

Supplementary Online Content

Nicholas RS, Han E, Raffel J, Chataway J, Friede T. Study populations in progressive multiple sclerosis have become less disabled over three decades: a systematic review and meta-analysis of 43 randomized placebo-controlled trials.

eFigure 1. Individual risk of bias assessments for the n=43 trials included in the review (green – low risk of bias; yellow – unclear risk of bias; red – high risk of bias).

eTable 1. References of the 43 studies included in the systematic review

eFigure 1. Individual risk of bias assessments for the n=43 trials included in the review (green – low risk of bias; yellow – unclear risk of bias; red – high risk of bias).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Anderson 2004	?	?	+	+	+	+
ASCEND 2016	+	+	+	+	+	+
Beutler 1996	+	?	+	+	+	+
Bornstein 1991	+	+	+	+	+	+
British and dutch MS azathioprine group 1988	?	?	+	+	+	+
Chataway 2014	+	+	+	+	+	+
Cohen 2002	+	+	+	+	+	+
Dubois 1998	+	+	+	+	+	+
Ellison 1989	+	+	+	+	+	+
European Study Group on IFNB-1b in SPMS 1998	+	+	+	+	+	+
Freedman 2011	+	+	+	+	+	+
Ghezzi 1989	?	?	+	+	+	+
Goodkin 1995	+	?	+	+	+	+
Goodkin 2000	+	+	+	+	+	+
Hartung 2002	+	+	+	+	+	+
Hawker 2009	?	?	+	+	+	+
Hommes 2004	+	+	+	+	+	+
Kapoor 2010	+	?	+	+	+	+
Karussis 1996	+	+	+	+	+	+
Kastrukoff 1990	+	?	+	?	+	+
Leary 2003	+	?	+	+	+	+
Likosky 1991	?	?	+	+	?	+
Lublin 2016	+	+	+	+	+	+
Milanese 1992	+	+	+	+	+	+
Milligan 1994	?	?	?	?	+	+
Montalban 2009	+	?	?	?	+	+
Montalban 2016	+	+	+	+	+	+
Mostert 2013	+	+	?	?	+	+
North American Study Group on IFNB-1b in SPMS 2004	+	+	+	+	+	+
Noseworthy 2000	+	?	+	+	+	+
Pohlau 2007	+	+	?	?	+	+
Rice 2000	+	?	+	+	+	+
Schreiber 2016	+	+	?	+	+	+
Skurkovich 2001	+	+	+	+	+	+
SPECTRIMS Study Group 2001	+	+	+	+	+	+
The Canadian Cooperative MS Study Group 1991	+	?	+	+	+	+
The MS Study Group 1990	?	?	+	+	+	+
Tourbah 2016	?	?	+	+	+	+
Vermersch 2012	+	+	?	?	+	+
Walker 2005	+	+	+	?	+	+
Warren 2006	?	?	?	?	+	+
Wolinsky 2007	?	?	+	+	+	+
Zajicek 2013	+	+	+	+	+	+

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- Montalban X HB, Rammohan K, Giovannoni G, et al, on behalf of the ORATORIO Clinical Investigators. Ocrelizumab versus placebo in in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220.
- Ghezzi A, Di Falco M, Locatelli C, Zaffaroni M, Caputo D, Marfano S. Clinical controlled randomized trial of azathioprine in multiple sclerosis. Gonsette RE, Delmotte. *Recent Advances in Multiple Sclerosis*. Amsterdam: Elsevier. 1989.
- Kapoor R, Ho P-R, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurology*. 2018; 17, 405–15.
- British and Dutch Multiple Sclerosis Azathioprine Trial Group. Double-masked trial of azathioprine in multiple sclerosis. *The Lancet*. 1988; 332(8604), 179-183.
- Ellison GW, Myers LW, Mickey MR, et al. A placebo-controlled, randomized, double-masked, variable dosage, clinical trial of azathioprine with and without methylprednisolone in multiple sclerosis. *Neurology*. 1989; 39(8),1018-1026.
- Kastrukoff LF, Oger JJ, Hashimoto SA, et al. Systemic lymphoblastoid interferon therapy in chronic progressive multiple sclerosis. I. Clinical and MRI evaluation. *Neurology*. 1990; 40(3): 479-486.
- The Multiple Sclerosis Study Group. Efficacy and toxicity of cyclosporine in chronic progressive multiple sclerosis: a randomized, double-blinded, placebo-controlled clinical trial. The Multiple Sclerosis Study Group. *Ann Neurol*. 1990; 27(6): 591-605.
- Likosky WH, Fireman B, Elmore R, et al. Intense immunosuppression in chronic progressive multiple sclerosis: the Kaiser study. *J Neurol Neurosurg Psych*. 1991; 54(12):1055-1060.

- Bornstein MB, Miller A, Slagle S, et al. A placebo-controlled, double-blind, randomized, two-center, pilot trial of Cop 1 in chronic progressive multiple sclerosis. *Neurology*. 1991; 41(4):533-539.
- Canadian Cooperative Multiple Sclerosis Study Group. The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. *The Lancet*. 1991; 337 (8739):441-446.
- Beutler E, Sipe JC, Romine JS, et al. The treatment of chronic progressive multiple sclerosis with cladribine. *PNAS*. 1996; 93(4):1716-1720.
- Milanese C, La Mantia L, Salmaggi A, Eoli M. A double blind study on azathioprine efficacy in multiple sclerosis: final report. *J Neurol*. 1993; 240(5):295-298.
- Milligan NM, Miller DH, Compston DA. A placebo-controlled trial of isoprinosine in patients with multiple sclerosis. *J Neurol Neurosurg Psych*. 1994; 57(2):164-168.
- Goodkin DE, Rudick RA, Medendorp SV, et al. Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol*. 1995; 37(1):30-40.
- Karussis DM, Meiner Z, Lehmann D, et al. Treatment of secondary progressive multiple sclerosis with the immunomodulator linomide: a double-blind, placebo-controlled pilot study with monthly magnetic resonance imaging evaluation. *Neurology*. 1996; 47(2):341-346.
- Kappos, L, European Study Group on Interferon-1b in Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon β -1b in treatment of secondary progressive multiple sclerosis. *The Lancet*. 1998; 352(9139):1491-1497.

Dubois B, D'hooghe M, De Lepeleire K, Ketelaer P, Opdenakker G, Carton H. Toxicity in a double-blind, placebo-controlled pilot trial with D-penicillamine and metacycline in secondary progressive multiple sclerosis. *Mult Scler*. 1998; 4(2):74-78.

Noseworthy JH, Wolinsky JS, Lublin FD, et al. Linomide in relapsing and secondary progressive MS: part I: trial design and clinical results. North American Linomide Investigators. *Neurology*. 2000; 54(9):1726-1733.

Rice GP, Filippi M, Comi G. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. *Neurology*. 2000; 54(5):1145-55.

Goodkin DE, Shulman M, Winkelhake J, et al. A phase I trial of solubilized DR2:MBP84-102 (AG284) in multiple sclerosis. *Neurology*. 2000; 54(7):1414-1420.

Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. *Neurology*. 2001; 56(11):1496-1504.

Skurkovich S, Boiko A, Beliaeva I, et al. Randomized study of antibodies to IFN-gamma and TNF-alpha in secondary progressive multiple sclerosis. *Mult Scler*. 2001;7(5):277-284.

Cohen JA, Cutter GR, Fischer JS, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology*. 2002; 59(5):679-687.

Hartung H, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *The Lancet*. 2002; 360(9350): 2018-2025.

Leary SM, Miller DH, Stevenson VL, Brex PA, Chard DT, Thompson AJ. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. *Neurology*. 2003;60 (1): 44-51.

- Andersen O, Elovaara I, Farkkila M, et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. *J Neurol Neurosurg Psych.* 2004; 75(5):706-710.
- Hommes OR, Sørensen PS, Fazekas F, et al. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *The Lancet.* 2004; 364(9440): 1149-1.
- Panitch H, Miller A, Paty D, Weinshenker B; North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology.* 2004; 63(10):1788-95.
- Walker JE, Giri SN, Margolin SB. A double-blind, randomized, controlled study of oral pirfenidone for treatment of secondary progressive multiple sclerosis. *Mult Scler.* 2005; 11(2): 149-158.
- Warren K, Catz I, Ferenczi L, Krantz M. Intravenous synthetic peptide MBP8298 delayed disease progression in an HLA Class II-defined cohort of patients with progressive multiple sclerosis: results of a 24-month double-blind placebo-controlled clinical trial and 5 years of follow-up treatment. *E J Neurol.* 2006; 13(8): 887-895.
- Pohlau D, Przuntek H, Sailer M, et al. Intravenous immunoglobulin in primary and secondary chronic progressive multiple sclerosis: a randomized placebo controlled multicentre study. *Mult Scler.* 2007;13(9):1107-17.
- Wolinsky JS, Narayana PA, O'Connor P, et al. Glatiramer acetate in primary progressive multiple sclerosis: Results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol.* 2007;61(1):14-24.

- Montalban X, Sastre-Garriga J, Tintore M, et al. A single-center, randomized, double-blind, placebo-controlled study of interferon beta-1b on primary progressive and transitional multiple sclerosis. *Mult Scler*. 2009;15(10):1195-1205.
- Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. 2009;66(4):460-471.
- Kapoor R, Furby J, Hayton T, et al. Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial. *The Lancet Neurology*. 2010; 9(7):681-688.
- Freedman MS, Bar-Or A, Oger J, et al. A phase III study evaluating the efficacy and safety of MBP8298 in secondary progressive MS. *Neurology*. 2011; 77(16):1551-1560.
- Vermersch P, Benrabah R, Schmidt N, et al. Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study. *BMC Neurology*. 2012; 12:36.
- Zajicek J, Ball S, Wright D, et al. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. *The Lancet Neurology*. 2013;12(9): 857-865.
- Mostert J, Heersema T, Mahajan M, Van Der Grond J, Van Buchem MA, De Keyser J. The effect of fluoxetine on progression in progressive multiple sclerosis: a double-blind, randomized, placebo-controlled trial. *ISRN Neurology*. 2013; 2013:370943.
- Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. *The Lancet*. 2014; 383(9936): 2213-2221.

- Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *The Lancet*. 2016; 387(10023): 1075-1084.
- Schreiber K, Magyari M, Sellebjerg F, et al. High-dose erythropoietin in patients with progressive multiple sclerosis: A randomized, placebo-controlled, phase 2 trial. *Mult Scler*. 2017; 23(5): 675-685.
- Tourbah A, Lebrun-Frenay C, Edan G, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. *Mult Scler*. 2016; 22(13): 1719-1731.