Clinical relevance of natalizumab tests for multiple sclerosis

Theo Rispens
Multiple Sclerosis

In multiple sclerosis the myelin sheath, which is a protective membrane that wraps around the axon of a nerve cell is destroyed with inflammation and scarring.

Main symptoms of Multiple sclerosis:

Central:
- Fatigue
- Cognitive impairment
- Depression
- Unstable mood

Visual:
- Nystagmus
- Optic neuritis
- Diplopia

Speech:
- Dysarthria

Throat:
- Dysphagia

Musculoskeletal:
- Weakness
- Spasms
- Ataxia

Sensation:
- Pain
- Hypoesthesia
- Paraesthesias

Bowel:
- Incontinence
- Diarrhea or constipation

Urinary:
- Incontinence
- Frequency or retention

Sanquin
Treatment of (relapsing-remitting) MS

1\textsuperscript{st} line
- IFN-\(\beta\) (Avonex, Rebif, Betaferon)
- Glatiramer acetate (Copaxone)

2\textsuperscript{nd} line
- natalizumab (Tysabri)
- fingolimod (Gilenya)
Natalizumab is effective treatment of relapsing-remitting MS

A Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis

David H. Miller, M.D., Omar A. Khan, M.D., William A. Sheremata, M.D., Lance D. Blumhardt, M.D., George P.A. Rice, M.D., Michele A. Libonati, M.S., Allison J. Willimer-Hulme, Ph.D., Catherine M. Dalton, M.B., Katherine A. Miszkiel, M.B., and Paul W. O’Connor, M.D., for the International Natalizumab Multiple Sclerosis Trial Group

Figure 1. Cumulative Mean Number of New Gadolinium-Enhancing Lesions on MRI in Each Group during Treatment.

Figure 2. Kaplan–Meier Plots of the Time to Sustained Progression of Disability among Patients Receiving Natalizumab, as Compared with Placebo.
Natalizumab reduced the risk of sustained progression of disability by 42 percent over two years (hazard ratio, 0.58; 95 percent confidence interval, 0.43 to 0.77). The cumulative probability of progression was 17 percent in the natalizumab group and 29 percent in the placebo group.
Natalizumab

natalizumab is an effective drug, but:

• expensive
• can be immunogenic
• associated with rare but life-threatening side effects
Natalizumab

IgG4 antibody
Directed against α4-integrin (VLA-4)
Interferes with lymphocyte migration across blood-brain barrier

Y. Yu et al. JBC 2013
Natalizumab: IgG4

Fab arm exchange:

\[ \text{natalizumab} \times \text{serum IgG4} \]

\[ \text{anti-lambda} \]

VLA-4

Measurement of natalizumab levels

Rispens et al., Anal Biochem 2011
Measuring natalizumab levels II

Background signals: Fc-Fc binding (I):

Eliminated using anti-idiotype F(ab’2) (II)

Rispens et al. J Immunol 2009; Rispens et al., Anal Biochem 2011
Measurement of natalizumab levels II

- rab. anti-natalizumab
- anti-IgG4
- natalizumab
- serum IgG4

OD vs IgG (ng/ml)

Rispens et al., Anal Biochem 2011
Measurement of natalizumab levels II

natalizumab (mg/l)

Rispens et al., Anal Biochem 2011
Clinical relevance of natalizumab concentration

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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>73</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>80.8%</td>
</tr>
<tr>
<td>Age at start natalizumab (years)</td>
<td>37 (8.0)</td>
</tr>
<tr>
<td>Disease duration at start natalizumab (months)</td>
<td>112 (72)</td>
</tr>
<tr>
<td>Previous DMT last two years (n, %)</td>
<td></td>
</tr>
<tr>
<td>Interferon-beta (IFN-β)</td>
<td>51 (69.9%)</td>
</tr>
<tr>
<td>Glatiramer-acetate (GA)</td>
<td>14 (19.2%)</td>
</tr>
<tr>
<td>IFN-β + GA</td>
<td>6 (8.2%)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td><strong>Annualized relapse rate (ARR)</strong></td>
<td></td>
</tr>
<tr>
<td>Within 12 months before natalizumab</td>
<td>1.26 (0.93)</td>
</tr>
<tr>
<td>Within 24 months before natalizumab</td>
<td>1.48 (0.68)</td>
</tr>
<tr>
<td><strong>EDSS at start natalizumab (median, IQR)a</strong></td>
<td>4.0 (2.5)</td>
</tr>
<tr>
<td>0–3.5 (n, %)</td>
<td>26 (37.1%)</td>
</tr>
<tr>
<td>≥4.0 (n, %)</td>
<td>44 (62.9%)</td>
</tr>
<tr>
<td><strong>Magnetic resonance imaging at start natalizumab (n, %)</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;9 T2 hyper intense lesions at baseline (n=73)</td>
<td>72 (98.6%)</td>
</tr>
<tr>
<td>Gadolinium enhancing lesions at baseline (n=71) b</td>
<td>45 (63.4%)</td>
</tr>
<tr>
<td><strong>Follow up duration during natalizumab (n, %)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>6 (8.2%)</td>
</tr>
<tr>
<td>1 year</td>
<td>36 (49.3%)</td>
</tr>
<tr>
<td>2 years</td>
<td>16 (21.9%)</td>
</tr>
<tr>
<td>3 years</td>
<td>15 (20.6%)</td>
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</tbody>
</table>
natalizumab: clinic vs PK

low serum natalizumab concentrations (< 1 μg/ml):

- 14.5 × higher odds ratio to develop Gd+ lesions (95% CI 2.2–96.4, p=0.006)
- 9.0 × higher odds ratio to have a relapse (95% CI 1.7–47.9, p=0.01)

Vennegoor et al., Mult. Sclerosis 2013
Anti-drug antibodies (ADA) to natalizumab assays:
bridging elisa (drug-sensitive)
antigen binding test (drug tolerant)
Antibodies to natalizumab at 12, 24, and 52 weeks

Vennegoor et al., Mult. Sclerosis 2013
correlation between anti-natalizumab antibodies and serum natalizumab concentration at week 24

(Spearman’s Rho −0.765, p<0.001)

Vennegoor et al., Mult. Sclerosis 2013
natalizumab: clinic vs ADA

Vennegoor et al., Mult. Sclerosis 2013
natalizumab: ADA vs PK in time naive patients

Unpublished data available upon request (t.rispens@sanquin.nl)
natalizumab: ADA vs PK in time
patients > 6 months

Unpublished data available upon request (t.rispens@sanquin.nl)
# Antibodies to Natalizumab: Assay Issues

<table>
<thead>
<tr>
<th>Study</th>
<th>ADA Incidence</th>
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<tbody>
<tr>
<td>Calabresi et al. <em>Neurology</em> 2007</td>
<td>9%</td>
</tr>
<tr>
<td>Lundkvist et al. <em>Multiple Sclerosis</em> 2012</td>
<td>4.1%</td>
</tr>
<tr>
<td>Oliver-Martos et al. <em>J. Neurology</em> 2013</td>
<td>15.7%</td>
</tr>
<tr>
<td>Vennegoor et al. <em>Multiple Sclerosis</em> 2013</td>
<td>58%</td>
</tr>
</tbody>
</table>

- Reported incidences of ADA vary widely
- Due in part to differences in assay technology
- In general, ADA assays difficult to standardize
- Measurement of drug levels circumvents this problem
Natalizumab and PML

Progressive multifocal leuкоencephalopathy (PML) is an opportunistic demyelating brain disease

Caused by JC virus

Ca. 30 – 80% of the general population is infected

Impaired cellular immunity, including natalizumab treatment, is associated with PML

Total reported cases of PML (Mar 2014): 439
Total deceased: 99
**Natalizumab and PML**

Table 1: Estimated PML Incidence Stratified by Risk Factor

<table>
<thead>
<tr>
<th>Tysabri Exposure†</th>
<th>Anti-JCV Antibody Positive*</th>
<th>Anti-JCV Antibody Positive*</th>
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<tbody>
<tr>
<td></td>
<td>No Prior Immunosuppressant Use</td>
<td>Prior Immunosuppressant Use</td>
</tr>
<tr>
<td>1-24 months</td>
<td>&lt;1/1,000</td>
<td>2/1,000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>4/1,000</td>
<td>11/1,000</td>
</tr>
</tbody>
</table>

*Anti-JCV Antibody Positive*

†Tysabri exposure refers to the duration of exposure to Natalizumab (Tysabri).

http://www.fda.gov/Drugs/DrugSafety/ucm288186.htm
Natalizumab and PML

Natalizumab has half-life of ca. 11 days to restore leucocyte transmigratory capacity swiftly, natalizumab levels can be decreased using plasma exchange (PLEX)

(Khatri et al. Neurology 2009)
A serum natalizumab concentration below 1 μg/ml results in VLA-4 desaturation.

Figure 2: Relationship between serum natalizumab concentration and α4-integrin saturation.

The steady-state correlation between serum natalizumab concentration (log scale) and α4-integrin saturation in plasma exchange (PLEX) patients is shown. At serum natalizumab concentrations below 1.0 μg/mL, there is reliable α4-integrin desaturation. To allow for re-equilibration, only data points ≥24 hours after each PLEX session are shown.
Monitoring natalizumab concentrations during plasma exchange (PLEX)

Efficiency of PLEX varies between patients

Monitoring of natalizumab concentrations can aid in optimizing PLEX

Unpublished data available upon request (t.rispens@sanquin.nl)
Conclusions

Natalizumab concentrations correlate with relapse and are inversely correlated with antibodies to natalizumab.

Many patients make antibodies; in many cases, antibody formation is transient.

Measurement of natalizumab concentrations can be a tool to optimize treatment of MS patients.

Monitoring natalizumab concentrations can help to optimize treatment intervention during PML.
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