When should disease-modifying treatments be discontinued in patients with multiple sclerosis?

An evidence-based review with expert recommendations.

Learning objective

- To understand the factors relevant to the decision of whether a patient should continue or discontinue their disease modifying treatment.
- To understand the circumstances in which discontinuation of disease modifying treatment is reasonable to consider.

Background and Rationale

- Disease modifying therapies (DMTs) are known to modify relapse rates and progression of disability early in relapsing remitting multiple sclerosis (RRMS).

- However, it remains unknown whether DMTs continue to be effective…
  - Late in the course of relapsing remitting MS
  - In older patients
  - In secondary progressive MS

- ***Objective:*** To review the literature relevant to discontinuation of DMTs, and to provide guidance on when DMTs may be discontinued.

Methods

- MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews (current to June 2016)
- **Search terms**: Multiple Sclerosis, Disease Modifying Treatments, treatment withdrawal, stopping medication, medication withdrawal
- Additional articles were identified from reference lists, review articles and recommendations of experts in the field
- **Classification of evidence**: American Academy of Neurology guidelines

Discontinuation of DMTs

- There have been no published randomized controlled trials investigating treatment discontinuation in MS.
- Several observational studies have suggested a return to baseline disease activity following discontinuation of interferon-beta (Wu *et al.*, 2005; Siger *et al.,* 2011) or natalizumab (O'Connor *et al.,* 2011; Prosperini *et al.*, 2015)
- Other observational studies included older patients with no disease activity on DMT for several years, and suggested positive outcomes for these patients upon DMT discontinuation (Olival *et al.*, 2013; Kister *et al.*, 2015; Kister *et al.,* 2016)

Discontinuation of DMTs – Olival *et al.*, 2013

- Prospective study of 40 patients who discontinued DMTs after minimum 5 years of continuous use of a single DMT without new disease activity
- Specific DMTs were not reported
- At 46 month follow-up…
  - 90% remained free of clinical attack
  - 85% had stable MRIs

Discontinuation of DMTs – Kister *et al.*, 2015

- 303 patients (age 40+ years) who discontinued DMTs after minimum 3 years continuous use of a single DMT, with no clinical relapses in the past 5 years.
- Majority of patients resumed DMT use due to an increase in disease activity following discontinuation.
- 25% reduction in rate of restarting DMT for every 10 year increase in age.

Discontinuation of DMTs – Kister *et al.*, 2016

- 485 patients (median age 45) discontinued DMT after minimum 3 years of treatment with a single DMT and no clinical relapses in the previous 5 years.
- 854 propensity-score matched individuals continued DMT
- Mean annualized relapse rates and time to first relapse were similar for those who discontinued DMT (0.27, 1.81 years) and those who continued (0.25, 2.01 years).
- Survival time to confirmed disability progression was shorter among those who discontinued DMT.
- 25% reduction in relapse risk ratio for every 10 year increase in age

Discontinuation of DMTs

- Independent predictors of remaining free of clinical relapse following discontinuation of DMT for patients with RRMS (Bsteh *et al*., 2016):
  - Age >45 yrs
  - Absence of clinical relapses for 4 years prior to discontinuation
  - Absence of contrast enhancing lesions
- Increasing age is associated with decreased likelihood of clinical relapse following discontinuation of DMT for patients with SPMS (Birnbaum, 2017)
- Two thirds of patients who discontinued natalizumab experienced clinical relapse, compared to one third of patients who discontinued first-line DMTs (Fagius *et al.*, 2017)

Rebound syndromes

- Several observational studies have reported a rebound syndrome following discontinuation of natalizumab.
  - Miravelle *et al.*, 2011; Rasenack and Derfuss, 2016; Sorensen *et al.*, 2014; Lo Re *et al.*, 2015; Salhofer-Polanyi *et al.*, 2014; Gueguen *et al.*, 2014
- Several randomized trials and observational studies have demonstrated a return to previous disease activity levels following natalizumab discontinuation, without rebound activity.
  - Kaufman *et al.*, 2015; Stüve *et al.*, 2009; O'Connor *et al.*, 2011
- Fingolimod discontinuation has been associated with rebound activity in case studies/series.
  - Ghezzi *et al.*, 2013; Hakiki *et al.*, 2012; Havla *et al.*, 2012; Beran *et al.*, 2013; Sempere *et al.*, 2013; Alroughani *et al.*, 2014; La Mantia *et al.*, 2014; Masuda *et al.*, 2014; Berger *et al.*, 2015; Faissner *et al.*, 2015; Davion *et al.*, 2016; Hatcher *et al.*, 2016

Natural history

- Disease activity in MS decreases with increasing patient age, with fewer clinical relapses and fewer new MRI lesions.
  - (Tremlett *et al.*, 2009; Confavreux *et al.*, 2003; Kalincik *et al.*, 2013)

- Relapses have less impact on disease progression with greater time from disease onset
  - (Tremlett *et al.*, 2009)

Safety and adverse effects

- DMTs are associated with side effects and more serious adverse effects.
- A potential safety risk of natalizumab and dimethylfumarate is progressive multifocal leukoencephalopathy.
- No DMTs have been confirmed as safe for use in pregnancy or breastfeeding

Proposed discontinuation guidelines

Discontinuation of DMTs is reasonable under the following circumstances:

1. Patients with SPMS who have ongoing progression and no new brain or spinal MRI lesions during the prior 12-24 months.

2. Patients with stable RRMS, age ≥65 years, who have had no new brain or spinal MRI lesions during the prior 12-24 months.

3. Patients with stable RRMS, age 55-65 years, who have had no new brain or spinal MRI lesions during the prior five years.

4. Patients who are pregnant, trying to conceive or breastfeeding.

Further directions

- Randomized controlled trial of discontinuation of DMTs in a low risk patient population
- Patients with stable relapsing remitting multiple sclerosis who are greater than 55 years of age, and have had no new brain or spinal MRI lesions during the previous five years.

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