Efficacy of FDA-approved Disease-modifying Therapies (DMTs) versus Active Comparator Medications for Relapsing-Remitting Multiple Sclerosis: A Systematic Review

Melissa Lingohr-Smith, PhD; Chloe Deitelzweig, Grace Lin, PhD; Jay Lin, PhD MBA

Novosys Health, Green Brook, NJ, USA

INTRODUCTION

- Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system that is estimated to affect between 850,000 and 914,000 adults in the US.[1]
- Among individuals diagnosed with MS, approximately 85% have a relapsing-remitting (RRMS) disease course, in which patients experience clinical attacks that are typically followed by periods of remission.[2]
- The treatment landscape for RRMS is rapidly evolving and it is important for treatment decision-makers and policymakers to have information on the comparative efficacy of disease-modifying therapies (DMTs).

OBJECTIVE

- To conduct a systematic search to identify phase III clinical trials that have compared the efficacy of more recently FDA-approved DMTs versus active comparator medications for the treatment of RRMS

METHODS

- A systematic literature search of PubMed was conducted in January of 2022 to identify phase III clinical trials conducted in the past 10 years in which the efficacy of DMTs versus active comparator medications in the treatment of RRMS was evaluated.
- Patient characteristics and efficacy data were extracted from the phase III clinical trial publications.
  - The primary efficacy outcome for this assessment was annualized relapse rate (ARR).
- The DMTs included the monoclonal antibody therapies, natalizumab, alemtuzumab, ocrelizumab, and ofatumumab and the oral therapies, ozanimod and ponesimod.
  - Comparator medications: injectable interferon beta-1a, oral teriflunomide

RESULTS

Table 1. Clinical Trial Publications and US FDA Approval Years of DMTs Included in Phase III Clinical Trials vs Comparator Medications

DMT	Trial	Publication	FDA Approval Year
Monoclonal antibodies			
Natalizumab	SENTINEL	Rudick RA, Stuart WH, Calabresi PA, et al. *N Engl J Med*. 2006;354:911-923.	2004
Alemtuzumab	CARE MS-1 CARE MS-2	Cohen JA, Coles AJ, Arnold DL, et al. *Lancet*. 2012;380:1819-1828. Coles AJ, Twyman CL, Arnold DL, et al. *Lancet*. 2012;380:1829-1839.	2014
Ocrelizumab	OPERA 1 & 2	Hauser SL, Bar-Or A, Comi G, et al. *N Engl J Med*. 2017;376:221-234.	2017
Ofatumumab	ASCLEPIOS 1 & 2	Hauser SL, Bar-Or A, Cohen JA, et al. *N Engl J Med*. 2020;383:546-557.	2020
Oral medications			
Ozanimod	RADIANCE	Cohen JA, Comi G, Selmaj KW, et al. *Lancet Neurol*. 2019;18:1021-1033.	2020
Ponesimod	OPTIMUM	Kappos L, Fox RJ, Burcklen M, et al. *JAMA Neurol*. 2021;78:558-567.	2021

Table 2. Annualized Relapse Rates (ARRs) of DMTs vs Comparator Medications in the Phase III Clinical Trials of Patients with RRMS

				DMT vs Comparator						
DMT	Trial	Comparator	Follow-up	Patient Count	Mean Age (years)	% female	ARR	Rate Ratio	Relative Reduction	p-value
Monoclonal antibodies										
Natalizumab (300mg; 4 wks) + interferon beta-1a	SENTINEL	Interferon beta-1a	116 wks	589/582	39/39	75/72%	0.34 vs 0.75	0.45	55%	<0.001
Alemtuzumab (12mg; 3 days)	CARE-MS-1	Interferon beta-1a	2 yrs	376/187	33/33	65/65%	0.18 vs 0.39	0.45	55%	<0.001
Alemtuzumab (12mg; 3 days)	CARE-MS-2	Interferon beta-1a	2 yrs	426/202	35/36	66/65%	0.26 vs 0.52	0.51	49%	<0.001
Ocrelizumab (600mg; 24 wks)	OPERA-1	Interferon beta-1a	96 wks	410/411	37/37	66/66%	0.16 vs 0.29	0.54	46%	<0.001
Ocrelizumab (600mg; 24 wks)	OPERA-2	Interferon beta-1a	96 wks	417/418	37/37	65/67%	0.16 vs 0.29	0.53	47%	<0.001
Ofatumumab (20mg; 4 wks)	ASCLEPIOS-1	Teriflunomide	1.6 yrs	465/462	39/38	68/69%	0.11 vs 0.22	0.49	51%	<0.001
Ofatumumab (20mg; 4 wks)	ASCLEPIOS-2	Teriflunomide	1.6 yrs	481/474	38/38	66/67%	0.10 vs 0.25	0.42	58%	<0.001
Oral medications										
Ozanimod (0.5mg; daily)	RADIANCE	Interferon beta-1a	2 yrs	439/441	35/35	65/69%	0.22 vs 0.28	0.79	21%	0.017
Ozanimod (1.0mg; daily)	RADIANCE	Interferon beta-1a	2 yrs	433/441	36/35	67/69%	0.17 vs 0.28	0.62	38%	<0.001
Ponesimod (20mg; daily)	OPTIMUM	Teriflunomide	108 wks	567/566	37/37	64/66%	0.20 vs 0.29	0.695	30.5%	<0.001

LIMITATIONS

- The ARRs of patients on the comparator medication, interferon beta-1a, varied across the clinical trials (0.28-0.75); however, the newer DMTs consistently demonstrated significant reductions in ARR vs interferon beta-1a.
- Since comparator medications differed with the new oral DMTs, further comparison studies, either clinical trials or real-world observational studies, are warranted.
- Inclusion of other key secondary clinical trial endpoints may be necessary to further differentiate the efficacy of newer DMTs vs comparator medications.
- Furthermore, trial extension studies in addition to real-world observational studies are needed to capture the long-term comparative effectiveness of DMTs.

CONCLUSIONS

- All of the more recently FDA-approved DMTs evaluated in this review provided a significant clinical benefit for relapse rate reduction over comparator medications.
- Innovations in the personalization of RRMS treatment may further improve the outcomes of patients with RRMS.

REFERENCES

1. Wallin MT, Culpepper, WJ, Campbell JD, et al. The prevalence of MS in the United States: a population-based estimate using health claims data. *Neurology*. 2019;92: e1029-e1040.
2. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. *Clin Med (Lond)*. 2016;16(Suppl 6):s53-s59.

DISCLOSURE

M Lingohr-Smith, C Deitelzweig, G Lin, and J Lin are employees of Novosys Health, which sponsored this study and preparation of this poster.

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