Teriflunomide

Table 1
Current and forthcoming drugs for the treatment of multiple sclerosis

Drug	Posology	FDA/EMA Approval
Interferon beta 1b	Subcutaneous per 48 h	1993/1995
Interferon beta 1a	Intramuscular per 1 wk	1996/1997
Interferon beta 1b	Subcutaneous 3 times per week	2002/1998
Pegylated interferon beta	Subcutaneous per 2 wk	2014/2014
Glatiramer acetate	Subcutaneous per 24 h per 48 h	 1996/2001 2014/2014
Natalizumab	Intravenous per 4 wk	2006/2006
Fingolimod	Oral per 24 h	2010/2011
Teriflunomide	Oral per 24 h	2012/2013
Alemtuzumab	Intravenous per 1 y[a]	2014/2013
Dimethyl fumarate	Oral per 12 h	2013/2014
Daclizumab	Subcutaneous per 4 wk	2016/2016
Ocrelizumab	Intravenous per 6 mo	2017/awaiting
Cladribine	Oral per 1 y[b]	Under EMA review

- **Approval:** FDA Approves Teriflunomide, 2012

- **Dosage and administration**: a Once-Daily, **Oral Treatment** as a pyrimidine synthesis inhibitor indicated for the treatment of patients with relapsing forms of multiple sclerosis

- **Mechanism of Action:** Teriflunomide is an immunomodulator with anti-inflammatory properties. It may involve a reduction in the number of activated lymphocytes in the central nervous system (CNS)

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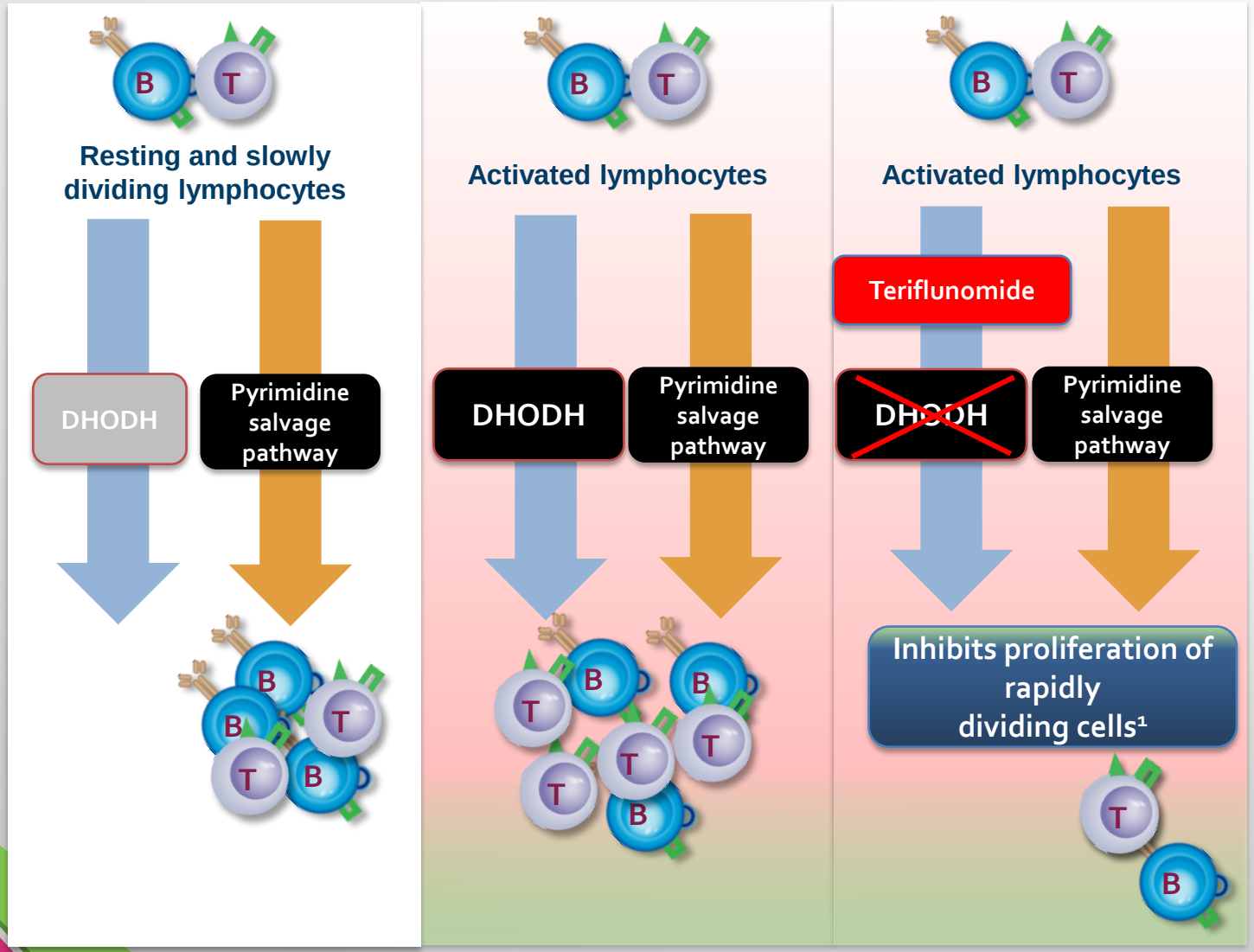
Mechanism of Action

Selective Dihydroorotate Dehydrogenase Inhibitor

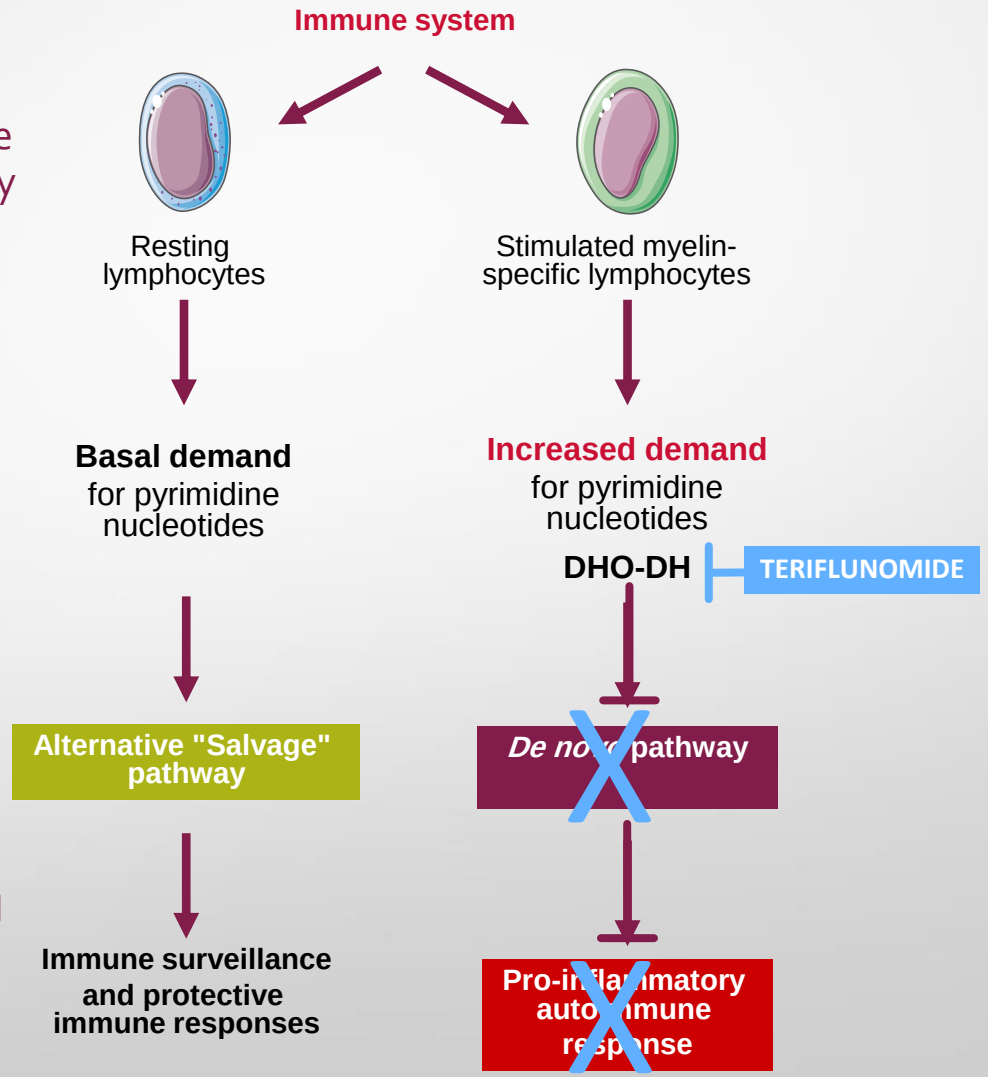


- *An oral disease-modifier Blocks de novo pyrimidine synthesis, reducing T- and B- cell proliferation and function in response to autoantigens*
- *Preserves replication and function of cells (e.g. haemopoietic cells, memory T-cells) living on the existing pyrimidine pool (salvage pathway)*

1. Breedveld et al. *Ann Rheum Dis.* 2000;59:841. 2. Bar-Or et al. *Drugs.* 2014;74:659.

Teriflunomide Proposed mechanism *

- Inhibits proliferation of stimulated T and B lymphocytes in the periphery thought to be responsible for the damaging inflammatory process in MS
- Selectively and reversibly inhibits dihydroorotate dehydrogenase (DHO-DH), a key enzyme in *de novo* pyrimidine synthesis required by rapidly dividing lymphocytes
  - Diminishes the numbers of activated T and B cells available to migrate into the CNS
- The pyrimidine salvage pathway is not affected by teriflunomide
  - Basic homeostatic cell functions of resting lymphocytes appear to be preserved
  - Normal immune surveillance is maintained



***The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood**

Gold & Wolinsky. *Acta Neurol Scand* 2011;12475–84

Targeting Rapidly dividing lymphocytes

Prior to Treatment

- CBC, LFT, Bili
- Check BP
- PPD
- Serum k, Renal function test
- Pregnancy Test
- Check acute or chronic infections

(Patients with acute or chronic infections should not start treatment until the infection(s) is resolved)

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During Treatment

Check BP **Periodically**

2. Check CBC if sign of Infection
3. Confirme patient uses repliable contraception
4. Monitor **ALT monthly for 6 months** then every 2 months**,**

- For ALT elevations > 2- and 3-fold need to weekly monitoring (EMEA)
- ALT >3-fold ULN: discontinued and patients underwent an accelerated elimination procedure.
- Consider additional monitoring when the drug is given with other potentially hepatotoxic drugs

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Hepatic Toxicity Grading

- Grade 1: >1 to ≤2.5 Times of ULN
- Grade 2: >2.5 to ≤5 Times of ULN
- Grade3: >5 to ≤20 Times of ULN
- Grade 4: ≥20 Times of ULN

Contraindications

- Severe Hepatic Impairment
- Pregnancy
- Breast-feeding women
- Women of Childbearing Potential Not Using Reliable Contraception
- Current treatment with Leflunomide
- severe renal impairment undergoing dialysis

Elimination of Teriflunomide

Teriflunomide elimination

is slowly from the plasma. Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mg/L (0.02 mcg/mL), although because of individual variations in drug clearance it may take as long as 2 years

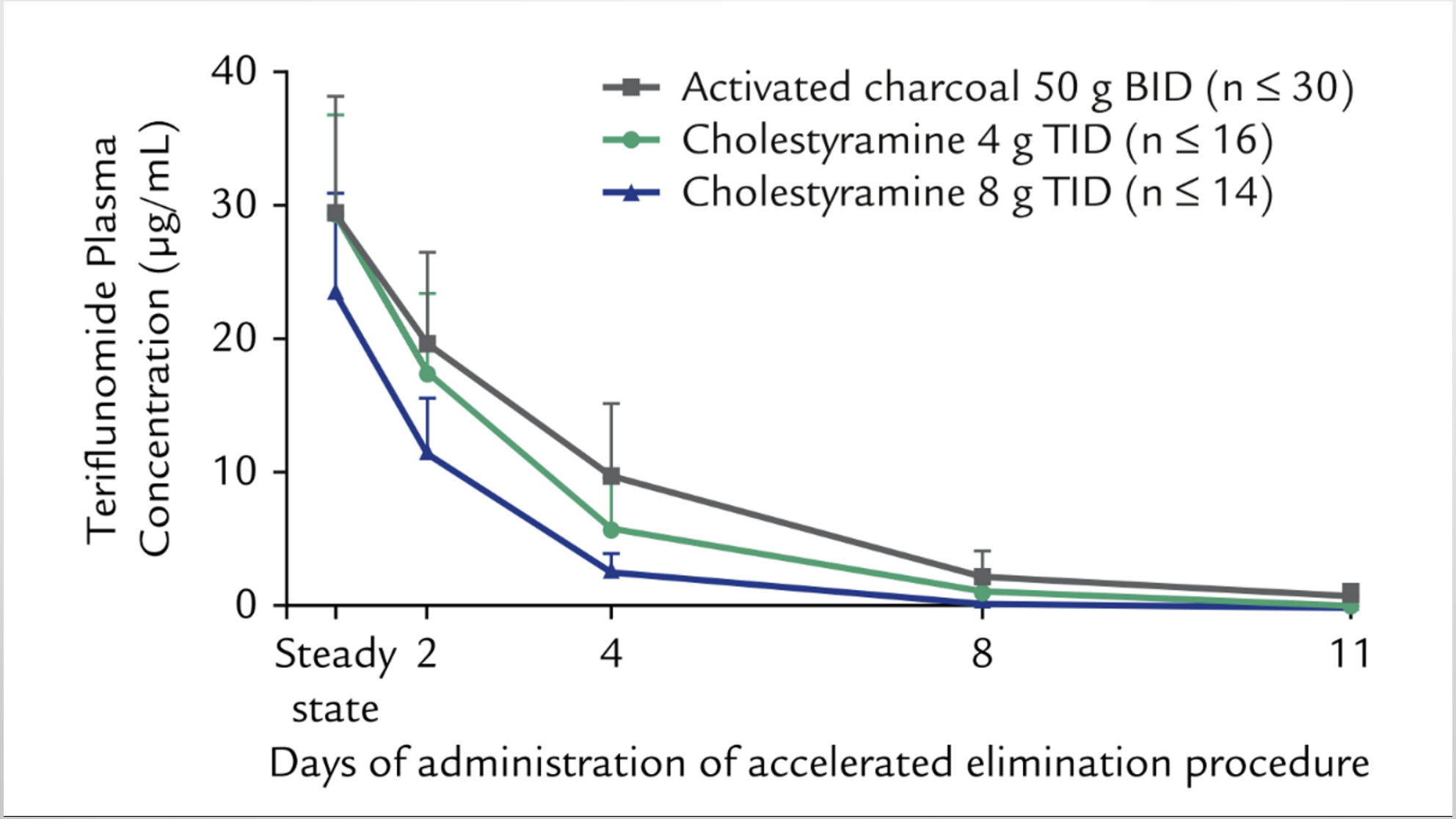
Elimination can be accelerated by either of the following procedures:

1. Administration of **cholestyramine 8 g every 8 hours for 11 days**
2. ***cholestyramine 4 g*** **every 8 hours for 11 days(**If cholestyramine 8 g is not well tolerated)
3. Administration of **50 g oral activated charcoal powder every 12 hours for 11 days**.

NOTE:

➢If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower .Teriflunomide plasma concentration rapidly.

➢It should be noted that patients receiving oral contraceptives while undergoing accelerated elimination should use alternative contraceptive methods because cholestyramine and activated charcoal may negatively affect the absorption of estrogens and progestogens



A.E. Miller , Clinical Therapeutics/Volume 37, 2015

Accelerated elimination indications

1. Pregnancy is confirmed
2. Skin and/or mucosal reactions develop that raise suspicions of severe generalized major skin reactions (Stevens–johnson syndrome or toxic epidermal necrolysis)
3. Serious infection develops
4. Hematologic disorders or severe hematologic reactions occur
5. Confirmed peripheral neuropathy develops
6. Woman wishes to become pregnant
7. Clinically significant overdose or toxicity of Teriflunomide occur

Safety of Teriflunomide

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Teriflunomide-associated adverse effects are :

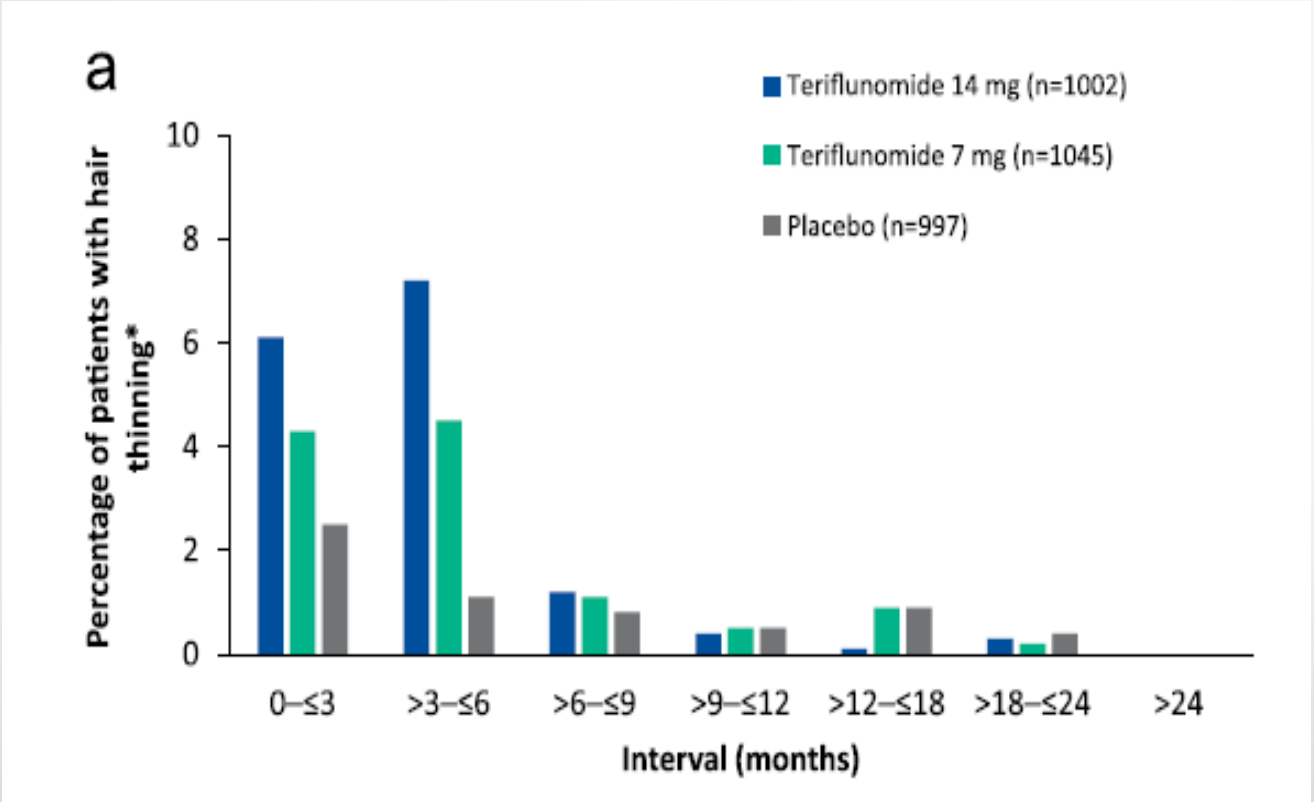
The most common:

- Headache
- Mild elevation of alanine aminotransferase (ALT)
- Diarrhea, nausea
- Transient hair thinning, or decreased hair density

Less commonly observed adverse effects:

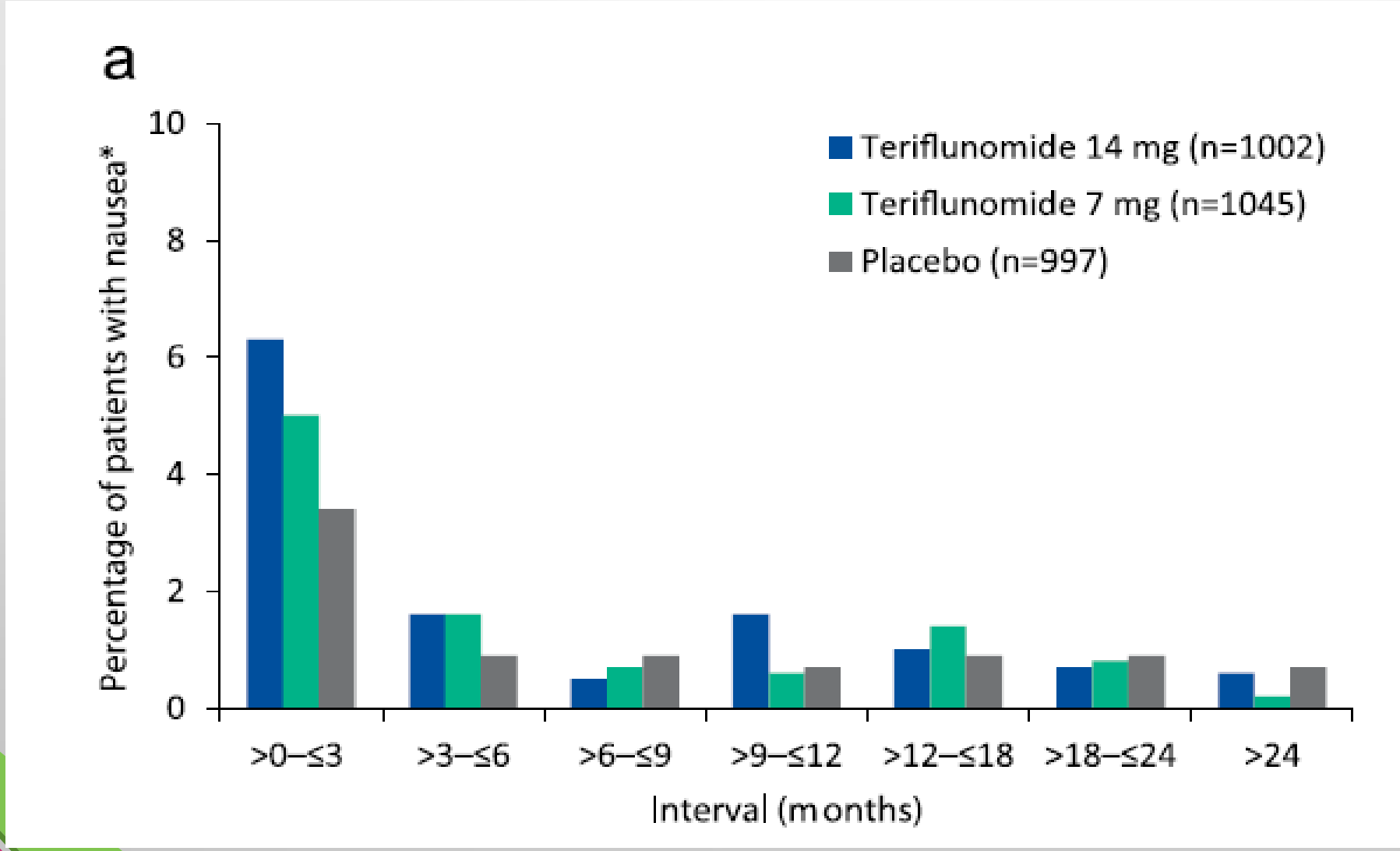
- Peripheral neuropathy
- Elevated blood pressure
- Neutropenia, and lymphopenia (transitory during the first 3–6 months of therapy)

Hair Thinning

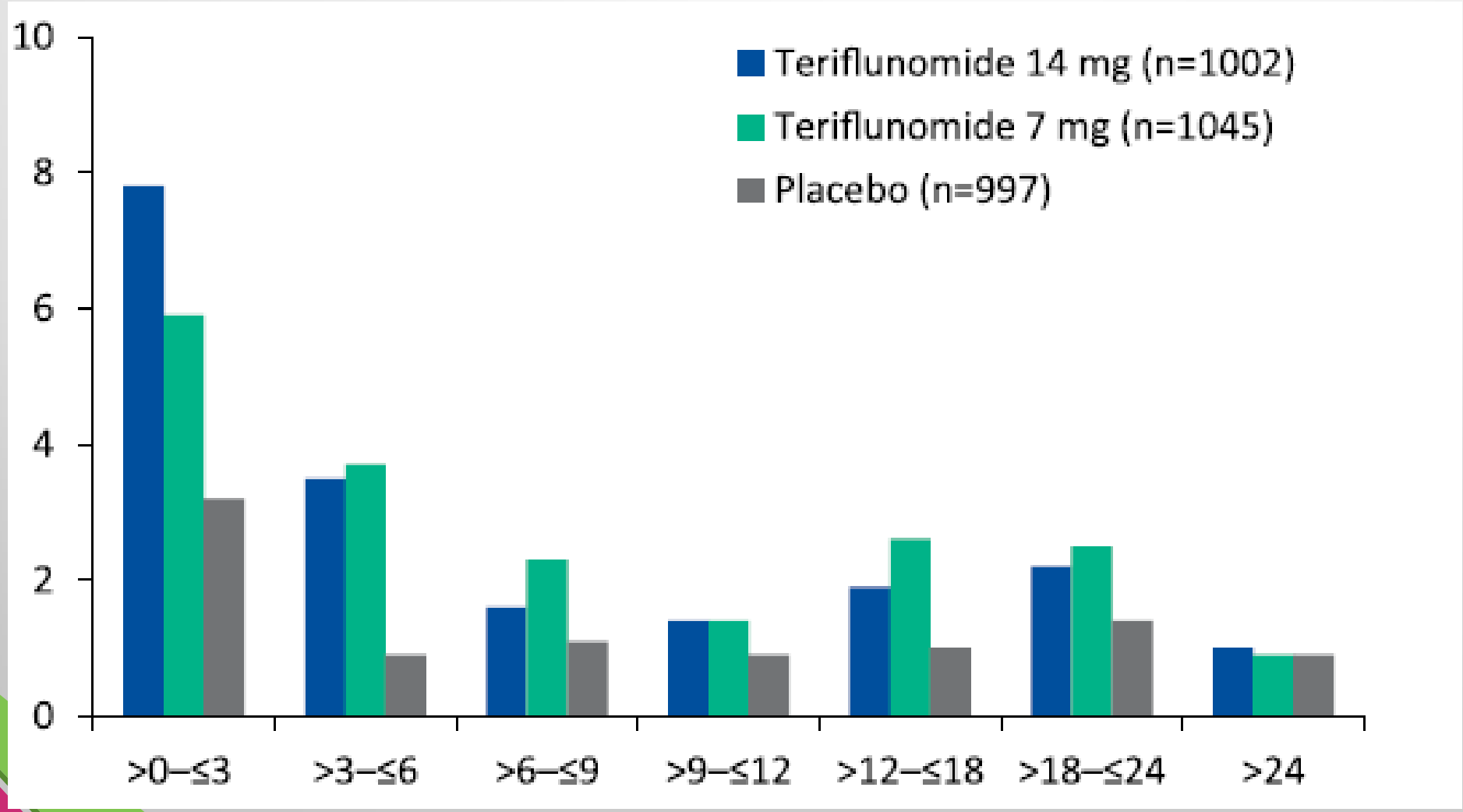


- Hair thinning occur in **only 13% of patients** taking Teriflunomide 14 mg
- Most cases were **mild to moderate**
- Occurred during the **first 6 months**, and resolved on study treatment

Neusea


a
Percentage of patients with nausea*
10
8
6
4
2
0
Teriflunomide 14 mg (n=1002)
Teriflunomide 7 mg (n=1045)
Placebo (n=997)
>0–≤3
>3–≤6
>6–≤9
>9–≤12
>12–≤18
>18–≤24
>24
Interval (months)

Diarrhea


10
8
6
4
2
0
Teriflunomide 14 mg (n=1002)
Teriflunomide 7 mg (n=1045)
Placebo (n=997)
>0–≤3
>3–≤6
>6–≤9
>9–≤12
>12–≤18
>18–≤24
>24

Hepatotoxicity

- Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) greater than two times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with Teriflunomide.
- ALT greater than three times the ULN occurred in (5%) of patients on 14 mg
- These elevations occurred mostly within the first year of treatment
- Half of the cases returned to normal without drug discontinuation

Hepatic injury

- If liver injury is suspected, discontinue teriflunomide and start an accelerated elimination procedure and monitor liver tests weekly until normalized.

- Human plasma concentrations of teriflunomide less than 0.02 mg/L (0.02 mcg/mL) are expected to have minimal risk.

Bone Marrow Effects

- A mean decrease in WBC count of approximately 15% (mainly neutrophils and lymphocytes).
- Platelet count of approximately 10%
- Occurred during the first 6 weeks and WBC count remained low during treatment
- Neutrophil count < 1500/L in 15%
- lymphocyte count <800/L in 10% of patients

Risk of Infection / Tuberculosis Screening

- Patients with **active acute or chronic infections should not** start treatment until the infection(s) is resolved

- If a patient develops a serious infection consider suspending treatment and using an accelerated elimination procedure

- No overall increase in the risk of serious infections was observed with Teriflunomide 7 mg (1.4%) or 14 mg (2.2%) compared to placebo (2.1%). However, one fatal case of klebsiella pneumonia sepsis occurred in a patient taking teriflunomide 14 mg for 1.7 years

Tuberculosis

- In clinical studies with Teriflunomide, cases of tuberculosis have been observed
- Prior to initiating, screen patients for latent tuberculosis infection with a tuberculin skin test.
- It has not been studied in patients with a positive tuberculosis screen, and the safety in individuals with latent tuberculosis infection is unknown.
- For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy.

Peripheral Neuropathy

- Incidence of peripheral neuropathy including both polyneuropathy and Mononeuropathy (carpal tunnel syndrome) confirmed by nerve conduction studies was 1.4%

May increase the risk for peripheral neuropathy

- Age older than 60 years
- Concomitant neurotoxic medications
- Diabetes

BP Monitoring

- HTN was reported as an adverse reaction in 4%-20% of patients
- Systolic and/or diastolic
- Check blood pressure before starting treatment and periodically thereafter
- Elevated blood pressure should be appropriately managed during treatment

Acute Renal Failure

- In placebo-controlled trials, 10 of 844 (1.2%) of AUBAGIO-treated subjects had transient acute renal failure with a creatinine measurement increased by 100% or more of their baseline serum creatinine value, compared to 0 of 421 placebo-treated subjects.
- Seven of the 10 subjects had a nadir creatinine clearance less than 30 cc/minute. In each of the 10 subjects, the serum creatinine level was normal on the next reported measurement (6-48 days from the increase in creatinine) with continued teriflunomide use.
- These increased creatinine measurements occurred between 12 weeks and 2 years after first dose of teriflunomide

Hyperkalemia

- Two teriflunomide-treated subjects had hyperkalemia >7.0 mmol/L with acute renal failure
- Check serum potassium level in AUBAGIO-treated patients with symptoms of hyperkalemia or with acute renal failure.

Skin Reactions

- Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients with rheumatoid arthritis receiving leflunomide.
- A similar risk would be expected for teriflunomide
- If a patient develops any of these conditions, stop therapy and perform an accelerated elimination procedure

Vaccination and malignancy

- Vaccination with live vaccines is not recommended
- There was no increased risk of malignancy with Teriflunomide treatment

- **Use in men**

The risk of male-mediated embryo-fetal toxicity through Teriflunomide treatment is considered low

- **Use in pregnancy (category x)**

Its recommended that women of childbearing potential only receive Teriflunomide after it has been confirmed that they are using a reliable form of contraceptive

- **Lactation**

Teriflunomide is not known whether excreted in human milk (decision should be made whether to discontinue nursing or to discontinue the drug)

Switching to TF

- No waiting period is required when initiating Teriflunomide after IFNb or GA, provided there are no laboratory abnormalities
- For other drugs consider case by case, Based on the half-life of Fingolimod, a 6-week interval is needed for clearance from the circulation, and a period of 1–2 months is commonly needed for lymphocytes to return to normal range
- Caution is required when switching patients from Natalizumab to Teriflunomide

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Procedure for Accelerated Elimination

- Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mg/L
- Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days.
- Use of the accelerated elimination procedure may potentially result in return of disease activity if the patient had been responding to treatment

Clinical trial of Teriflunomide

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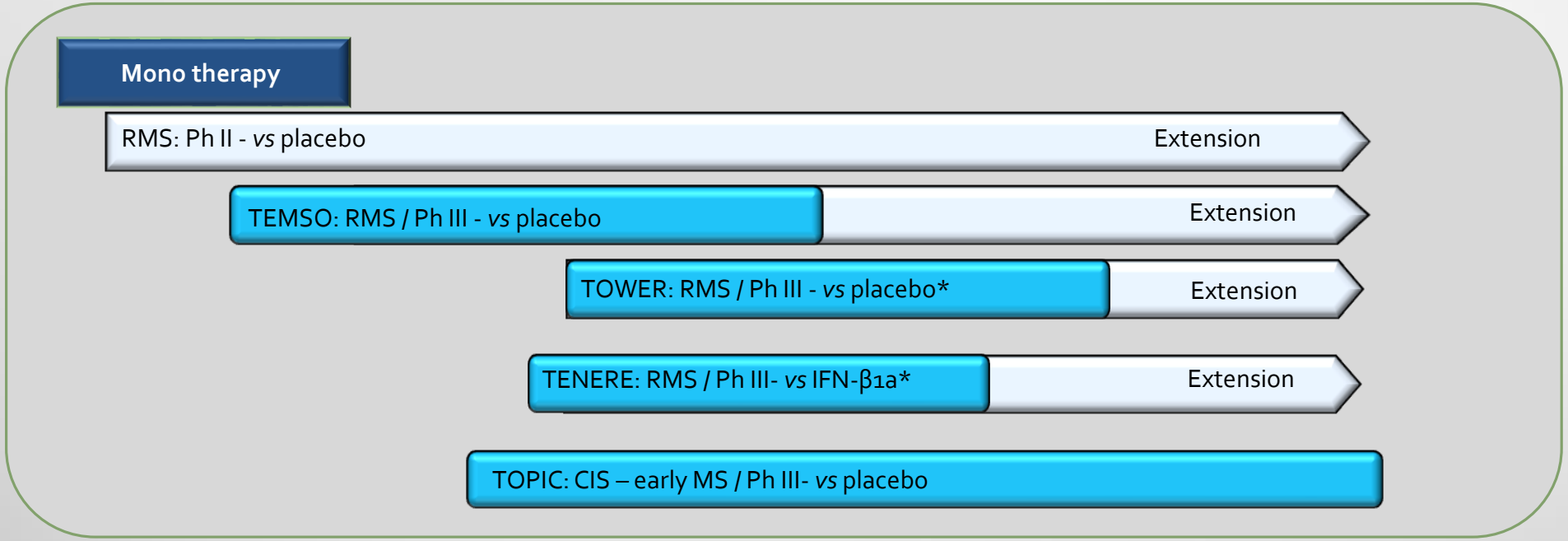
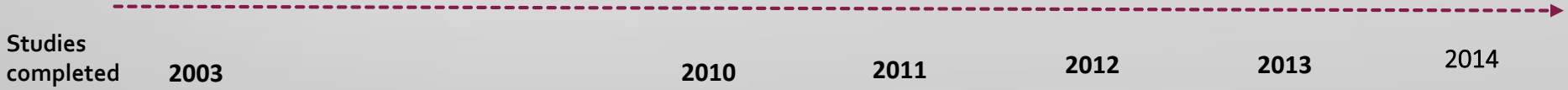
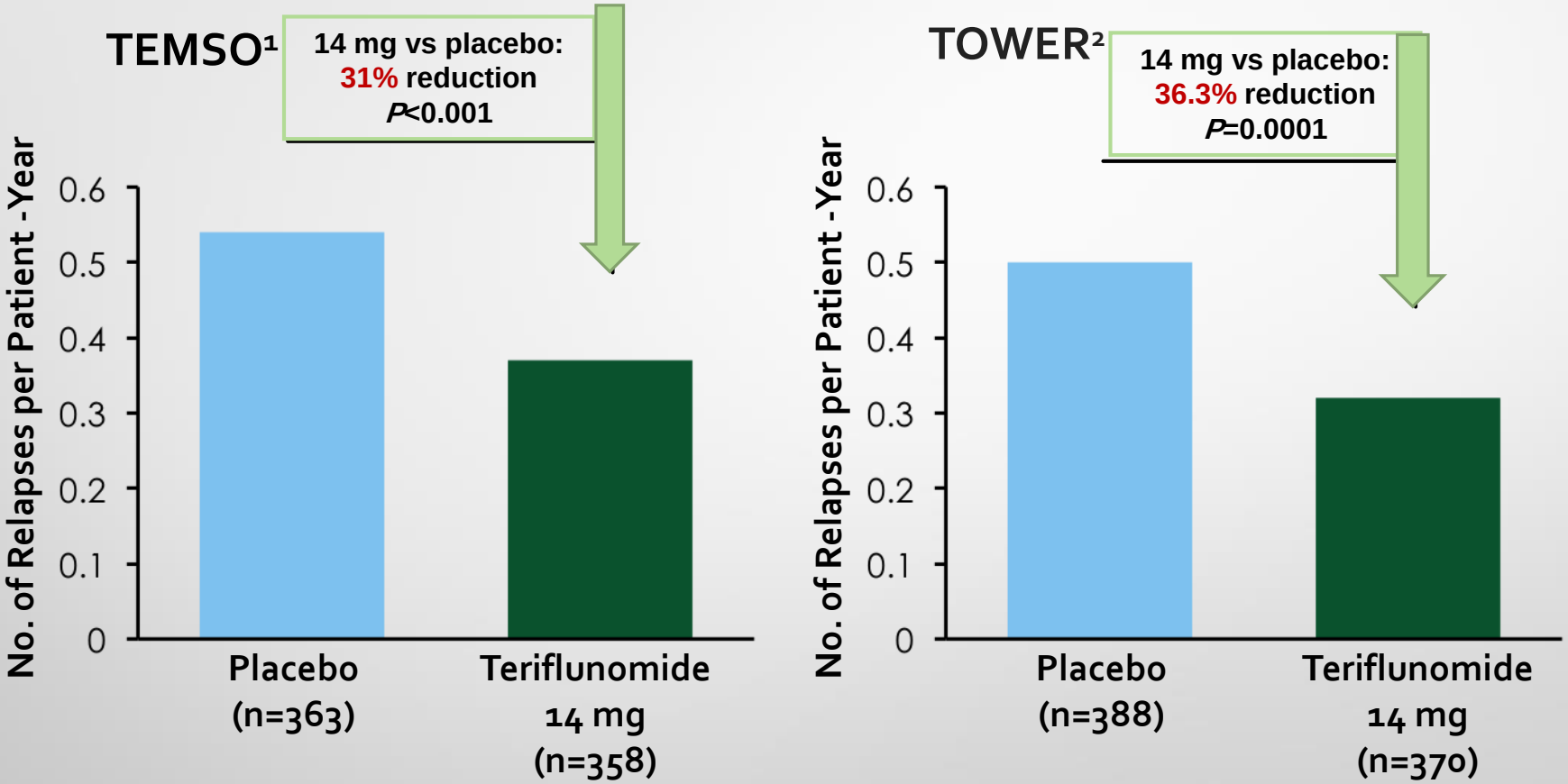
Teriflunomide: Clinical Trials





* Extensions ongoing for TOWER and TENERE.
CIS, clinically isolated syndrome; GA, glatiramer acetate; IFN, interferon

Annualized Relapse Rate (ARR)



*The rate was derived from an analysis of the number of relapses with the use of a Poisson regression model adjusted for treatment and score on the EDSS at baseline and for geographic region and the log of time during treatment serving as an offset variable.

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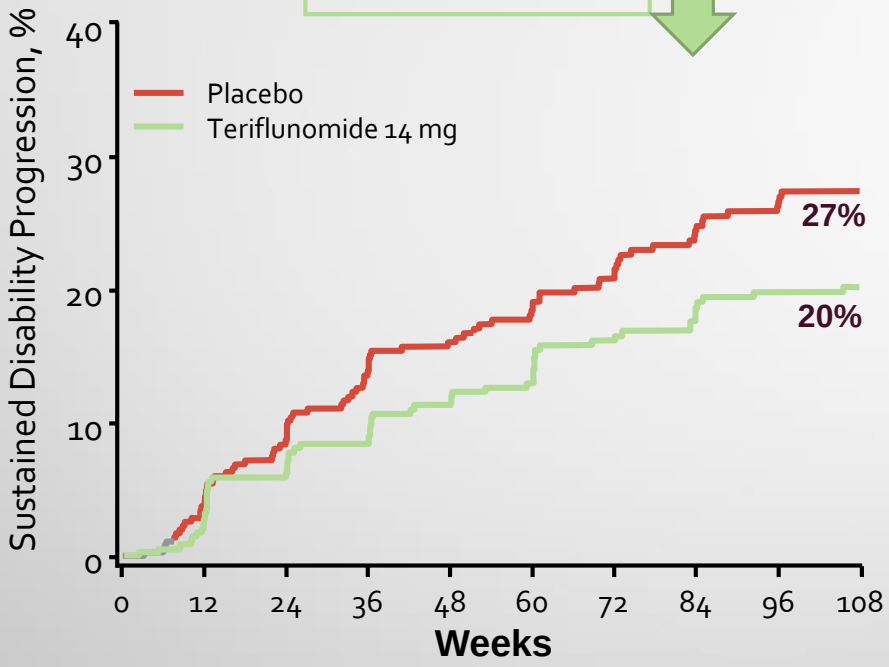
1. O'Connor P, et al. *N Eng J Med.* 2011;365:1293-1303. 2. Confavreux C, et al. *Lancet Neurol.* 2014;13:247-256

Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial

12-Week Confirmed Disability Progression

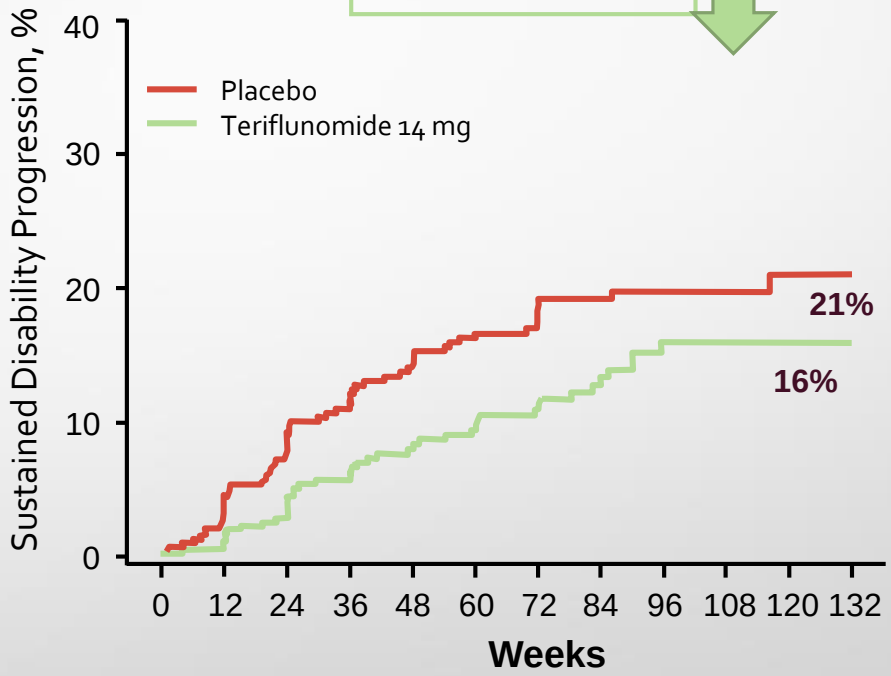
TEMSO[1]

14 mg vs placebo:
30% RRR
***P*=0.03**



TOWER[2]

14 mg vs placebo:
32% RRR
***P*=0.044**

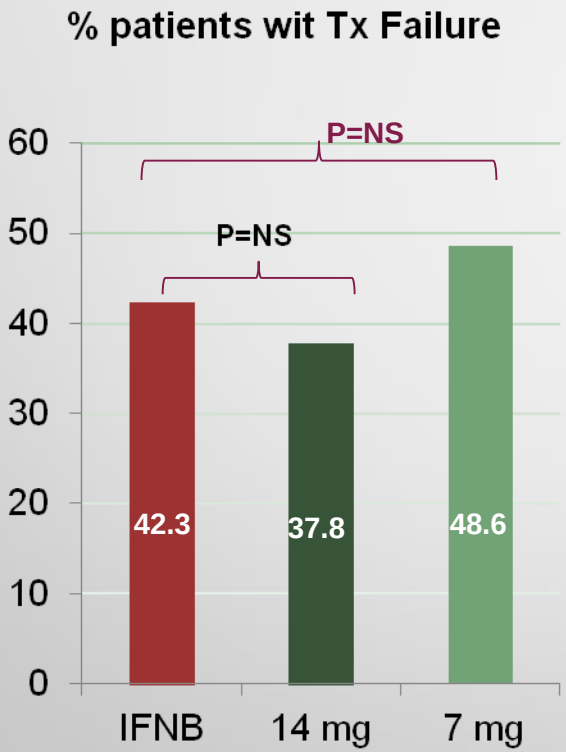


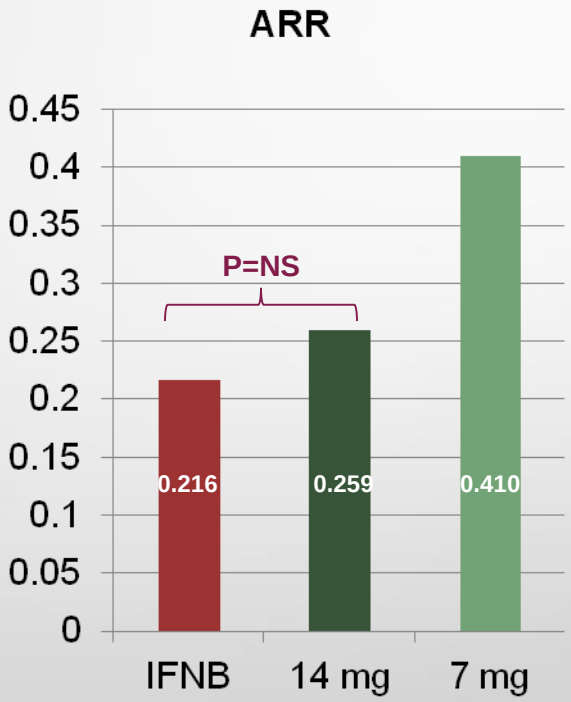
RRR = relative risk reduction.
*Sustained disability progression was defined as at least a 1-point increase from baseline EDSS score ≤5.5 (or at least a 0.5-point increase for those with a baseline EDSS score >5.5) sustained for at least 12 weeks.

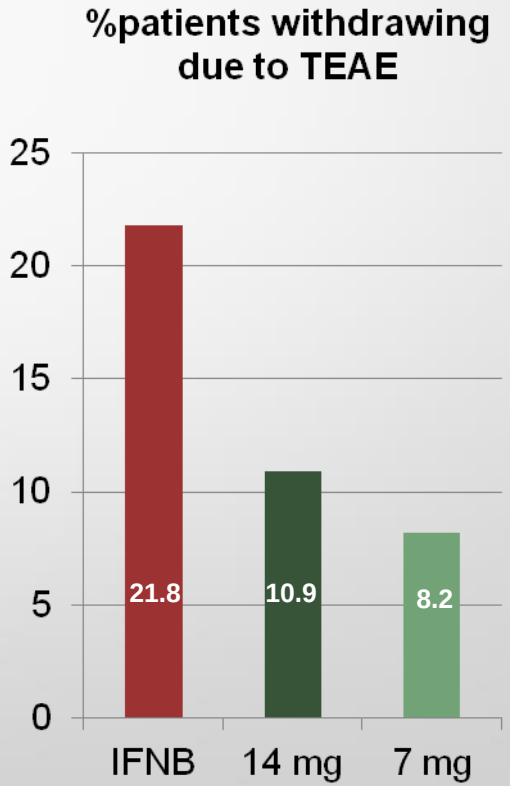
1. O'Connor P, et al. *N Eng J Med*. 2011;365:1293-1303. 2. Confavreux C, et al. *Lancet Neurol*. 2014;13:247-256.

TENERE (Phase III Trial)

Patients reported greater treatment satisfaction and less fatigue with Teriflunomide than with IFNb







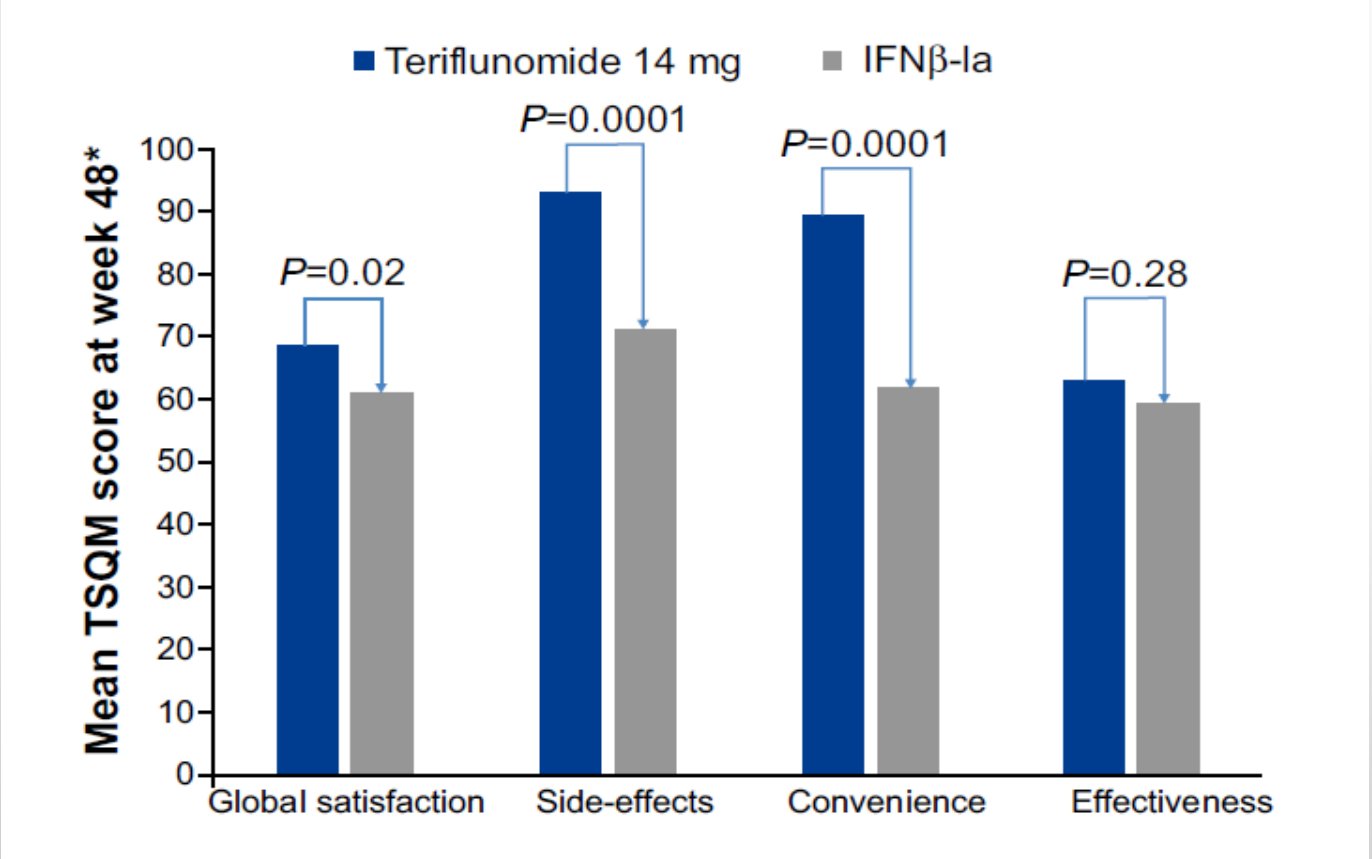
- Primary end point : Treatment failure (Defined as occurrence of relapse or withdrawal from study due to treatment emergent adverse event (TEAE) or any other cause)
- Secondary end point : Annualized relapse rate

Genzyme Press Release; December 20, 2011

Patient Preference and Adherence
Dovepress
open access to scientific and medical research
Open Access Full Text Article
REVIEW

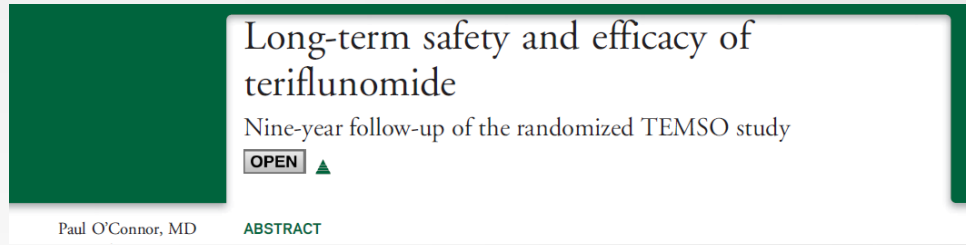
Teriflunomide for the treatment of relapsing–remitting multiple sclerosis: patient preference and adherence

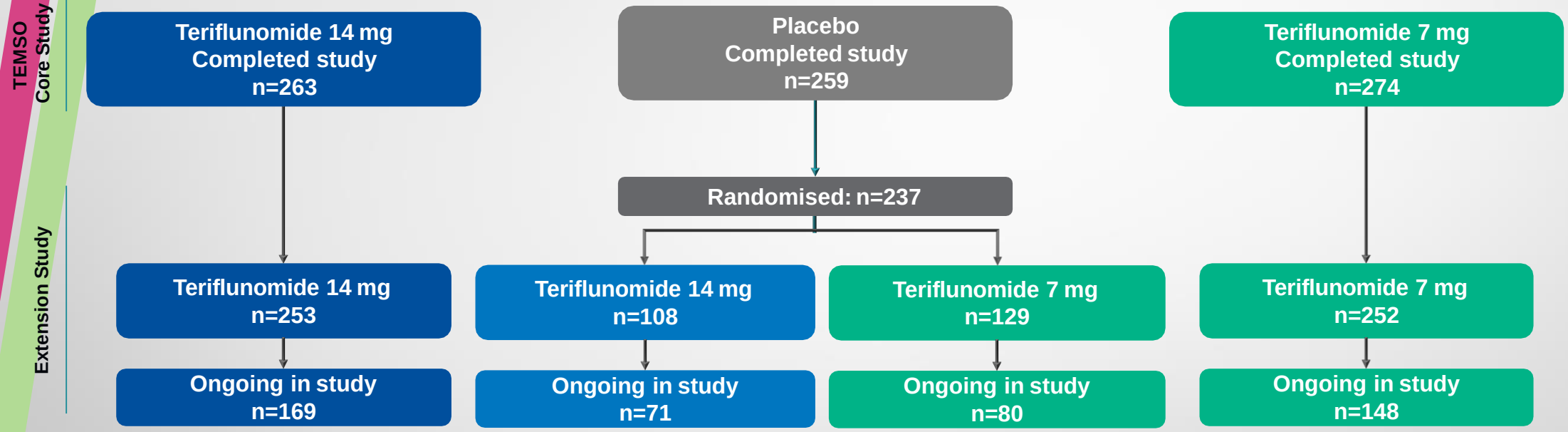
This article was published in the following Dove Press journal:
Patient Preference and Adherence
9 February 2015
Number of times this article has been viewed



Treatment satisfaction at week 48 was significantly improved with teriflunomide 14 mg compared with sc IFNβ-1a in the TSQM domains of global satisfaction, side-effects, and convenience.

TEMSO Extension: Patient Disposition



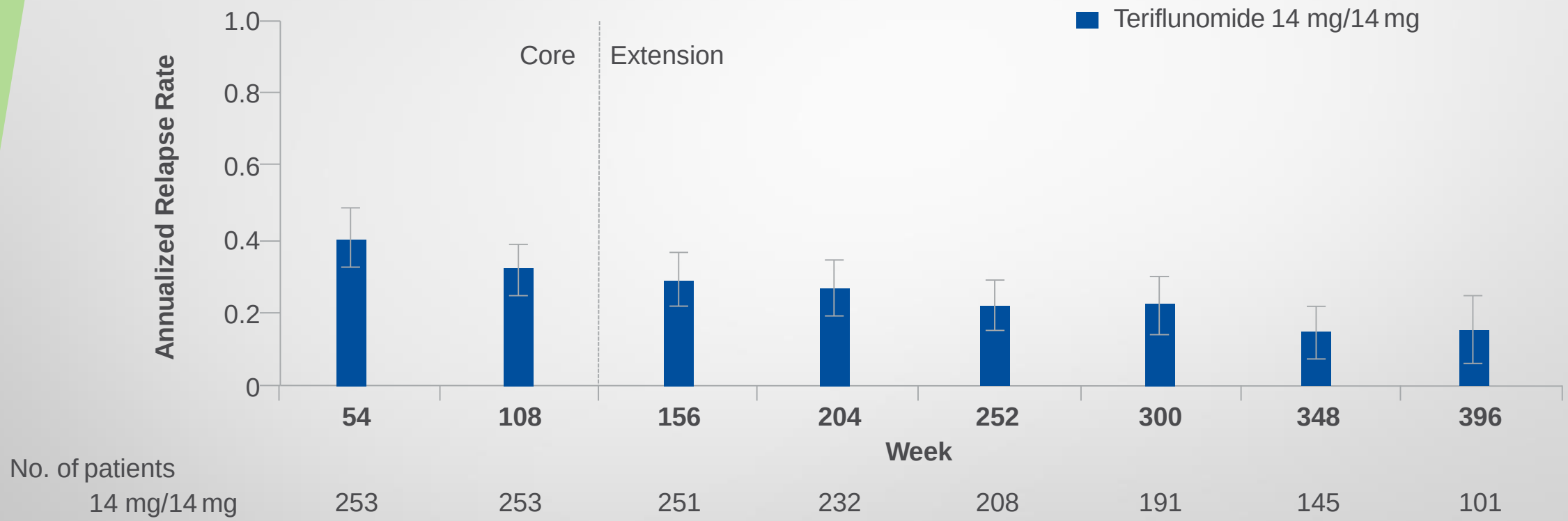


Out of the 742 patients that opted into the extension study, 468 (63%) remained in the study up to 9 years (core plus 7 years of the extension study)

O'Connor et al Neurology 2016, Epub

TEMSO Extension: ARR up to 8 Years

ARR remained low throughout the extension



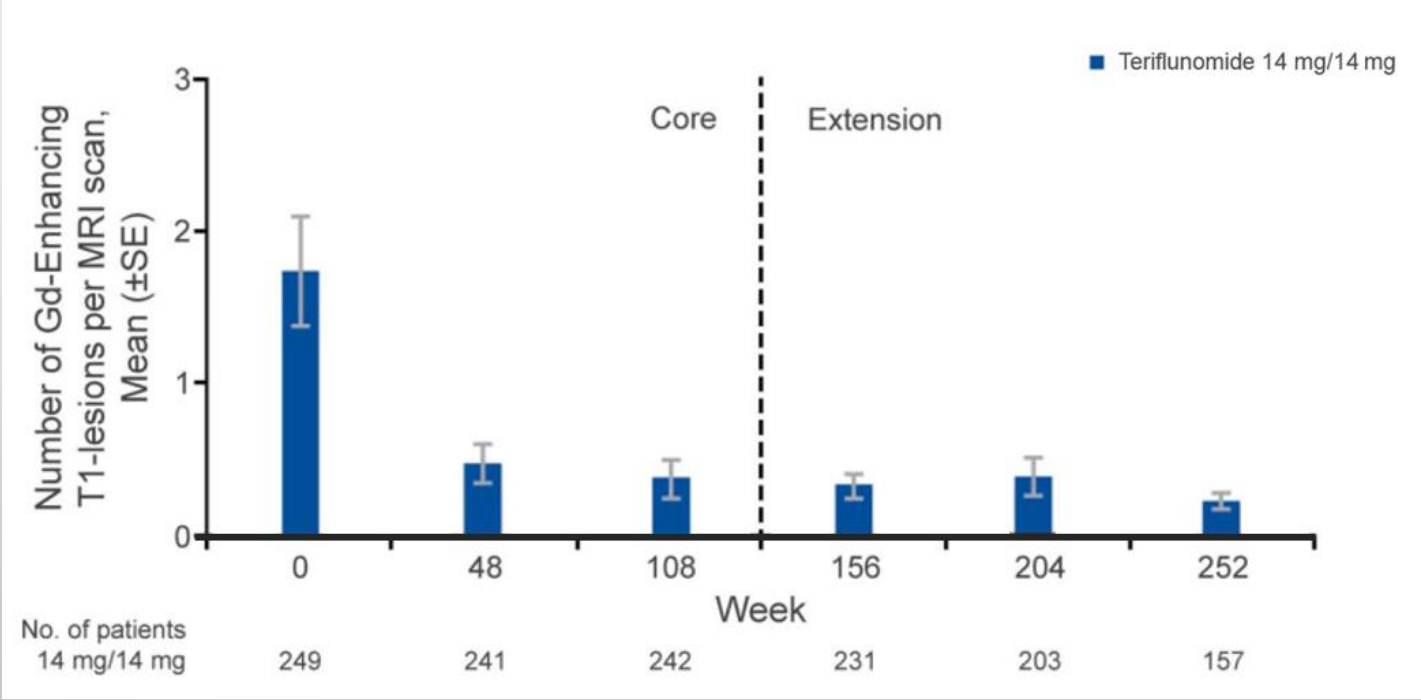
No. of patients								
14 mg/14 mg	253	253	251	232	208	191	145	101

Modified intent-to-treat population. “Week” refers to time since start of core study: Week 108 is the end of the core study/start of the extension study. Error bars show 95% confidence intervals. O’Connor et al., *Neurology* 2016. Epub ahead of print

TEMSO Extension: Nember of Gd-enhancing T1 lesions

- A decrease in the mean number of Gd-enhancing T1 lesions for the group of patients who received placebo in the core study as they switched to Teriflunomide in the extension

- Most patients (80%) did not have Gd-enhancing T1 lesions during the study



Long-term safety and efficacy of teriflunomide

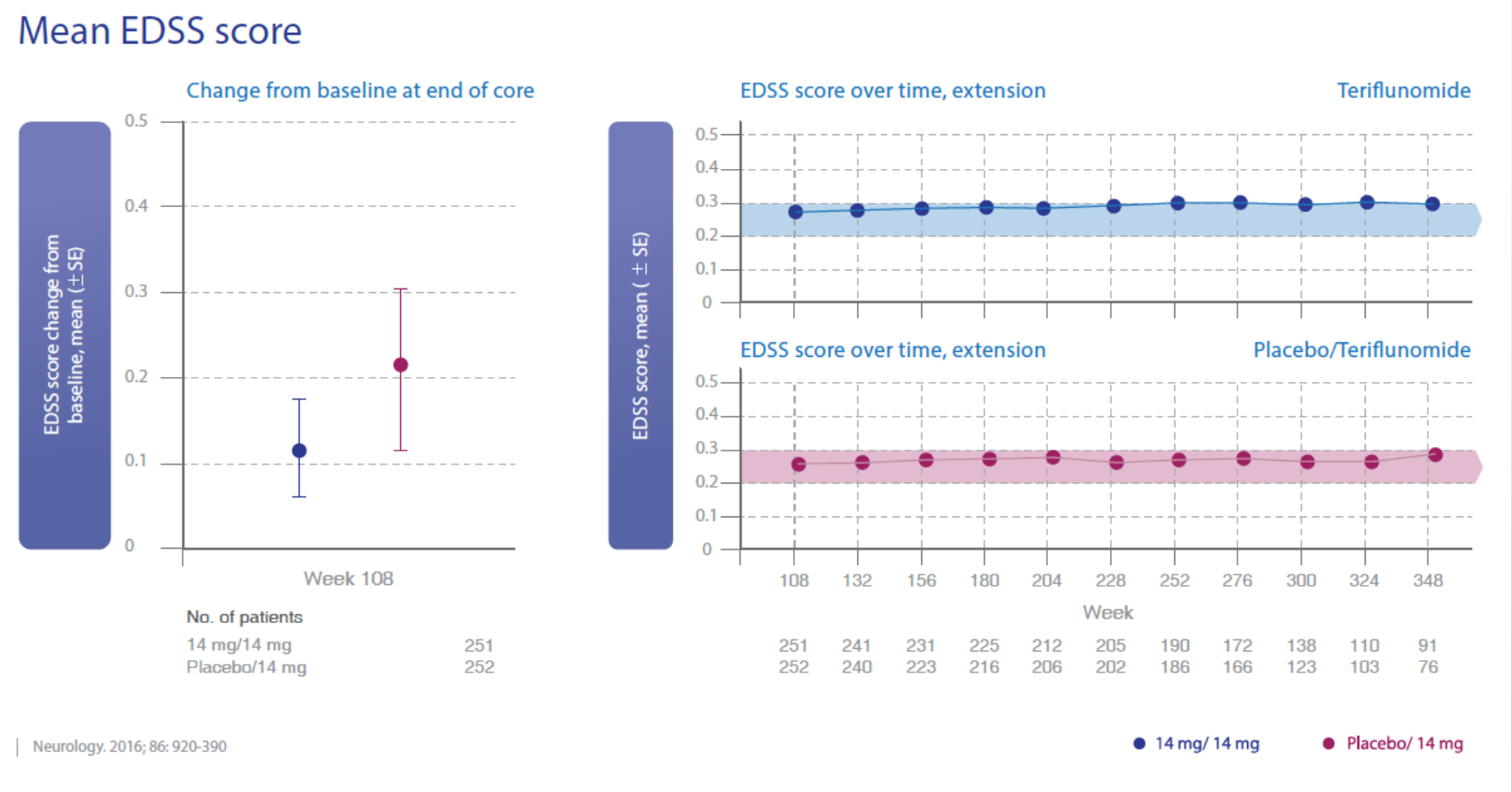
Nine-year follow-up of the randomized TEMSO study

OPEN

Paul O'Connor, MD

ABSTRACT

Efficacy of Teriflunomide is maintained with long-term treatment



Neurology. 2016; 86: 920-390

Effect of Teriflunomide on severe relapses

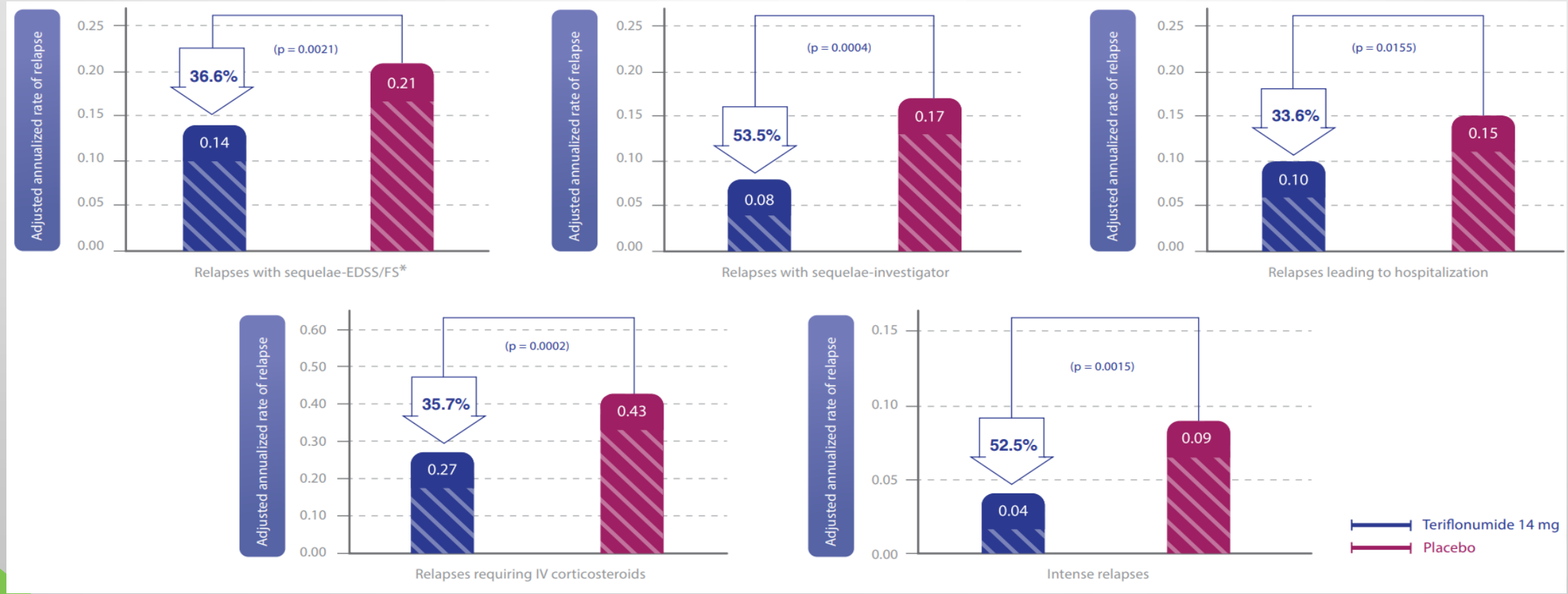
J Neurol
DOI 10.1007/s00415-014-7395-7

ORIGINAL COMMUNICATION

Teriflunomide reduces relapses with sequelae and relapses leading to hospitalizations: results from the TOWER study

Aaron E. Miller · Richard Macdonell · Giancarlo Comi · Mark S. Freedman · Ludwig Kappos · Mathias Mäurer · Tomas P. Olsson · Jerry S. Wolinsky · Sylvie Bozzi · Catherine Dive-Pouletty · Paul W. O'Connor

Teriflunomide demonstrates consistent and beneficial outcomes on relapses with sequelae and relapses requiring healthcare resources

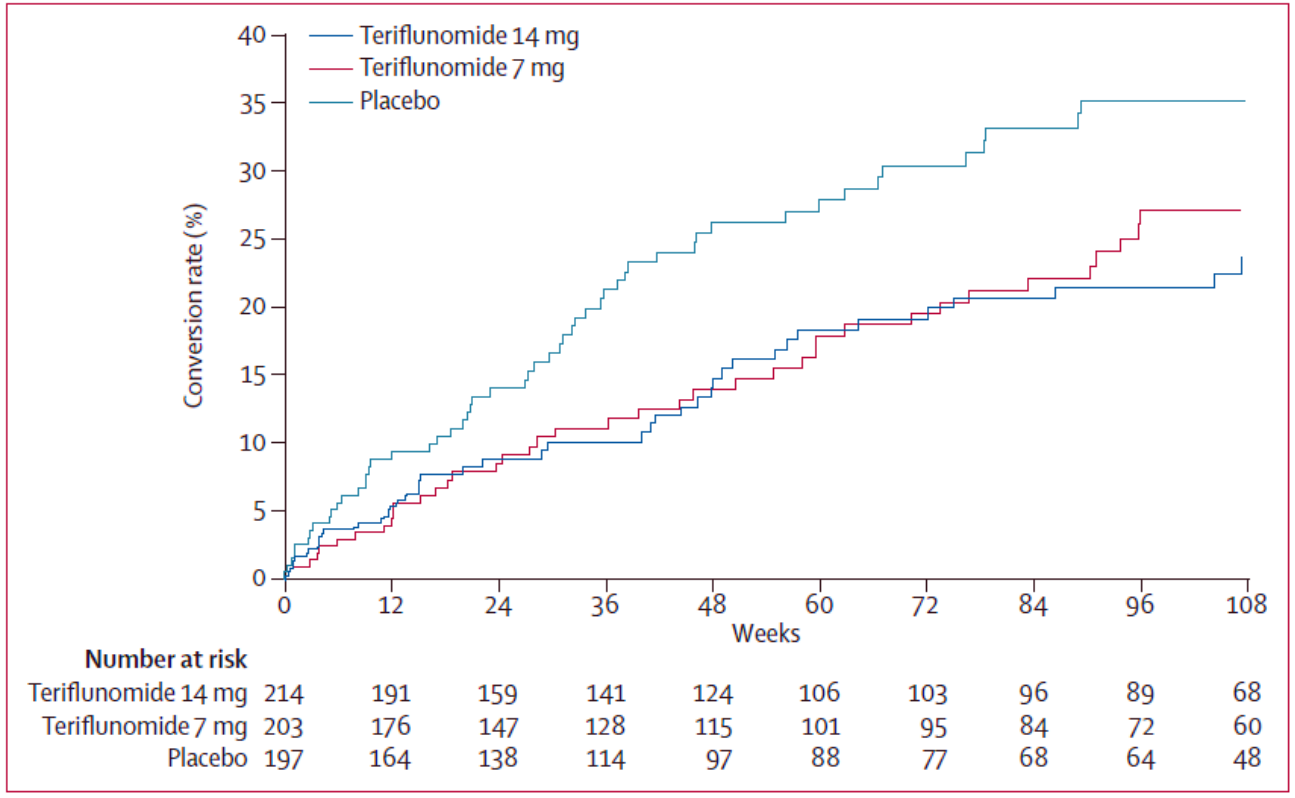


Topic study

- Compared with placebo, Teriflunomide **significantly reduced** the risk of relapse defining clinically definite multiple sclerosis at the 14 mg dose (hazard ratio [HR] 0.574) and at the 7 mg dose (0.628)

Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial

*Aaron E Miller, Jerry S Wolinsky, Ludwig Kappos, Giancarlo Comi, Mark S Freedman, Tomas P Olsson, Deborah Bauer, Myriam Benamor, Philippe Truffinet, Paul W O'Connor, for the TOPIC Study Group**



summary

- Teriflunomide acts selectively and reversibly on DHODH to decrease proliferation of T and B autoreactive lymphocytes

- Teriflunomide was found to be an effective first-line therapy option for patients who are:

✓ Newly diagnosis

✓ Switching from other DMTs

✓ Changing therapy because of side effects of current treatment

✓ Dissatisfied with current treatment

- Teriflunomide is the only oral DMT that shows significant reduction in 12-week disability worsening in 2 phase III trials

- Efficacy of Teriflunomide is maintained with long-term treatment

- Teriflunomide has a favorable benefit risk profile for relapsing MS patient

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