, and promotion of remyelination. The aim of this study was to provide an overall assessment of the existing trials of safety and effectiveness of IVIG in relapsing-remitting MS compared to other drugs currently available for the treatment of disease activity in MS.

**Methods:** A systematic search strategy was applied to MEDLINE (PubMed and Ovid Medline (1990- Nov 2014)), Cochrane Library 2014, and Trip Database 2014, CRD. The reference lists from the identified trials, MS clinical handbooks and guidelines for the use of IVIG were studied. This article was conducted without language restrictions. Randomized controlled trials of IVIG in MS were selected. Sixteen double-blinded trials were randomly selected. Ten trials were excluded and we performed a meta-analysis on the six trials (537 participants) of IVIG in comparison to placebo. The methodological quality of the trials was assessed using Jadad checklist.

**Results:** The meta-analysis showed a significant beneficial effect on proportion of relapse-free patients (OR: 1.693; 95% CI-1.205-2.380), on the proportion of patients who improved (OR:2.977; 95% CI 1.769-5.010; p=0.0001) and deteriorated (OR:0.522; 95% CI0.330-0.827; p=0.006) between placebo and IVIG-treated patients. In addition, there was a reduction in the annual relapse rate in the IVIG group compared to placebo, which was statistically significant (SMD=-0.218; 95% CI-0.412 to -0.024; p=0.028). The results of the meta-analysis did not show significant differences between Expanded Disability Status Scale (EDSS) changes from baseline (SMD,-0.025; 95% CI,-0.211 to 0.161; p=0.860).

**Conclusion:** IVIG can be considered as an alternative therapeutic option, second-line therapy or adjuvant therapy, considering its beneficial effects (high tolerance, need to be injected with longer intervals, etc.) for treating relapsing-remitting MS patients.

**Keywords:** Multiple sclerosis, Relapsing-remitting Multiple Sclerosis, Intravenous Immunoglobulin, Meta-analysis.

**Cite this article as:** Olyaeemanesh A, Rahmani M, Goudarzi R, Rahimdel A. Safety and effectiveness assessment of intravenous immunoglobulin in the treatment of relapsing-remitting multiple sclerosis: A meta-analysis. *Med J Islam Repub Iran* 2016 (23 February). Vol. 30:336.

### Introduction

Multiple sclerosis (MS) is a chronic and

debilitating, progressive inflammatory and degenerative disease of the central nervous

<sup>1</sup>. Assistant Professor, National Institute for Health Research, Tehran University of Medical Sciences, Tehran, Iran. [arolyaee@gmail.com](mailto:arolyaee@gmail.com)

<sup>2</sup>. (**Corresponding author**) MSc Student in Health Technology Assessment at Health School Department of Yazd University of Medical Sciences, Iran. [Rahmani.mahbobeh@yahoo.com](mailto:Rahmani.mahbobeh@yahoo.com)

<sup>3</sup>. Assistant Professor, PhD in Health Economics, Kerman University of Medical Sciences, Kerman, Iran. [rgoudarzi@yahoo.com](mailto:rgoudarzi@yahoo.com)

<sup>4</sup>. MD, Assistant Professor of Neurology, Shahid Sadooghi Hospital, Yazd University of Medical Science, Yazd, Iran.

[Rahimdel30142@yahoo.com](mailto:Rahimdel30142@yahoo.com)

system (CNS) which affects the brain and spinal cord, in which infiltrating lymphocytes, predominantly T-cells and macrophages lead to damage of the myelin sheath (1-5).

The cause and pathogenesis of MS remain to be unknown (6,7), although it is thought to be autoimmune in nature. A variety of genetic, immunological, and environmental factors have been implicated in triggering the onset and progression of the disease, which is characterized by immune-mediated tissue injury directed against CNS myelin antigens(8).

MS is one of the most common contributors to neurological disability among young and middle-aged adults. The peak age of the onset is approximately 30 years, and the disease occurs in twice as many women as men (2,8).

The estimated number of people with MS has increased from 2.1 million in 2008 to 2.3 million in 2013. The MS prevalence rate in Tehran, capital city of Iran, is estimated to be 51.9 per 100,000 population in 2010; and in Isfahan, one of the large cities of Iran, is estimated to be 43.8 per 100,000 population in 2007 (10).

Intravenous immunoglobulin (IVIg) is a blood product, which is prepared from pools of plasma of at least three thousand and up to a hundred thousand healthy blood donors. Initially used at a “replacement dose” for patients who have antibody deficiencies, IVIg is now increasingly being used for the treatment of autoimmune and systemic inflammatory diseases as an immunomodulatory agent (11).

IVIg exerts may have a number of positive effects on multiple sclerosis (MS): Reduction of inflammation, inhibition of macrophages and promotion of remyelination, and increased number of activated pro-inflammatory T-cells (Th1); a reduced number of regulatory T-cells (Th2), and an increased number of B-cells produce IVIg antibodies against myelin proteins (12,13).

A number of trails have indicated effects on MS (Sorensen et al., 1998; Lewanska et al., 2002,...). It is, therefore, important to

establish the efficacy of intravenous immunoglobulin treatment to ensure that people with MS are not exposed to a potentially harmful drug without good evidence of efficacy, and that resources are not unnecessarily devoted to an unproven therapy.

### *Objective*

We conducted a meta-analysis of the trials in order to provide an overall evaluation of the safety and effectiveness of IVIG in relapsing–remitting MS compared to other drugs currently available for the treatment of disease activity in MS.

### **Methods**

#### *Criteria for Considering the Studies for Meta-analysis*

*Types of Studies:* We searched randomized controlled trials, which assessed the safety, efficacy and effectiveness of intravenous immunoglobulins for MS.

*Types of Participants:* Trial participants were diagnosed with definite MS (according to the McDonald diagnostic criteria)(4). Participants may have had relapsing- remitting MS.

*Types of Interventions:* We limited this meta-analysis to trials of intravenous immunoglobulins for relapsing- remitting MS.

#### *Types of Outcome Measures:*

Progression of the disease was evaluated using the Expanded Disability Status Scale (EDSS).

- 1) The proportion of patients remaining relapse- free at the end of the treatment period
- 2) Annualized relapse rate, relapse rate, expressed as the number of relapses per annum in each treatment arm
- 3) The proportion of patients improved in EDSS
- 4) The proportion of patients deteriorated in EDSS.

#### *Search Methods to Identify the Studies*

*Electronic Searches:* A systematic search was conducted (From 1990 to 2014, which was updated in 2015/6) to identify all relevant published and unpublished random-

ized controlled trials (Fig. 5).

For this review, the following databases were searched: MEDLINE (PubMed and Ovid Medline), Cochrane library, CRD, Trip Database, FDA, Google scholar, and NAHTA (Table 7).

*Searching other Resources:* To find more resources and studies that may have not been found in the electronic search, we searched the reference lists of the identified trials. Moreover, the clinical handbooks of Multiple sclerosis and guidelines for the use of intravenous immunoglobulin were searched.

#### *Data Collection and Analysis*

From 748 sources of the initial search, we identified 16 trials. To be included in the review, a trial had to meet the following criteria: (1) Allocation concealment had to be adequate (Unclear allocation concealment was accepted if every other methodological factor was of the best possible standard); (2) Treated and non-treated groups had adequate baseline comparability; (3) Patients and the treating physicians were blind to the treatment allocation; (4) All analyses had to be intended- to- treat analyses.

We excluded 10 trials: Five trials differed in the type of drug used in the control group, and three trials did not measure the desired outcomes, one trial was conducted only on pregnant women, and one trial did not clearly specify the target group. We performed a quality evaluation of evidence for trails in this review by Cochrane Reviewer's Handbook, which discusses the methodological quality under the following headings: (1) Selection bias; (2) Performance bias; (3) Attrition bias; and (4) Detection bias. In addition, we performed a quality evaluation of evidence for trials included in this review by Jadad checklist.

For the quantitative outcomes of EDSS score and annual relapse rate, the combination of results was based on the use of the effect size (SMD),  $\Delta/\sigma$ , where  $\Delta$  is the difference in the mean results for IVIG and placebo and  $\sigma$  is the common (population)

standard deviation (SD). These quantities are estimated for each study by the difference in the mean scores and the pooled estimated SD,  $\sigma$ . Note that the ratio of these estimates is biased and a bias adjustment as described by Begg's test was considered in the analysis. These results were pooled together using weights based on the sample size for each trial and study preparation, using basic techniques described by Begg's test. However, before pooling all of the results, a chi-square test for homogeneity was conducted. If this test was significant, an attempt was made to eliminate the result(s) that may have caused the heterogeneity, and the remaining findings were then combined.

For the qualitative outcomes of relapse-free, improved and deterioration rates, effect size is simply the difference in the proportions between the active and placebo groups. These values are weighted based on the difference in proportions. A test of homogeneity of results was also used following a simple modification of the chi-square procedure mentioned above. In addition, odds ratios were computed for each study and overall, 95% confidence interval was assumed. These calculations were implemented using Stata / SE 11.

## **Results**

### *Patients and Study Design*

We identified six published studies, which met our inclusion criteria (Fazekas et al., 1997; Achiron et al., 1998; Strasser et al., 2000; Lewanska et al., 2002; Kocer et al., 2004; Fazekas et al., 2008). Also, we considered a meta-analysis by Sorensen et al., (2002) which included four trials, and a meta-analysis by Gray et al., (2009) which included 10 randomized trials of intravenous immunoglobulins for the treatment of MS (4,14). Thus, we performed a more comprehensive meta-analysis.

In the six included trials, 537 patients were enrolled. Patient characteristics, IVIG dosage, and trial duration, etc. are presented in Table 1. The dosage of IVIG varied considerably from 0.15 to 0.2g/kg body-

Table 1. Design, Patient Characteristics, IVIG Doses and Trial Duration

RCT Study	Design	N	MS duration (years)	Mean age (years)	EDSS	Trial duration	Dose (months)
Fazekas et al. (1997)	PG	IVIG:75 Placebo:73	IVIG:6.8 Placebo:7.3	IVIG:36.7±2.4 Placebo:37.2±2.3	IVIG:3.3 Placebo:3.3	24	0.15–0.2g/kg
Achiron et al. (1998)	PG	IVIG:20 Placebo:20	IVIG:4.1 Placebo:3.95	IVIG:35.4±2.1 Placebo:33.8±2.4	IVIG:2.9 Placebo:2.82	24	0.4g/kg
Strasser et al. (2000)	PG	IVIG:75 Placebo:75	IVIG:6.8±4.6 Placebo:7.3±5.7	IVIG:36.7±10.4 Placebo:37.3±9.8	IVIG:3.33±1.39 Placebo:3.37±1.67	24	0.2g/kg
Lewanska et al. (2002)	PG	IVIG:17 IVIG:15 Placebo:17	IVIG:10.7±7.57 IVIG:7.2±5.48 Placebo:7.5±4.7	IVIG:38±6.96 IVIG:31.1±6.08 Placebo:41.8±6.98	IVIG:3.0±1.35 IVIG:3.0±2.08 Placebo:2.97±1.58	12	0.2g/kg 0.4g/kg
Kocer et al. (2004)	PG	IVIG:12 Placebo:12	IVIG:2-14 Placebo:2-14	IVIG:22-56 Placebo:22-39	IVIG:2.46±1.82 Placebo:1.96±1.60	9	0.4g/kg
Fazekas et al. (2008)	PG	IVIG:44 IVIG:42 Placebo:41	IVIG:2.8±1.9 IVIG:2.7±2.1 Placebo:2.3±1.5	IVIG:31.9±7.5 IVIG:34.4±7.9 Placebo:33.0±8.7	IVIG:1.8±0.9 IVIG:2.1±1.1 Placebo:2.1±1.2	12	0.2g/kg 0.4g/kg

PG= parallel groups; IVIG= intravenous immunoglobulin; EDSS= Expanded Disability Status Scale; MS= multiple sclerosis

weight monthly in the study by Fazekas et al. (1997) to 0.4 g/kg bodyweight monthly in the study by Fazekas et al. (2008) and Lewanska et al. (2002). All the six trials had used a parallel-group design.

#### Description of Studies

In the study by Fazekas et al. (1997), the primary outcome measures were the change in EDSS and the proportion of patients who improved, remained stable or worsened in disability, defined as an increase or decrease of at least 1.0 point in the EDSS score by the end of the study. Secondary outcome measures included the annual relapse rate and the proportion of relapse-free patients (15).

In the Achiron et al. (1998) study, they used the annual relapse rate, proportion of relapse-free patients and median time to first relapse as the primary study endpoints. The changes in neurological disability measured on the EDSS scale, mean annual severity of exacerbations and mean MRI lesion score were used as the secondary outcome endpoint. All outcomes were measured at baseline and after 1 and 2 years (16).

In the study of Strasser et al. (2000), the change in EDSS and the proportion of patients who improved, remained stable or worsened in disability were the primary

outcomes measured. The secondary endpoints were the number of confirmed relapses, the annual relapse rate, time to first relapse during the study period and proportion of relapse-free patients (17).

In the study of Lewanska et al. (2002), two groups were treated with two doses of IVIG 0.4 g/kg and 0.2 g/kg, and one group with placebo. The annual relapse rate and a comparison between pre-study relapse rate and relapse rate during the study period were considered as primary outcomes. The secondary clinical outcomes included the proportion of relapse-free patients, mean changes in the EDSS, and the proportion of patients with worsening, mean changes in the NRSS (Neurological Rating Scale Score), change of mean lesion volume on T2-weighted, the mean number of new lesions on T2-weighted and the mean number of gadolinium-enhancing lesions on T1-weighted scans every 3 months (18).

In the study of Kocer et al. (2004), endpoints measured included the proportion of patients who improved, remained stable or deteriorated of clinical disability, changes in the EDSS, the number and volume of lesions on MRI in all sites (19).

In the Fazekas et al. (2008) study, they used the proportion of relapse-free patients and annualized relapse rate as the primary efficacy endpoint. Secondary outcome

Table 2. EDSS in Baseline (Mean ± SD)

Study	SMD	[95% Conf. Interval]		% Weight
Achiron (1998)	0.199	-0.422	0.821	8.95
Strasser (2000)	-0.026	-0.348	0.296	33.30
Lewanska (2002) 0.4g/kg	0.016	-0.678	0.711	7.17
Lewanska (2002) 0.2g/kg	0.041	-0.632	0.713	7.65
Koçer (2004)	0.292	-0.513	1.097	5.34
Fazekas (2008) 0.4g/kg	0.000	-0.430	0.430	18.68
Fazekas (2008) 0.2g/kg	-0.284	-0.712	0.143	18.91
I-V pooled SMD	-0.025	-0.211	0.161	p=0.860

SMD= Standardized mean difference; IVIG=Intravenous immunoglobulin; EDSS= Expanded Disability Status Scale

Table 3. Change in EDSS (Mean ± SD)

Study	SMD	[95% Conf. Interval]		% Weight
Fazekas (1997)	0.073	-0.250	0.395	53.37
Achiron (1998)	-0.209	-0.831	0.412	14.35
Lewanska (2002) 0.4g/kg	-0.168	-0.842	0.505	12.22
Lewanska (2002) 0.2g/kg	-0.172	-0.868	0.523	11.46
Koçer (2004)	-0.240	-1.044	0.563	8.59
I-V pooled SMD	-0.052	-0.288	0.183	P=0.633

SMD= Standardized mean difference; IVIG=Intravenous immunoglobulin; EDSS= Expanded Disability Status Scale

measures included change in burden of disease volume, change in brain parenchymal fraction, ratio and cumulative number of unique newly active lesions (20).

*Progression of Disease (Disability)*

The five trials enrolling patients had not showed significant differences between EDSS from baseline (SMD,-0.025; 95% CI, -0.211 to 0.161; p= 0.860; Table 2, Fig. 1). Thus, the trials were comparable in this respect. There were no evidence of heterogeneity among the studies (p= 0.860,  $\chi^2=2.57$ ,  $I^2=0.0\%$ ).

Four trials showed a trend towards a reduction in EDSS score during the IVIG treatment when compared to the baseline.

The decrease in EDSS score was defined as an effect size (SMD) -0.052 with a 95% confidence interval from -0.288 to 0.183 (p= 0.663), and the difference was not statistically significant (Table 3, Fig. 2). There was evidence of heterogeneity among the studies although it was not statistically significant.

Four studies reported the proportion of patients who improved, and five studies provided an analysis of the proportion of patients who deteriorated. Fazekas et al. (1997) and Achiron et al. (1998) defined improvement and deterioration by a change of one point or more in the EDSS at the end of the study; Strasser et al. (2000) changed at least 1.0 EDSS grade during the trial and Kocer et al. (2004) did not determine the definition improvement. The meta-analysis revealed a significant difference in the proportion of patients who improved on IVIG compared to placebo treatment. A test for heterogeneity across the studies was significant for this variable (p= 0.0001). Also, the meta-analysis revealed a strong trend in the proportion that deteriorated between placebo and IVIG-treated patients (Table 4). However, there was a large degree of heterogeneity in these results (p=0.009).

Proportion of Relapse-free Patients: Four trails reported the proportion of relapse-free patients (Fazekas et al. 1997; Achiron et al.

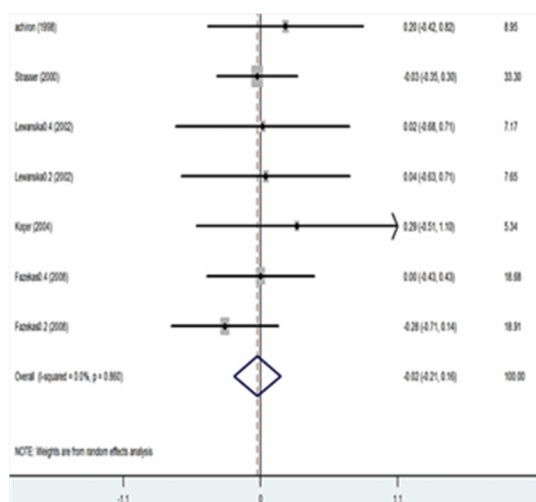


Fig. 1. EDSS in Baseline (Mean ± SD)

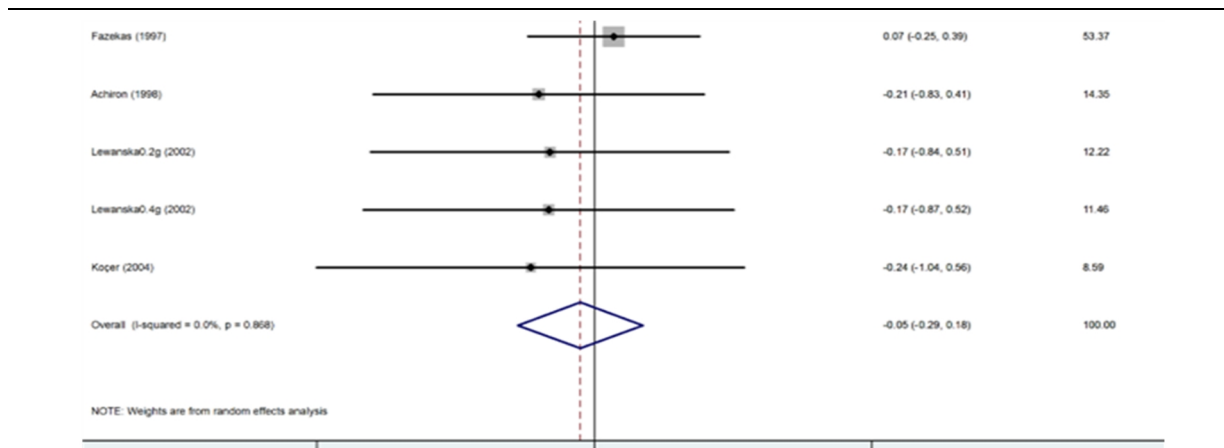


Fig. 2. Change in EDSS (Mean ± SD)

1998; Lewanska et al. 2000; Fazekas et al. 2008). This proportion was statistically higher for those treated with IVIg with a pooled odds Ratio (OR) of 1.693 with a 95% confidence interval of 1.205- 2.380. The difference was statistically significant with a p-value of 0.002. In addition, no evidence of heterogeneity was found among the studies (p= 0.007), indicating that the results were consistent over the trials. The odds-ratios for being relapse-free with 95% confidence intervals for each study and the

overview results are given in Table 5, Fig. 3.

**Relapse Rate:** Four studies reported the annual relapse rate in patients at baseline, which the meta-analysis did not show any significant difference between IVIG and placebo groups (SMD= 0.136; 95%CI, -0.090 to 0.361; p= 0.238) (Fig. 4).

Table 6 demonstrates the changes in the annual relapse rate in four trails (Fazekas et al. 1997; Achiron et al. 1998; Lewanska et al. 2000; Fazekas et al. 2008) after treat-

Table 4. Proportion of Patients with Improvement or Deterioration in EDSS

Study	IVIG	Placebo	OR (95%CI)	% Weight
Improved				
Fazekas (1997)	0.31	0.14	2.787 (1.217-6.379)	42.20
Achiron (1998)	0.24	0.11	3.000 (0.507-17.740)	9.43
Strasser (2000)	0.34	0.14	3.343 (1.473-5.585)	46.65
Koçer (2004)	0.25	0.083	3.667 (0.323-41.590)	4.72
M-H pooled OR			3.080 (1.769-5.282)	
Deteriorated				
Fazekas et al. (1997)	0.16	0.23	0.627 (0.276-1.427)	30.31
Achiron et al. (1998)	0.14	0.17	0.706 (0.136-3.658)	7.12
Strasser et al.(2000)	0.18	0.23	0.756 (0.333-0.857)	29.35
Lewanska et al. (2002) 0.2g/kg	0.24	0.47	0.346 (0.080-1.507)	12.81
Lewanska et al. (2002) 0.4g/kg	0.07	0.47	0.080 (0.009-0.756)	14.66
Kocer (2004)	0.08	0.25	0.273 (0.024-3.093)	5.76
M-H pooledOR			0.534 (0.333-0.857)	

IVIG= Intravenous immunoglobulin; EDSS=Expanded Disability Status Scale; OR= odds ratio

Table 5. Proportion of Relapse-free Patients

Study	IVIG		Placebo		OR (95%CI)	% Weight
	Events	NonEvents	Events	NonEvents		
Fazekas (1997)	40	35	26	47	2.066 (1.068-3.996)	24.01
Achiron (1998)	6	14	1	19	8.143 (0.878-75.479)	1.37
Strasser (2000)	40	35	26	49	2.066 (1.068-3.996)	24.01
Lewanska (2002) 0.2g/kg	8	9	2	15	6.667 (1.151-38.598)	2.07
Lewanska (2002) 0.4g/kg	8	7	2	15	8.571 (1.430-51.362)	1.71
Fazekas (2008) 0.2g/kg	25	19	28	31	0.611 (0.251-1.485)	24.44
Fazekas (2008) 0.4g/kg	25	25	28	31	0.611 (0.251-1.485)	22.40
D+L pooled OR	152	136	113	207	1.690 (1.202-2.375)	

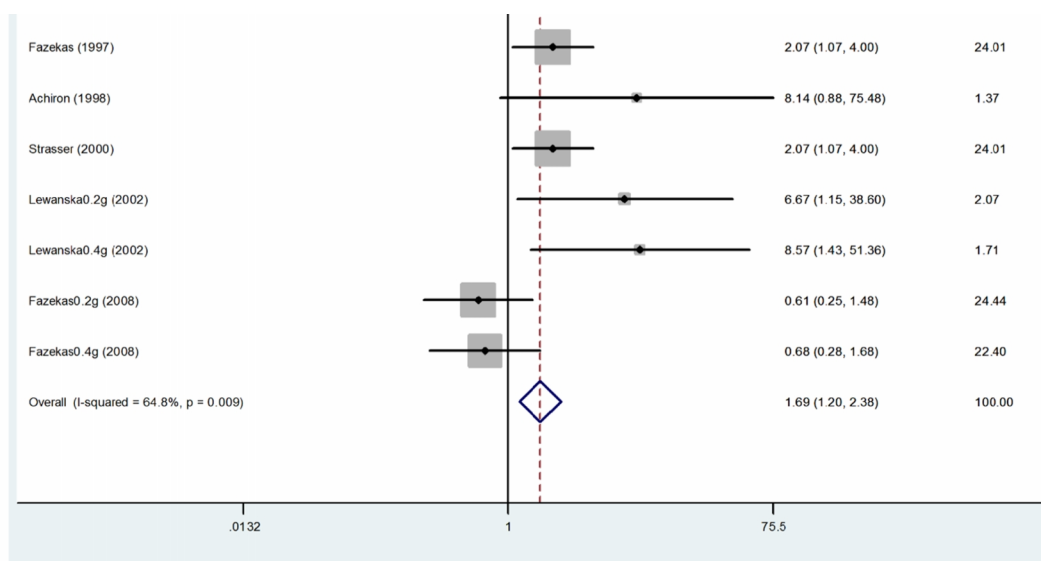


Fig. 3. Proportion of Relapse-Free Patients

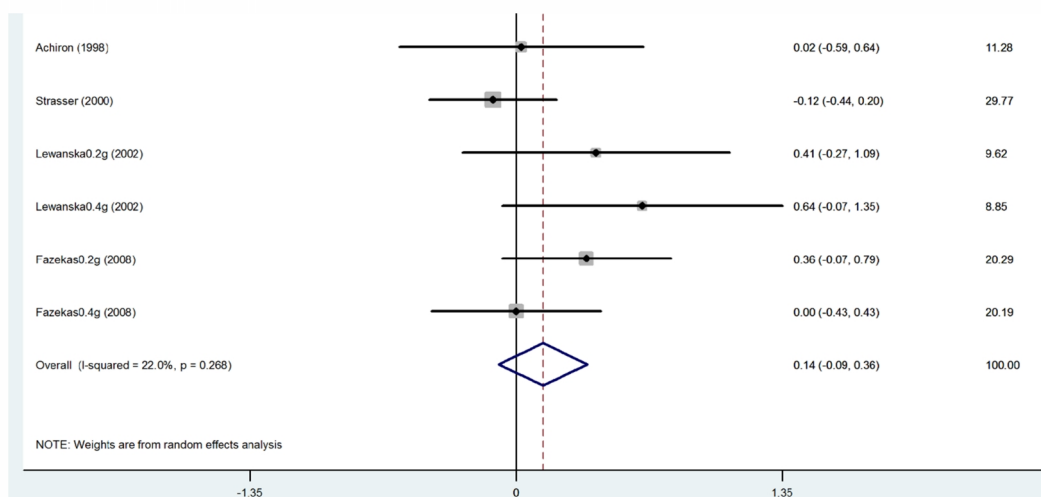


Fig. 4. Annual Relapse Rate at Baseline

ment with IVIG, or placebo. The pooled results revealed significant differences in the number of relapses experienced on an annual basis in favor of IVIG (SMD= -0.218; 95% CI -0.412 to -0.024; p=0.028) (Fig. 5).

### Discussion

The present research confirms that intra-

venous immunoglobulin has a beneficial effect on the annual relapse rate, proportion of relapse-free patients, on the proportion of patients deteriorated and improved, and on clinical disability in patients with relapsing-remitting MS. Despite the difference between the included trials (design, duration, dose and endpoint), the results seemed

Table 6. Annual Relapse Rate

Study	SMD	[95% Conf. Interval]	% Weight
Fazekas (1997)	-0.482	-0.809 -0.155	35.23
Achiron (1998)	-1.215	-1.892 -0.538	8.21
Lewanska (2002) 0.2g/kg	-0.347	-1.025 0.330	8.20
Lewanska (2002) 0.4g	-0.425	-1.128 0.277	7.63
Fazekas (2008) 0.2g	0.315	-0.113 0.744	20.54
Fazekas (2008) 0.4g	0.235	-0.197 0.667	20.19
I-V pooled SMD	-0.218	-0.412 -0.024	p=0.001

SMD=Standardized mean difference; IVIG=Intravenous immunoglobulin

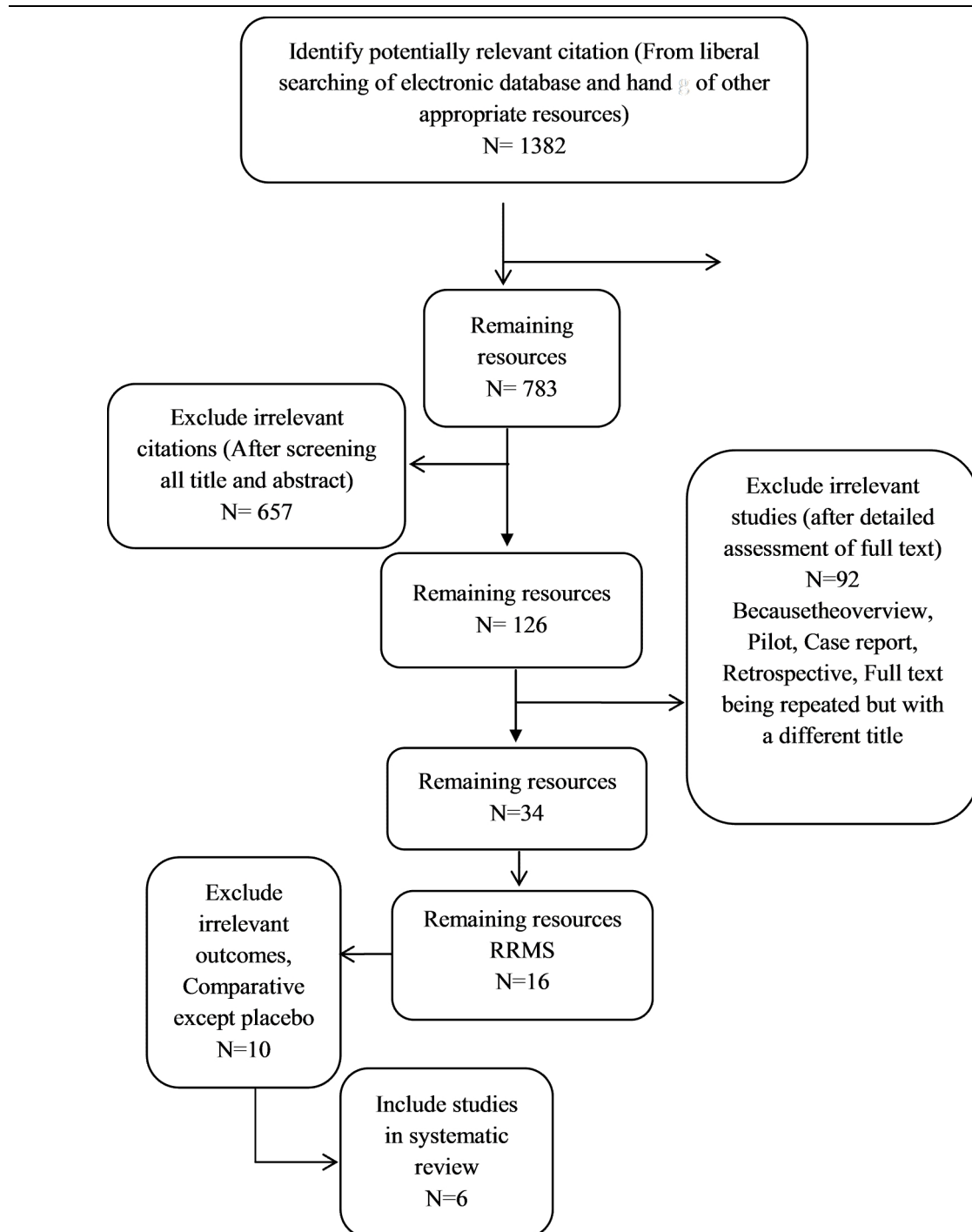


Fig. 5. The Process of Identifying Related Articles

remarkably consistent in the meta-analysis.

The results of the present overview revealed that IVIg does not have an effect on the EDSS scores compared to placebo; and although it was decreased, it was not statistically significant. The difference in the annual relapse rate between IVIG and placebo-treated patients was a result of a strong

reduction in the annual relapse rate on therapy compared to baseline in the IVIG group. The proportion of relapse-free patients increased in the IVIg compared to placebo treatment. The increase in the proportion of the patients improved clinically indicated a positive association with receiving IVIg treatment compared to placebo in



Table 7. Ovid MEDLINE(R) 1946 to June Week 2 2014

39	37 or 38	18
38	7 and 12 and 32	12
37	6 and 11 and 31	18
36	limit 35 to humans	106
35	34 or 33	108
34	7 and 12 and 20	89
33	6 and 11 and 19	108
32	or/23-30	117585
31	or/21-29	131483
30	(Meta Analysis or Systematic Review or Biomedical Technology Assessment or Economic Evaluation).sh. [Embaseterms]	49981
29	(meta regression\$ or metaregression\$ or mega regression\$.ti,ab.	2431
28	(meta analy\$ or metaanaly\$ or met analy\$ or metanaly\$ or health technology assessment\$ or HTA or HTAs or biomedical technology assessment\$ or bio-medical technology assessment\$.ti,ab.	61061
27	(handsearch\$ or hand search\$.ti,ab.	5121
26	(data synthes\$ or data extraction\$ or data abstraction\$.ti,ab.	12169
25	((integrative adj2 (review\$ or overview\$)) or (collaborative adj (review\$ or overview\$)) or pool\$ analy\$.ti,ab.	5368
24	((quantitative adj (review\$ or overview\$ or synthes\$)) or (research adj (integration\$ or overview\$)).ti,ab.	936
23	((systematic\$ adj (literature review\$ or review\$ or overview\$)) or (methodologic\$ adj (literature review\$ or review\$ or overview\$))).ti,ab.	49971
22	Meta-Analysis as Topic.sh. or exp Technology Assessment, Biomedical/ [Medlineterms]	23081
21	Meta-Analysis.pt. [Medlineterm]	49981
20	or/15-18	950487
19	or/13-17	1220916
18	*Major Clinical Study/ or *Multicenter Study/) or exp Controlled Clinical Trial/ [Embaseterms](	88875
17	(control\$ adj2 (study or studies or trial\$.ti,ab.	263773
16	((tripl\$ adj (blind\$ or dumm\$ or mask\$)) or (trebl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.	339
15	(random\$ or rct\$ or sham\$ or placebo\$ or (singl\$ adj (blind\$ or dumm\$ or mask\$)) or (doubl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.	786960
14	(Multicenter Study or Randomized Controlled Trial or Controlled Clinical Trial).pt. [Medlineterms]	577370
13	exp Controlled Clinical Trials as Topic/ or Double-Blind Method.sh. or Random Allocation.sh. or Single-Blind Method.sh. or Multicenter Studies as Topic.sh. [Medlineterms]	313388
12	or/9-10	218492
11	or/8-9	218492
10	multiple sclerosis".sh. [Embaseterm]"	39830
9	(sclerosis Multiple \$ or multiple sclerosis\$ or MS).ti,ab.	212879
8	multiple sclerosis".sh. [Medlineterm]"	39830
7	or/2-5	13515
6	or/1-4	16941
5	Immunoglobulin".sh. [Embaseterm]	0
4	(alphaglobin\$ or baygam\$ or endobulin\$ or gamagard\$ or gamimmune\$ or gamimmune\$ or gamunex\$ or gammimmune\$ or gammimmune\$ or gam?agard\$ or gam?aguard\$ or gammaglobulin\$ or gammonativ\$ or (globulin adj n) or igivnex\$ or intraglobin\$ or intraglobulin\$ or iveegam\$ or octagam\$ or polygam\$ or sandoglobulin\$ or venimmune\$ or venoglobulin\$.ti,ab.	2936
3	(ivig or igiv or igv or ivigg or ivgg).ti,ab.	5208
2	((intravenous\$ adj (antibod\$ or gammaglobulin\$ or gamma globulin\$ or immunoglobulin? or immune globulin?)) or iv immunoglobulin? or intravenous ig or modified immune globulin?).ti,ab.	9879
1	Immunoglobulins Intravenous".sh. [Medlineterm]"	9826

patients.

The results of similar studies that have been done in this field in other countries (Sorensen 2002 (14), Fergusson 2004 (21)

and Gary 2009 (4)) are largely similar to the results obtained in this study.

The studies that were entered into the meta- analysis used different doses of IVIG

and only two trails compared two different doses of IVIG with placebo (Lewanska et al. 2000; Fazekas et al. 2008), and these two trails can help select the optimal dose of IVIG. However, the decisions made considering the use of each of the doses are associated with the frequent and severe side effects. Unfortunately, the two mentioned studies did not show any difference between the two doses.

Several studies have shown that immunoglobulin was well tolerated, and did not report any severe related side effects; the most common mild side effects included headache, nausea, fever, dizziness, chills, rash and fatigue.

Most of the studies compared the effectiveness of this drug with placebo. However, to determine the effectiveness of this drug, it needs to be compared with other MS drugs. However, unfortunately, few studies (3 trials and one intervention study) have done this comparison. The study conducted by Kalanie et al. 2004 (22) compared the efficacy of this drug with interferon beta-1a (Avonex) in RRMS patients. This study showed a reduction of relapse rates by using IVIG compared to interferon beta-1a better safety profile for IVIG in the studied Iranian population. In the two other studies (Visser et al. 2004 and Sorensen et al. 2004), IVIG was used as add-on to methylprednisolone and was compared to IV methylprednisolone only in the treatment of relapses in MS, and in both studies there was no significant difference between the groups in terms of relapse and measured outcomes (23,24).

Although studies have shown beneficial effects of immunoglobulin in measuring variable diseases activities, the evidence, with regards to the short duration and the number of participants in the trials, was not sufficient, and more accurate assessment of the patients is needed. Thus, based on the results of this meta-analysis, immunoglobulin can be considered as an alternative option, second-line therapy, or adjuvant therapy considering its beneficial effect (high tolerance, need to be injected with longer

intervals, etc.) for treating relapsing–remitting MS patients.

### Acknowledgments

We thank the National Institute of Health Research and Yazd University of Medical Sciences for providing facilities for this review. It should also be noted that this article has been adapted from a Master's thesis.

### References

1. Achiron A, Kishner I, Sarova-Pinhas I, Raz H, Faibel M, Stern Y, et al. Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Archives of Neurology* 2004; 61(10):1515-20.
2. Yamamoto D, Campbell JD. Cost-effectiveness of multiple sclerosis disease-modifying therapies: a systematic review of the literature. *Autoimmune diseases* 2012;2012.
3. Tsang BK, Macdonell R. Multiple sclerosis-diagnosis, management and prognosis. *Aust Fam Physician* 2011 Dec;40(12):948-55.
4. Gray O MG, Forbes RB. Intravenous immunoglobulins for multiple sclerosis. *Cochrane Database of Systematic Reviews* 2010.
5. Sorensen PS. The role of intravenous immunoglobulin in the treatment of multiple sclerosis. *J Neurol Sci* 2003 Feb 15;206(2):123-30.
6. Lewanska M, Selmaj K. [Immunotherapy of intravenous immunoglobulin preparations in neurologic diseases]. *Postepy Hig Med Dosw* 2002;56 Suppl:69-83.
7. Clegg A, Bryant J, Milne R. Disease-modifying drugs for multiple sclerosis: a rapid and systematic review. *Health Technology Assessment (Winchester, England)* 2000;4(9):i-iv, 1-101.
8. Achiron A, Miron S. Intravenous immunoglobulin and multiple sclerosis. *Clin Rev Allergy Immunol* 2005 Dec;29(3):247-54.
9. Organization WH. Multiple sclerosis resources in the world 2013. 2013.
10. Ebrahimi HA, Sedighi B. Prevalence of multiple sclerosis and environmental factors in Kerman province, Iran. *Neurology Asia* 2013;18(4).
11. Sibénil S, Elluru S, Negi V-S, Ephrem A, Misra N, Delignat S, et al. Intravenous immunoglobulin in autoimmune and inflammatory diseases: more than mere transfer of antibodies. *Transfusion and Apheresis Science* 2007;37(1):103-7.
12. Sorensen PS. Treatment of multiple sclerosis with intravenous immunoglobulin: review of clinical trials. *Neurol Sci* 2003 Oct;24 Suppl 4:S227-30.

13. Fernández Liguori N, Rojas JI, Klajn DS, Ciapponi A. Intravenous immunoglobulin to prevent relapses during pregnancy and postpartum in multiple sclerosis. *The Cochrane Library*. 2013.
14. Sorensen PS, Fazekas F, Lee M. Intravenous immunoglobulin G for the treatment of relapsing-remitting multiple sclerosis: a meta-analysis. *Eur J Neurol* 2002 Nov;9(6):557-63.
15. Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. Austrian Immunoglobulin in Multiple Sclerosis Study Group. *Lancet* 1997 Mar 1;349(9052):589-93.
16. Achiron A, Gabbay U, Gilad R, Hassin-Baer S, Barak Y, Gornish M, et al. Intravenous immunoglobulin treatment in multiple sclerosis Effect on relapses. *Neurology* 1998;50(2):398-402.
17. Strasser-Fuchs S, Fazekas F, Deisenhammer F, Nahler G, Mamoli B. The Austrian Immunoglobulin in MS (AIMS) study: final analysis. *Mult Scler* 2000 Oct;6 Suppl 2:S9-13.
18. Lewańska M, Siger-Zajdel M, Selmaj K. No difference in efficacy of two different doses of intravenous immunoglobulins in MS: clinical and MRI assessment. *European Journal of Neurology* 2002;9(6):565-72.
19. Kocer B, Yildirim-Gurel S, Tali ET, Irkec C, Isik S. The role of qualitative and quantitative MRI assessment of multiple sclerosis lesions according to their in evaluating the efficacy of intravenous immunoglobulin G. *Neuroradiology* 2004 Apr; 46(4):287-90.
20. Fazekas F, Lublin FD, Li D, Freedman MS, Hartung HP, Rieckmann P, et al. Intravenous immunoglobulin in relapsing-remitting multiple sclerosis: a dose-finding trial. *Neurology* 2008 Jul 22;71(4):265-71.
21. Fergusson D, Hutton B, Sharma M, Tinmouth A, Wilson K, Cameron DW, et al. Use of intravenous immunoglobulin for treatment of neurologic conditions: a systematic review. *Transfusion* 2005 Oct;45(10):1640-57.
22. Kalanie H, Gharagozli K, Hemmatie A, Ghorbanie M, Kalanie AR. Interferon Beta-1a and intravenous immunoglobulin treatment for multiple sclerosis in Iran. *Eur Neurol* 2004;52(4):202-6.
23. Visser LH, Beekman R, Tijssen CC, Uitdehaag BM, Lee ML, Movig KL, et al. A randomized, double-blind, placebo-controlled pilot study of i.v. immune globulins in combination with i.v. methylprednisolone in the treatment of relapses in patients with MS. *Mult Scler* 2004 Feb;10(1):89-91.
24. Sorensen PS, Haas J, Sellebjerg F, Olsson T, Ravnborg M. IV immunoglobulins as add-on treatment to methylprednisolone for acute relapses in MS. *Neurology* 2004;63(11):2028-33.