Poster DX36

Characterizing the Natalizumab "Wearing Off" Effect

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Background

- Natalizumab (Tysabri®, Biogen Idec) is a selective alpha-4 integrin antagonist that inhibits leukocyte migration into the central nervous system (CNS).
- Many clinicians who use natalizumab are aware of a "wearing off" effect (WOE) experienced by patients between infusions.
  - Specifically, patients frequently describe transient increased fatigue, malaise, constitutional symptoms, or worsening of baseline MS symptoms in the days prior to their infusion.

Objective

- To characterize the prevalence and clinical features of the natalizumab WOE in our patient population.

Methods

- A cross-sectional observational study was performed over a 3-month period.
- All patients being treated at the MS Center at St. Elizabeth's who received a minimum of 6 doses of natalizumab were given a questionnaire during their infusion to assess the presence, timing, and duration of WOE symptoms.

Results

- A total of 89 patients were surveyed.
- The population surveyed consisted of 72% with relapsing-remitting MS (RRMS) and 28% with secondary progressive MS (SPMS).
  - 75% were female and 25% were male
  - Mean age = 46 years
- Natalizumab dosage regimen:
  - 82% received natalizumab every 4 weeks
  - 10% received natalizumab every 6 weeks
  - 8% received natalizumab every 8 weeks
- 61% of patients reported symptoms consistent with WOE (Table 1).
  - Fatigue was the most prominent symptom reported.
  - 72% of SPMS patients compared with 56% of RRMS patients experienced WOE.
- Most symptoms were mild-moderate in severity; however, 12% reported ≥1 severe symptom (Table 2).
- Onset of WOE began an average of 5.5 days prior to an infusion and almost always resolved within 2 days after an infusion (Figure 1).
- Most patients reported onset of symptoms 4-9 days prior to their dose, regardless of the dosing interval (Figure 1).

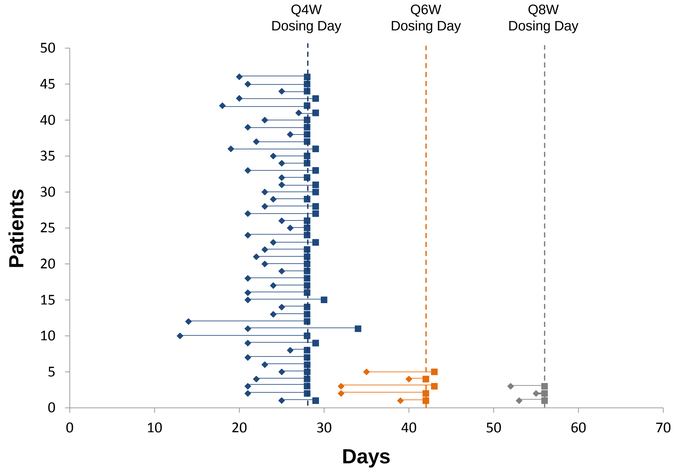
Table 1. Frequency of WOE Symptoms

Fatigue	**94%**
Myalgias/arthralgias	**70%**
Malaise	**59%**
Worsening of MS symptoms	**57%**
Other symptoms	**50%**

Table 2. Symptom Frequency and Timing Based on Dosing Frequency

		Dose Frequency		
	Total (n=89)	**Q4W (n=73)**	**Q6W (n=9)**	**Q8W (n=7)**
% with symptoms	61%	63%	56%	43%
Of those with symptoms, % with symptoms every dose	76%	78%	60%	67%
Average onset (no. of days before dose)	5.5	5.6	6.4	2.7
Average duration (days)	6.5	6.7	7.2	2.7
% with ≥1 severe symptom	12%	10%	33%	14%

Figure 1. Temporal Relationship of WOE Symptoms and Natalizumab Dosing*



*Diamond indicates onset of WOE symptoms and square indicates resolution of WOE symptoms. Each line represents a unique patient.

Discussion

- The natalizumab WOE occurred in nearly two-thirds of this patient group and has been widely observed by other clinicians.
- The most common symptoms were a combination of mild to moderate fatigue, myalgias/arthralgias, and malaise.
- The onset of WOE occurred in the week prior to dosing, with an average duration of 5 to 6 days. Almost all patients had complete resolution of symptoms within 2 days of treatment, and in many, symptoms disappeared during the infusion or later the same day.
- Patients were somewhat less likely to experience WOE as the time between infusions increased (Table 2), but interestingly, symptoms began in the week prior to their infusion, regardless of the dosing interval.
- WOE was slightly more frequent in patients with SPMS (72%) compared with RRMS (56%).
- The main mechanism of action of natalizumab is presumed to be the reduction of migration of lymphocytes into the CNS.
- Other reported effects include altered levels of interleukins 17, 13, 10, osteoptin, and matrix metalloproteinase in the cerebrospinal fluid (CSF) and peripheral white blood cells.[1]
- Treatment with natalizumab has been shown to lower CSF levels of TNFα and INFγ when measured after 12 months,[2] but it is not clear how cytokine levels vary throughout the dosing cycle.
- A possible cause of WOE might be fluctuating CSF cytokine levels prior to each natalizumab dose.
- It is possible that WOE is a placebo/anti-placebo effect, but the consistency in character and timing of reported symptoms across patients suggests otherwise.

Conclusions

- The natalizumab wearing off effect (WOE) is frequently observed but remains poorly understood.
- For many patients, WOE causes significant discomfort and distress, sometimes generating concern of a possible MS relapse or the onset of PML.
- Reducing the impact of WOE would improve natalizumab tolerance and have a significant impact on patients' quality of life.
- Further studies of the causes and frequency of WOE are indicated.

References

1. Khademi M, et al. Eur J Neurol. 2008; 15:309-312.
2. Khademi M, et al. Eur J Neurol. 2009; 16:528-536.