COMPARING OUTCOMES FROM CLINICAL STUDIES OF ORAL DISEASE-MODIFYING THERAPIES (DIMETHYL FUMARATE, FINGOLIMOD, AND TERIFLUNOMIDE) IN RELAPSING MS: ASSESSING ABSOLUTE DIFFERENCES USING A NUMBER NEEDED TO TREAT ANALYSIS

Freedman MS, Montalban X, Miller AE, et al.
Multiple Sclerosis and Related Disorders. 2016;10:204-212.

"It has been recommended to utilize both relative and absolute risk reduction (and its inverse, number needed to treat [NNT]) in any cross-trial comparison to provide a more reliable measure of comparative efficacy and thus "therapeutic gain""

—Freedman MS, Montalban X, Miller AE, et al

"Number needed to treat (NNT) is a statistically valid and increasingly used tool for evaluating comparative efficacy of different therapies and can provide physicians with a relatively simple assessment of potential treatment efficacy that may assist with treatment planning decisions."

—Freedman MS, Montalban X, Miller AE, et al

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BACKGROUND

Objectives

Gain insight into the comparative efficacy of 3 oral DMTs (dimethyl fumarate, fingolimod, and teriflunomide) in treating relapsing-remitting multiple sclerosis (RRMS), utilizing both absolute risk reduction and its inverse, NNT.

- The absolute risk reduction is the actual difference (absolute difference) in treatment effect between the control and treatment group
- NNT is the number of patients that need to be treated in order to prevent a specific outcome and is calculated as the inverse of the absolute risk reduction

Methods

- Post hoc analyses of individual and pooled data from pivotal trials of dimethyl fumarate (DEFINE, CONFIRM), fingolimod (FREEDOMS, FREEDOMS II), and teriflunomide (TEMSO, TOWER) were used to determine NNTs to prevent relapse and disability worsening
- NNTs were calculated using data from patients receiving placebo or dimethyl fumarate 240 mg bid, fingolimod 0.5 qd, or teriflunomide 14 mg qd
- Endpoints:
  —MS relapses
  —Relapses with severity features
  —Disability worsening
- In all NNT analyses, lower NNTs reflect greater benefit for the respective therapeutic intervention

Secondary end points (TEMSO)

- 12-week disability progression
- MRI parameters

	dimethyl fumarate		fingolimod		teriflunomide	
	DEFINE* (N=1234)	CONFIRM* (N=1417)	FREEDOMS* (N=1272)	FREEDOMS II*† (N=1083)	TEMSO* (N=1086)	TOWER* (N=1165)
Age, median (min:max)	39 (18:56)	37 (18:56)	37 (17:55)	41 (18:57)	38 (18:55)	38 (18:56)
Female, %	74	70	69.9	77.9	72.1	71.2
Time since diagnosis, mean (SD)	5.5 (5.49)	4.7 (5.01)	6.5 (4.8)	NR	5.33 (5.48)	5.16 (5.67)
Number of relapses, mean (SD) in previous year	1.3 (0.70)	1.4 (0.70)	1.5 (0.77)	1.5 (0.9)	1.4 (0.7)	1.4 (0.7)
MS subtype, %						
RRMS	100	100	100	100	91.4	97.5
SPMS	0	0	0	0	4.7	0.8
PRMS	0	0	0	0	3.9	1.7
EDSS score						
Mean (SD)	2.42 (1.240)	2.56 (1.194)	2.40 (1.32)	2.43 (1.30)	2.68 (1.30)	2.71 (1.37)
Median (min:max)	2.0 (0.0:6.5)	2.5 (0.0:5.5)	2.0 (0.0:5.5)	2.5 (0.0:6.5)	2.5 (0.0:6.0)	2.0 (0.0:6.5)

*Randomized and treated patients (including active treatment groups not included in the NNT analyses).
†Total population data have not been published (data presented are derived from indivddual treatment groups).

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KEY RESULTS

NNT to prevent 1 relapse was comparable between all 3 DMTs

	dimethyl fumarate 240 mg bid		fingolimod 0.5 mg qd		teriflunomide 14 mg qd	
	DEFINE	CONFIRM	FREEDOMS	FREEDOMS II	TEMSO	TOWER
ARR: Placebo Intervention	 0.36 0.17	 0.40 0.22	 0.40 0.18	 0.40 0.21	 0.54 0.37	 0.50 0.32
Absolute ARR reduction‡	-0.19 (*P*<0.001)	-0.017 (*P*=0.109)	-0.22 (*P*<0.001)	-0.19 (*P*<0.0001)	-0.17 (*P*<0.001)	-0.18 (*P*=0.0001)
NNT	**5.3**	**5.6**	**4.5**	**5.3**	**5.9**	**5.6**

NNT to prevent 1 relapse leading to hospitalisation was lower with teriflunomide vs dimethyl fumarate and fingolimod§

	dimethyl fumarate 240 mg bid		fingolimod 0.5 mg qd		teriflunomide 14 mg qd	
	DEFINE	CONFIRM	FREEDOMS	FREEDOMS II	TEMSO	TOWER
ARR: Placebo Intervention	 0.056 0.036	 0.055 0.038	 0.18 0.07	 0.023 0.011	 0.15 0.10	 0.16 0.09
Absolute ARR reduction‡	-0.020 (*P*=0.017)	-0.017 (*P*=0.109)	-0.110 (*P*≤0.001)	-0.012 (NS)	-0.05 (*P*<0.001)	-0.07 (*P*=0.0155)
NNT	**50.0**	**58.8**	**9.1**	**83.3**	**20.0**	**14.3**

Only teriflunomide 14 mg showed consistent NNT to prevent 1 patient with disability worsening across 2 Phase III trials

	dimethyl fumarate 240 mg bid		fingolimod 0.5 mg qd		teriflunomide 14 mg qd	
	DEFINE	CONFIRM	FREEDOMS	FREEDOMS II	TEMSO	TOWER
Proportion of patients with confirmed disability worsening (CDW)‖: Placebo Intervention	 0.27 0.16	 0.17 0.13	 0.241 0.177	 0.290 0.253	 0.273 0.202\	 0.197 0.158
Absolute ARR reduction‡	0.62 (*P*=0.005)	0.79 (*P*=0.25)	0.70 (*P*=0.02)	0.83 (*P*=0.227)	0.70 (*P*=0.0279)	0.68 (*P*=0.0442)
NNT	**10.8**	**30.2**	**15.3**	**23.5**	**13.7**	**17.1**

‡Absolute reductions were calculated at ARR for placebo-treated patients minus ARR for patients treated with intervention.
§Results from fingolimod studies were inconsistent; therefore, clear comparative conclusions cannot be made.
‖3-month CDW at 2 years.

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SUMMARY

- Absolute risk reduction and NNT present alternative ways to evaluate efficacy. The two measurements help minimize discrepancies across trials by comparing absolute differences between placebo and treatment groups
- Teriflunomide 14 mg is the only oral DMT to demonstrate significant reduction in risk of confirmed disability worsening in 2 pivotal Phase III trials and consistent NNTs to prevent 1 patient with disability worsening
- NNTs to prevent 1 relapse were broadly comparable between dimethyl fumarate, fingolimod, and teriflunomide
- NNT to prevent 1 relapse leading to hospitalization were considerably lower for teriflunomide compared with dimethyl fumarate

'…Clinicians frequently compare study outcomes on the basis of relative reductions in a specific endpoint, commonly in terms of the ARR in MS, to inform prescribing decisions. However, such comparisons do not give a full picture of the therapeutic benefit of the respective interventions. The use, therefore, of evidence-based approaches such as NNT can provide additional information on the relative benefit/risk profiles of specific treatments.'

—Freedman MS, Montalban X, Miller AE, et al

'Of the three DMTs evaluated, only teriflunomide showed consistent and significant reductions in the risk of disability worsening in each of the individual studies, which was reflected in lower NNTs in TEMSO and TOWER compared with CONFIRM and FREEDOMS II…'

—Freedman MS, Montalban X, Miller AE, et al

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