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**IMMUNOMODULATORS AND IMMUNOSUPPRESSANTS** FOR PATIENTS WITH RELAPSING-REMITTING MULTIPLE **SCLEROSIS: A NETWORK META-ANALYSIS** 



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# **Objectives**

The aim of this study was to synthesize the evidence of clinical outcomes for alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferons, natalizumab, ocrelizumab, peginterferon and teriflunomide in adults with relapsing-remitting multiple sclerosis.

## **Methods**

- A systematic review was performed by Medline, Scopus and manual search (May 2017);
- Bayesian network meta-analyzes were conducted, of randomized clinical trials that evaluated any of the disease modifying therapies head-to-head or against placebo;
- For efficacy, the annualized relapse rate was considered, whereas safety was evaluated through discontinuation due to adverse events in 96 weeks;
- Surface Under the Cumulative Ranking analysis (SUCRA), Cochrane tool for risk of bias (v2.0) [1] and GRADE • [2] were used to ranking therapies, assess methodological bias, and quality of general evidence, respectively; Statistical analyses were performed using software R v. 3.4.1/R studio 1.0.153 [3].

## Results

weeks.

Thirty-three studies were included in the meta-analyzes (Figure 1 and 2). All therapies were most effective than placebo. The highest rates, considering the outcome annualized relapse rate were alemtuzumab, natalizumab, and ocrelizumab [Hazard Ratio versus placebo, of 0.31 (95%) Credibility Interval (Crl) 0.26, 0.38), 0.31 (95% Crl 0.27, 0.36)

and 0.37 (95%Crl 0.31, 0.36), respectively] (Figure 3), without significant differences between these three therapies. Discontinuation due to adverse events (96-weeks) revealed similarity across all therapies compared to placebo (Figure 4).





Interferon 1a 44

Figure 2. Network meta-analysis of discontinuaton due to adverse events in 96

Interferon 1b 250

Figure 1. Network meta-analysis of annualized relapse rate.

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,	Compared with Placebo	Hazard Ratio (95% Crl)
> - ) )	Alemtuzumab	0.31 (0.26, 0.38)
, 	Natalizumab	0.31 (0.27, 0.36)
))	Ocrelizumab	0.37 (0.31, 0.46)
)	Cladribine	0.42 (0.34, 0.52)

Compared with Pla	acebo	
Alemtuzumab		
Natalizumab		•
Ocrelizumab		
Cladribine		

Risk Ratio (95% Crl)
0.68 (0.21, 3.10)
1.40 (0.52, 4.20)
1.00 (0.32, 4.50)
1.50 (0.46, 5.20)

Fingolimod		0.47 (0.41, 0.53)
Daclizumab	<b></b>	0.47 (0.42, 0.54)
Dimethyl fumarate	<b></b>	0.48 (0.42, 0.55)
Peginterferon	<b>_</b>	0.64 (0.51, 0.80)
Glatiramer acetate 40	<b>_</b>	0.66 (0.55, 0.78)
Glatiramer acetate 20		0.69 (0.62, 0.76)
Interferon 1a 44	<b></b>	0.69 (0.60, 0.79)
Teriflunomide 14	<b></b>	0.69 (0.58, 0.81)
Interferon 1b 250	<b></b>	0.70 (0.61, 0.82)
Teriflunomide 7		0.73 (0.63, 0.85)
Interferon 1a 30	_ <b></b>	0.84 (0.77, 0.93)
0.2		1

Figure 3. Forest plot of network meta-analysis comparing all therapies with placebo for annualized relapse rate, ranked by SUCRA.

1.30 (0.35, 5.00) Fingolimod Daclizumab Not available **Dimethyl fumarate** 1.30 (0.69, 2.80) Peginterferon Not available Glatiramer acetate 40 Not available Glatiramer acetate 20 1.40 (0.79, 3.80) Interferon 1a 44 1.80 (0.79, 6.20) **Teriflunomide 14** Not available Interferon 1b 250 1.40 (0.47, 6.40) **Teriflunomide 7** Not available 1.30 (0.35, 5.00) Interferon 1a 30 0.2

Figure 4. Forest plot of network meta-analysis comparing all therapies with placebo for discontinuation due to adverse events in 96 weeks.

### **Conclusions**

Alemtuzumab, natalizumab, and ocrelizumab are the best choices considering clinical efficacy without compromising patient's safety (high quality evidence).

### References

**1** - Higgins J et al. Cochrane Methods Cochrane Database Syst Rev 2016; : Suppl.1. 2 - GRADE Working Group. BMJ 2004; 328: 1490-0;

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