Natalizumab (Tysabri, Antegren)

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Mechanism of Action

- Humanized IgG4κ monoclonal antibody against α4- integrin
- block interaction between the α4β7 integrin and addressin, VCAM-1 on vascular endothelial cells, and with CS-1and/or osteopontin expressed by parenchymal cells in the brain (MAdCAM-1 on gut endothelial cells)

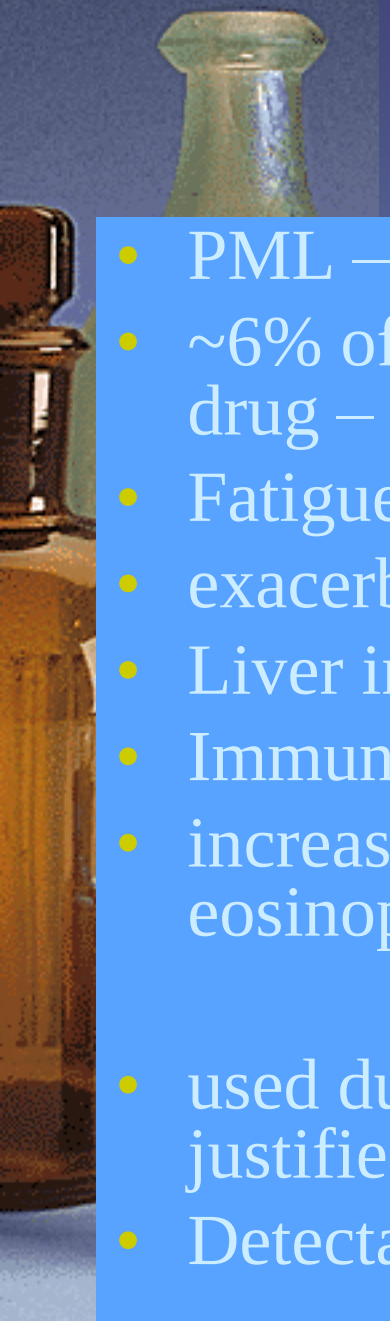
Pharmacodynamics

- half-life:11 ± 4 days,
- volume of distribution: 5.7 ± 1.9 L,
- Clearance: 16 ± 5 mL/hour,
- maximum observed serum concentration: 110 ± 52 mcg/mL
- Mean average steady-state trough concentrations ranged from 23 mcg/mL to 29 mcg/mL

Indication / Dosing

- Multiple Sclerosis – monotherapy for highly active relapsing remitting MS despite standard tx
  - reduce relapses in individuals with MS by 68% vs. placebo
- Crohn's Disease – unresponsive to TNFα block
  - Increases remissions and maintain symptom free status

- 300 mg infused intravenously over approximately one hour, every four weeks
- must be administered within 8 hours of preparation



Adverse Effects

- PML – when in combination with interferon β-1a
- ~6% of individuals develop persistent antibodies to the drug – low risk of anaphylaxis
- Fatigue, headache, nausea
- exacerbation of Crohn's disease
- Liver injury
- Immunosuppression/infection
- increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells

- used during pregnancy only if the potential benefit justifies the potential risk to the fetus
- Detectable in breast milk

References

- *en.wikipedia.org/wiki/Natalizumab*
- *http://www.tysabri.com/en_US/tysb/site/pdfs/TYSABRI-pi.pdf*

Clinical Trials - MS

- two randomized, double-blind, placebo-controlled trials in patients with multiple sclerosis. Both studies enrolled patients who experienced at least one clinical relapse during the prior year and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.0
- primary endpoint at 2 years was time to onset of sustained increase in disability, defined as an increase of at least 1 point on the EDSS from baseline EDSS $\geq$ 1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS=0 that was sustained for 12 weeks

Table 4. Clinical and MRI Endpoints in Study MS1 (Monotherapy Study) at 2 Years

	TYSABRI n=627	Placebo n=315
Clinical Endpoints		
Percentage with sustained increase in disability	17%	29%
Relative Risk Reduction	42% (95% CI 23%, 57%)	
Annualized relapse rate	0.22	0.67
Relative reduction (percentage)	67%	
Percentage of patients remaining relapse-free	67%	41%
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	5.0
Percentage of patients with*:		
0 lesions	57%	15%
1 lesion	17%	10%
2 lesions	8%	8%
3 or more lesions	18%	68%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with:		
0 lesions	97%	72%
1 lesion	2%	12%
2 or more lesions	1%	16%

All analyses were intent-to-treat. For each endpoint, $p<0.001$. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS and age; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

Annualized relapse rate is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

*Values do not total 100% due to rounding.

Table 5. Clinical and MRI Endpoints in Study MS2 (Add-On Study) at 2 Years

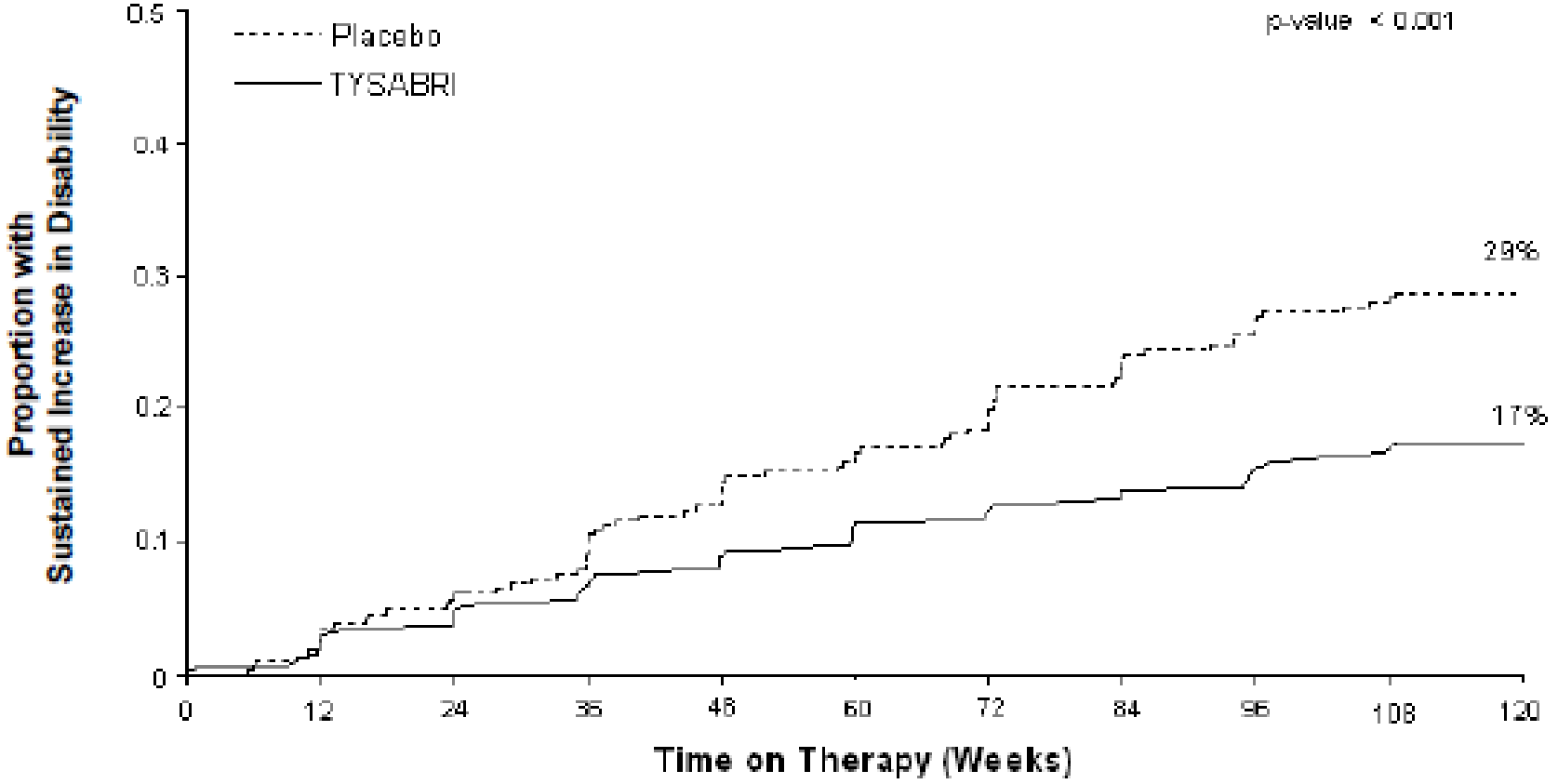
	TYSABRI plus AVONEX n=589	Placebo plus AVONEX n=582
Clinical Endpoints		
Percentage with sustained increase in disability	23%	29%
Relative Risk Reduction	24% (95% CI 4%, 39%)	
Annualized relapse rate	0.33	0.75
Relative reduction (percentage)	56%	
Percentage of patients remaining relapse-free	54%	32%
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	3.0
Percentage of patients with*:		
0 lesions	67%	30%
1 lesion	13%	9%
2 lesions	7%	10%
3 or more lesions	14%	50%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with*:		
0 lesions	96%	75%
1 lesion	2%	12%
2 or more lesions	1%	14%

All analyses were intent-to-treat. For disability accumulation $p=0.024$, for all other endpoints, $p<0.001$. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

Annualized relapse rate is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

*Values do not total 100% due to rounding.

Figure 1. Time to Increase in Disability Sustained for 12 Weeks in Study MS1



Clinical Trials - CD

- three randomized, double-blind,placebo-controlled clinical trials in 1414 adult patients with moderately to severely activeCrohn's disease
- Concomitant inhibitors of TNF-α were not permitted
- Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunosuppressants (e.g., 6-mercatopurine, azathioprine, or methotrexate) were permitted, and 89% of patients continued to receive at least one of these medications

Table 6. Induction of Clinical Response and Remission in Study CD2

	TYSABRI n=259	Placebo n=250	Treatment Difference (95% CI)
Clinical Response at:			
Week 8	56%	40%	16% (8%, 26%)
Week 12	60%	44%	16% (7%, 25%)
Both Weeks 8 & 12*	48%	32%	16% (7%, 24%)
Clinical Remission at:			
Week 8	32%	21%	11% (3%, 19%)
Week 12	37%	25%	12% (4%, 21%)
Both Weeks 8 & 12*	26%	16%	10% (3%, 18%)

*p <0.005
Response is defined as a ≥70-point reduction in CDAI score from baseline.
Remission is defined as CDAI <150.

Table 7. Maintenance of Clinical Response and Remission in Study CD3

	TYSABRI	Placebo	Treatment Difference (95% CI)
	n=164	n=167	
Clinical Response through:			
Month 9*	61%	29%	32% (21%, 43%)
Month 15	54%	20%	34% (23%, 44%)
	n=128†	n=118†	
Clinical Remission through:			
Month 9*	45%	26%	19% (6%, 31%)
Month 15	40%	15%	25% (13%, 36%)

*p<0.005
†Number of patients included for analysis of "through" Month 9 and Month 15 includes only those in remission upon entry into Study CD3.
Response is defined as CDAI <220 and a ≥70-point reduction in CDAI score compared to Baseline from Study CD1.
Remission is defined as CDAI <150.