

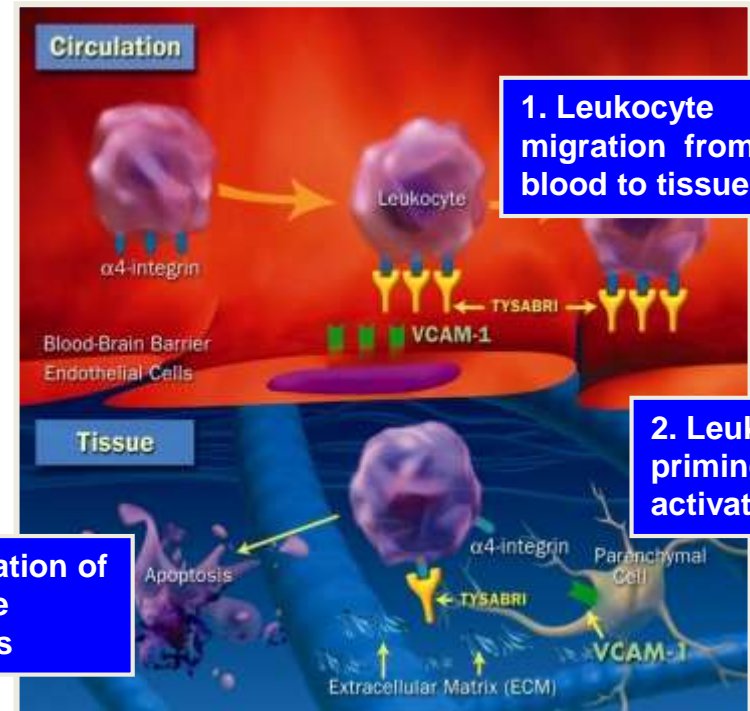
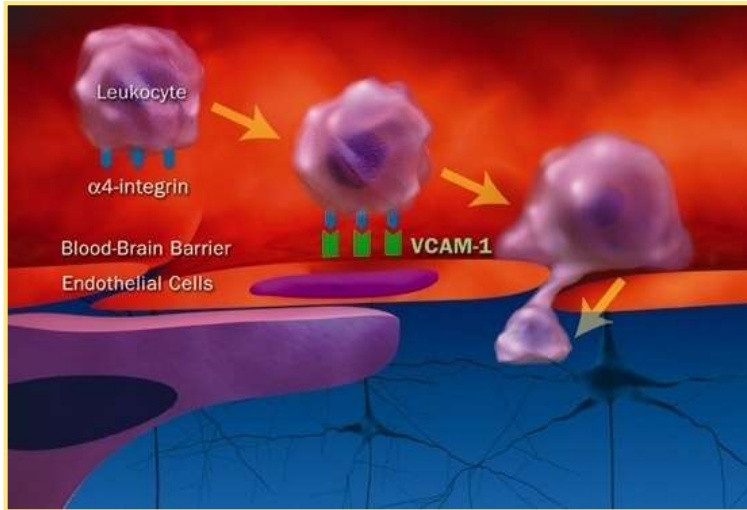
Natalizumab Audit

August 2007 - November 2010

Dr Hina N Abbasi

Natalizumab

- Natalizumab is a humanized monoclonal antibody that binds α 4-integrin, an adhesion molecule, on the surface of activated T-cells and other mononuclear leukocytes which play a pivotal role in the inflammatory pathogenesis of MS
- Natalizumab, by binding to α 4-integrin blocks the interaction of this adhesion molecule to its receptor vascular cell adhesion molecule – 1 (VCAM-1) and subsequently inhibits the migration of inflammatory cells across the blood brain barrier
- Inhibits Leukocyte priming and activation
- Modulation of Leukocyte apoptosis



1. Leukocyte migration from blood to tissue

2. Leukocyte priming and activation

3. Modulation of leukocyte apoptosis

Lobb RR et al. *J Clin Invest.* 1994;94:1722-1728 Cannella B et al. *Ann Neurol.* 1995;37:424-435. TYSABRI SmPC; Yednock TA et al. *Nature.* 1992;356:63-66

Natalizumab

- Following two pivotal studies (SENTINEL study; AFFIRM study) Natalizumab was approved for use in patients with relapsing remitting MS by the U.S Food and Drug Administration in 2004.
- It was subsequently withdrawn from market in 2005 after it was linked to three cases of Progressive Multifocal Leukoencephalopathy (PML) including two patients receiving it for MS and one patient receiving it for Crohn's disease.
- Both MS patients received Tysabri for over 2 years in addition to IFN-1a.
- The Crohn's patient received eight doses of Tysabri over 18 months and was also on Azothioprine.
- One MS and one Crohn's patient died.

Natalizumab

- Natalizumab was re-licensed as a single disease modifying treatment in July 2007 for two groups of patients
 - Patients who have failed on a full and adequate course of a beta-interferon/copaxone (normally one year of treatment). Patients should have at least 1 relapse in the previous year while on therapy, and have at least 9T2 hyper intense lesions on cranial MRI or at least 1 Gad-enhancing lesion.
 - Patients with rapidly evolving severe relapsing remitting MS defined by 2 or more disabling relapses in one year, and 1 or more Gad-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI.

- As of December 01, 2016, there have been 698 confirmed PML cases worldwide
- As of September 30, 2016, approximately 161,300 patients received natalizumab in post-marketing setting worldwide.

Efficacy of Natalizumab

68%

reduction in relapse rate vs placebo over 2 years ($p < 0.001$)

54%

reduction in the risk of EDSS progression, sustained for 24 weeks, as assessed over 2 years ($p < 0.001$)

28%

of patients free from **all** of the following measures of disease activity: relapses, Gd+ lesions, T1 weighted hypointense and T2 weighted hyperintense lesions and disability progression at 2 years ²

ITT Population

Other adverse effects

- Opportunistic infections including PML
- Allergic reactions 4%
- Anaphylactic reactions <1%
- Infusion reactions (dizziness, nausea, urticaria, rigors) 23%
- Abnormal liver enzymes, hyperbilirubinaemia, jaundice.
- Headache, dizziness, nausea, vomiting, arthralgia, rigors, fatigue
- Anti-natalizumab antibodies (6%)

Natalizumab Audit

Southern General Hospital

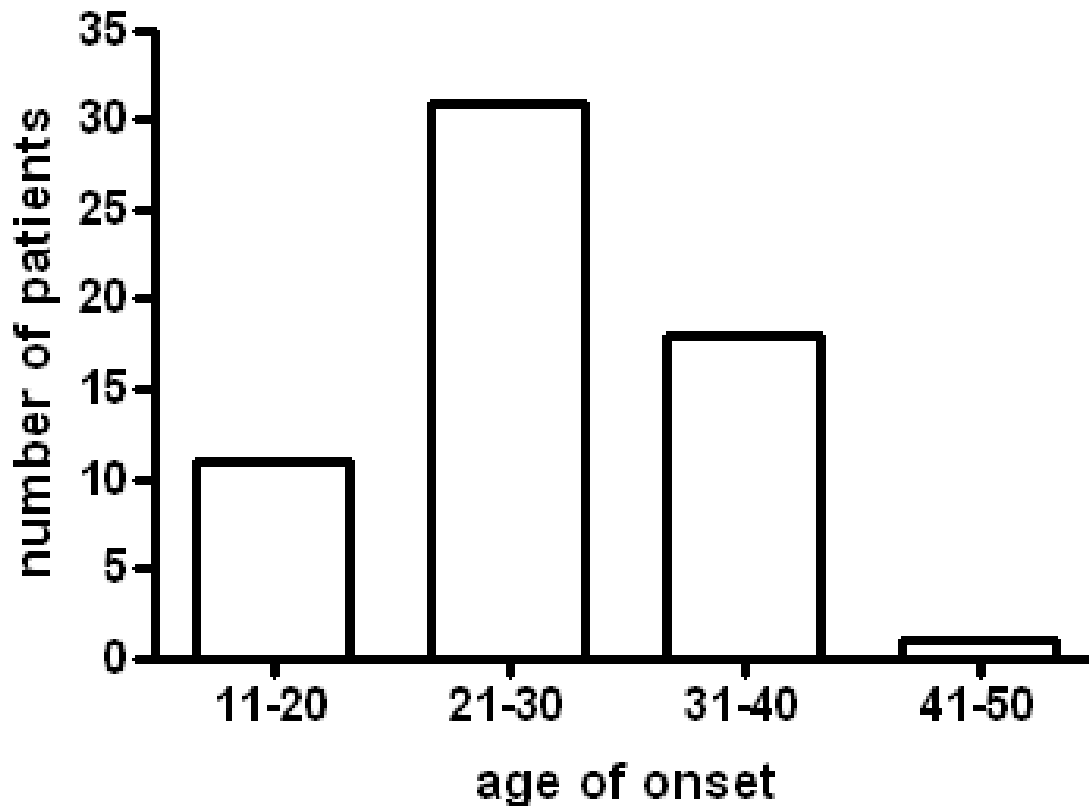
August 2007 – November 2010

Age/Sex

- Total 61 Patients
- Female 43
- Male 18
- Mean age 33
- Range 17 – 51 year

Age of onset of disease

- Minimum 14
- Maximum 43
- mean 26.8



Type of presentation

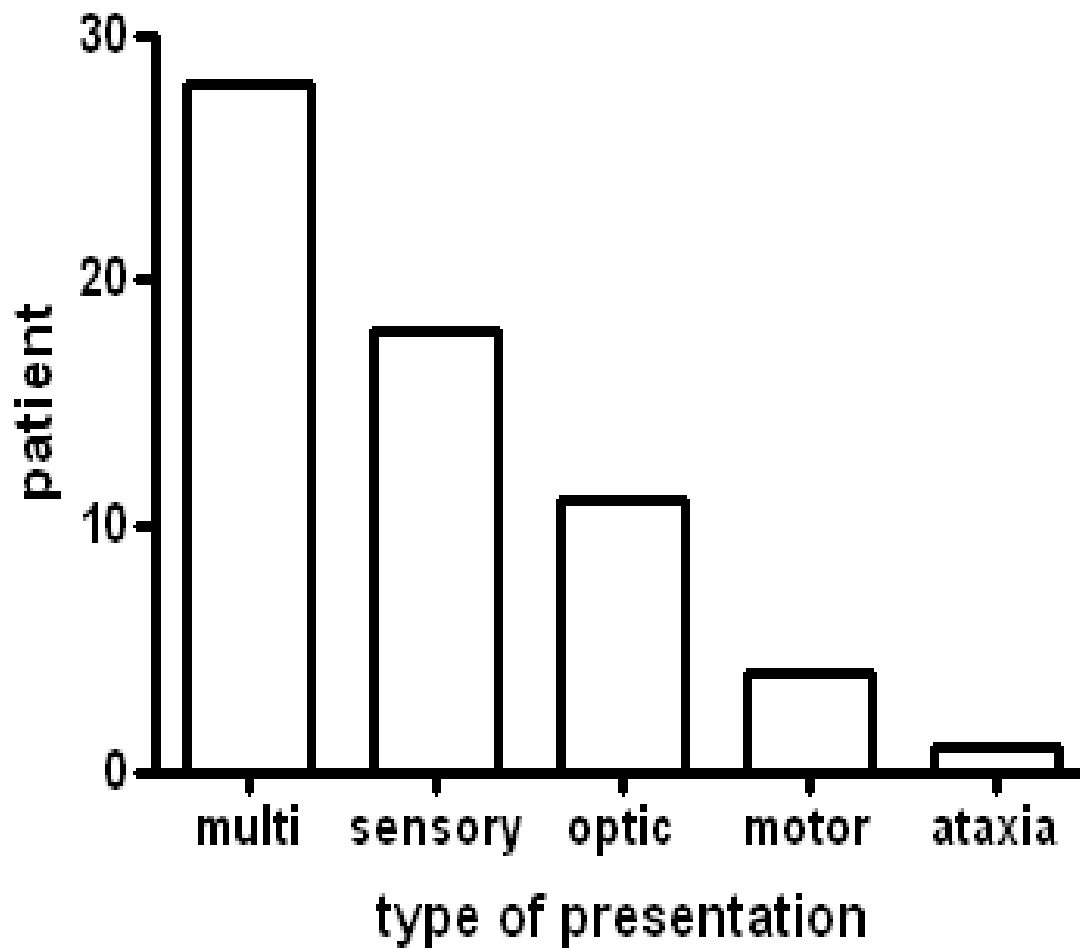
1 ataxia

4 motor

11 optic

18 sensory

27 multifocal



Time between 1st and 2nd relapse

- Minimum time 1 month
- Maximum time 180 months (15 years)
- Average time 18.75 months

Number of relapse before starting Natalizumab

- Total number of relapses (Minimum) 2
- Total number of relapses (Maximum) 14
- Median relapses rate 5.0
- Mean relapse rate 6.2

Duration of symptoms from onset of MS till starting Natalizumab

- Mean 5.0 years
- Maximum 25 years
- Minimum 2 months

Previous Treatments

Acute treatments

- Steroids 59
- Plasma exchange 9
- IVIG 1

Disease modifying treatment

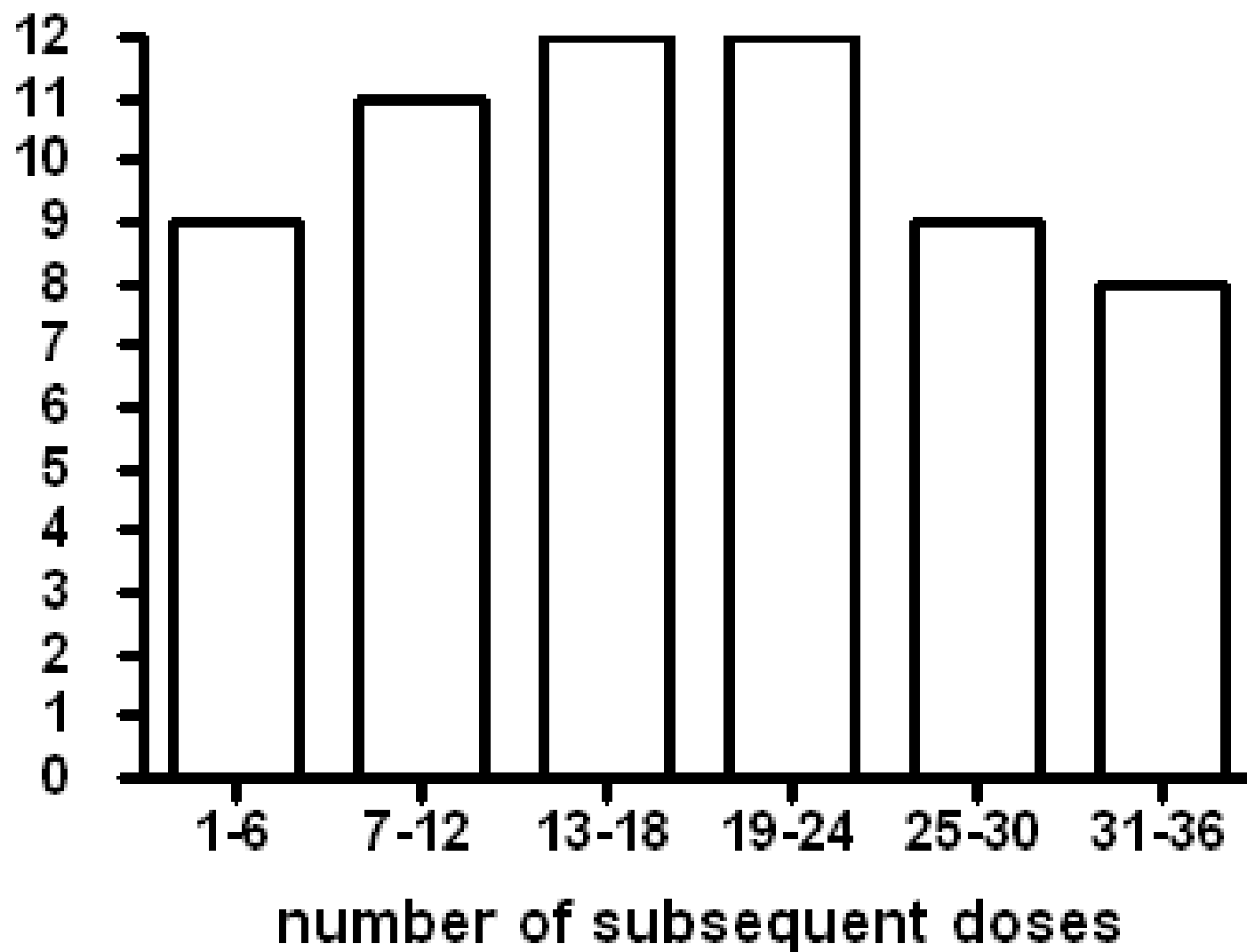
1. Interferon 34
2. Copaxone 11
3. Mitoxantrone 2

Not given interferon 24

Reason for discontinuing interferon

- Lack of response 27
- No documentation 1
- Side Effects 9
- Anti bodies against Interferon 1

Number of Natalizumab doses

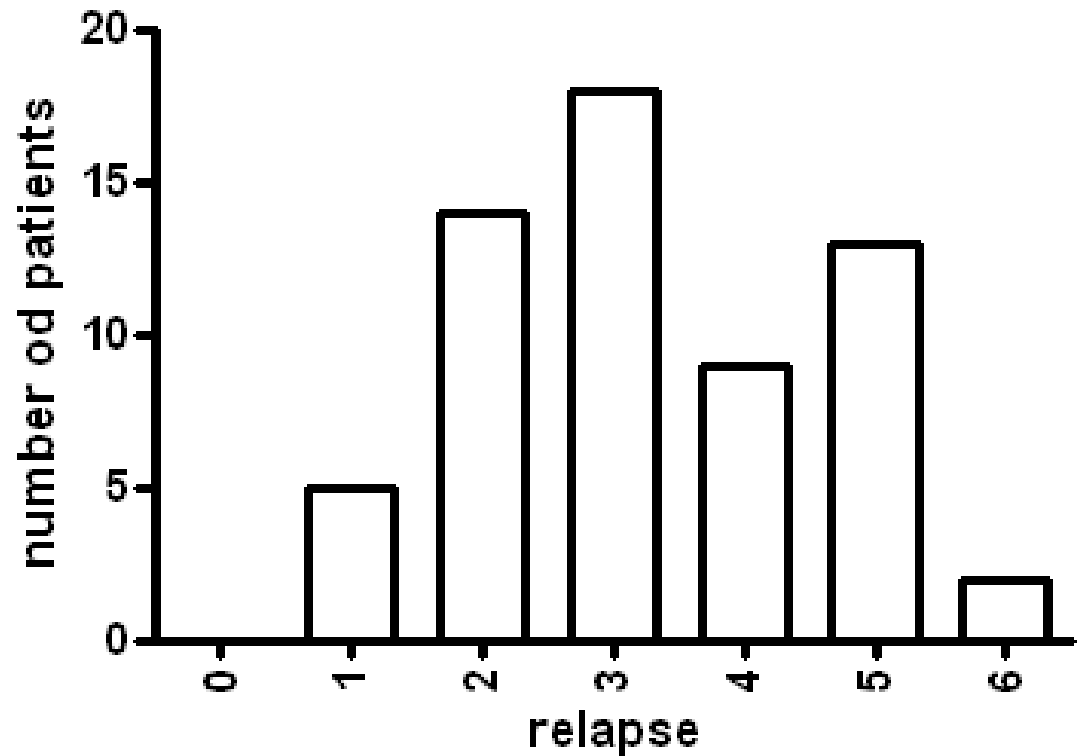


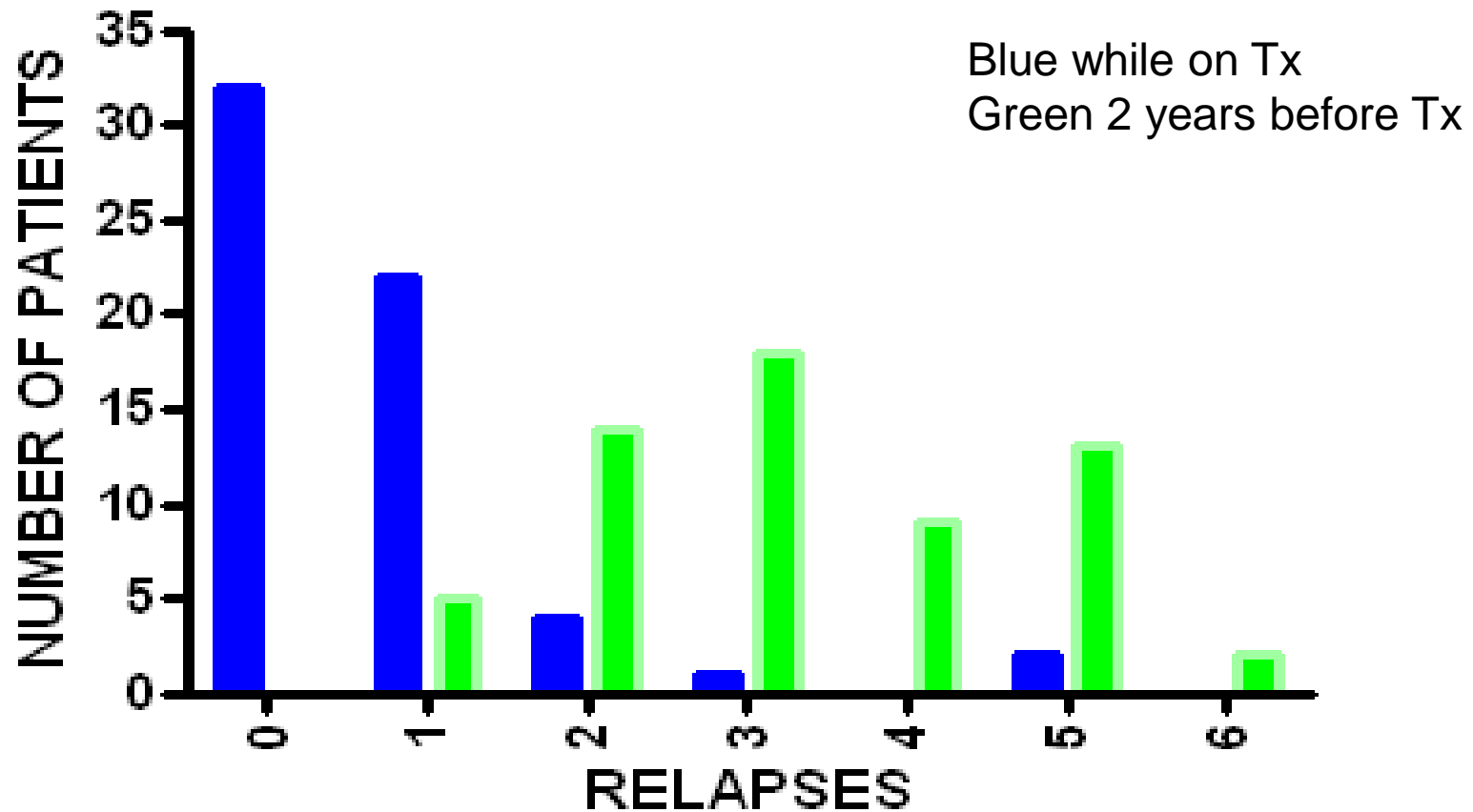
Relapse in last 2 years before starting Natalizumab

Minimum 1

Maximum 6

Mean 3.2





Comparison b/w relapse in 2 years before and after treatment

	on TX	2 YEARS B4
Minimum	0.0	1.0
Maximum	5.0	6.0
Median	0.0	3.0

Severity of Relapse while on treatment

- Mild 11
- Moderate 8
- Severe 6

NUMBER OF PATIENTS

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5

EDSS

Red before
Blue on tx

Post dose

Pre dose

- **Max** 8.5
- **Median** 5
- **Mean** 4.30
- **Mini** 0

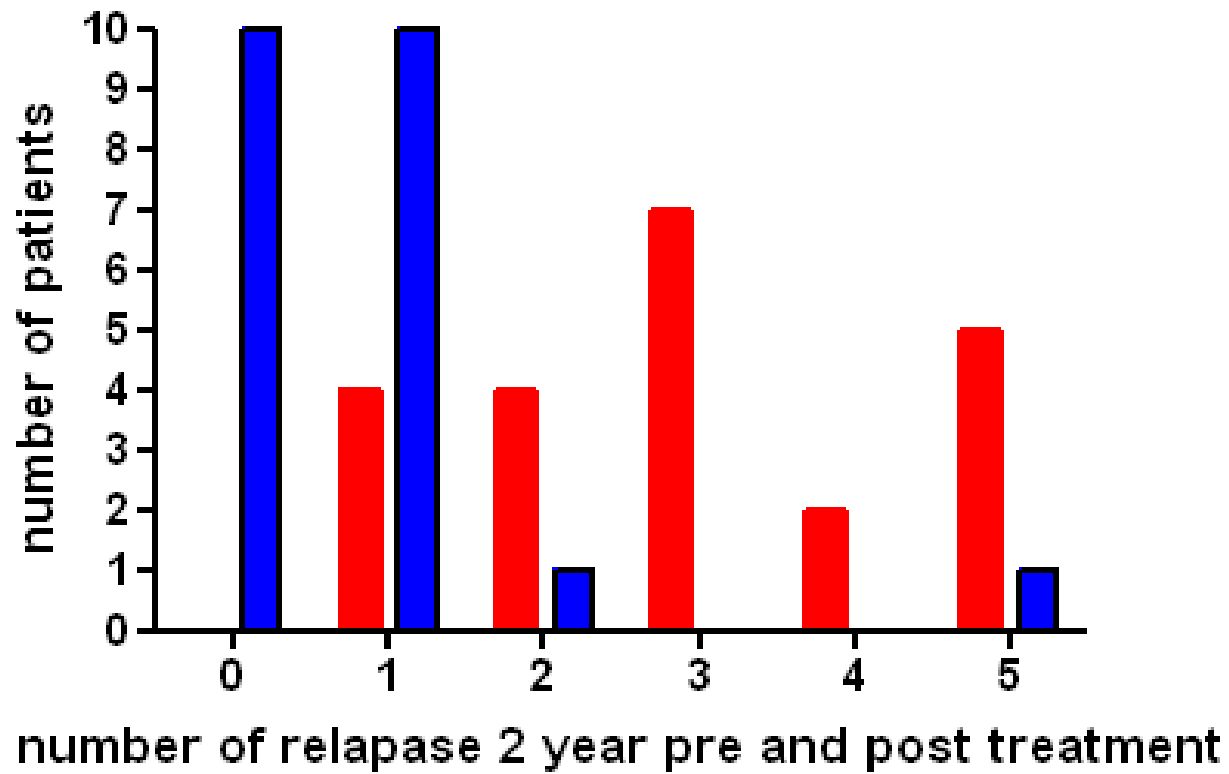
- **Max** 8.5
- **Median** 6
- **Mean** 5.2
- **Mini** 1



22 patients had been on treatment for **24** months and more

- | • Relapse 2 year Pre TX | Relapse 2 year post TX |
|--------------------------------|-------------------------------|
| • Minimum 1 | minimum 0 |
| • Median 3 | median 1 |
| • Maximum 5 | maximum 5 |
-
- | • EDSS 2 year Pre TX | EDSS 2 year post TX |
|-----------------------------|----------------------------|
| • Minimum 3 | minimum 0 |
| • Median 6 | median 6 |
| • Maximum 8.5 | maximum 8.5 |

PATIENTS ON TREATMENT FOR 24 MONTHS AND MORE



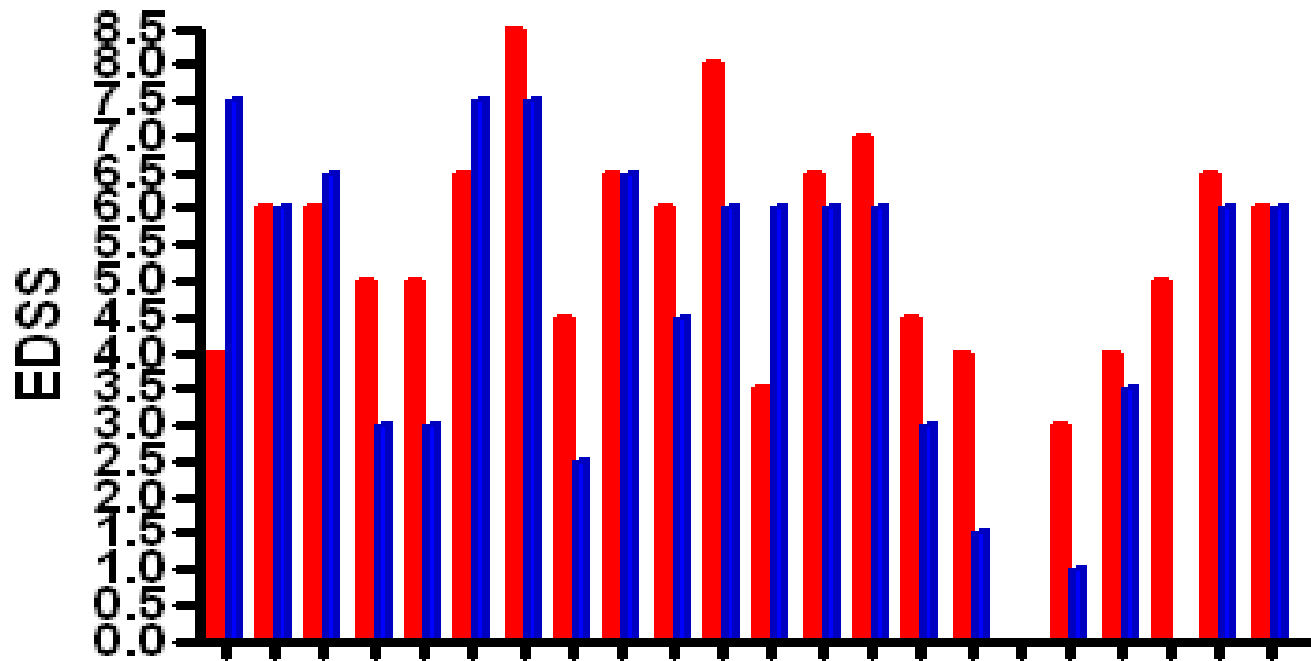
PATIENTS ON TREATMENT FOR 24 MONTHS AND MORE

secondary progression = 5

significant improvement in = 7

stable disease = 7

stopped and restarted b/c of relapse = 3



EDSS COMPARISON OVER 24 MONTHS PRE AND POST TX

PATIENTS ON TREATMENT FOR 24 MONTHS AND MORE

- Secondary progression **5**
- **1** had Good response but JC virus antibodies rising so stopped
- Significant improvement **6**
- Stable disease **7**
- Wanted to stop had relapse so restarted **3**

- **EDSS not done in 7 patients(pre tx)**
- **EDSS not done in 10 patients (post tx)**

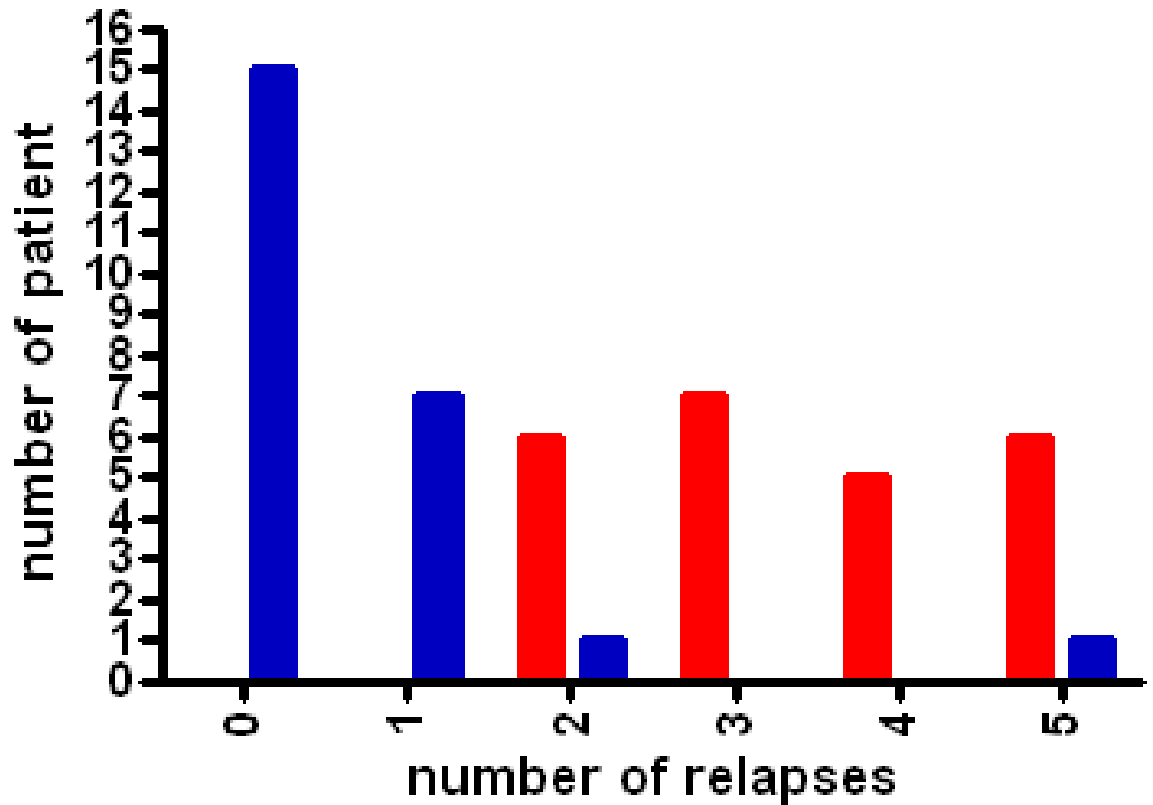
24 patients who had treatment for 12-23months

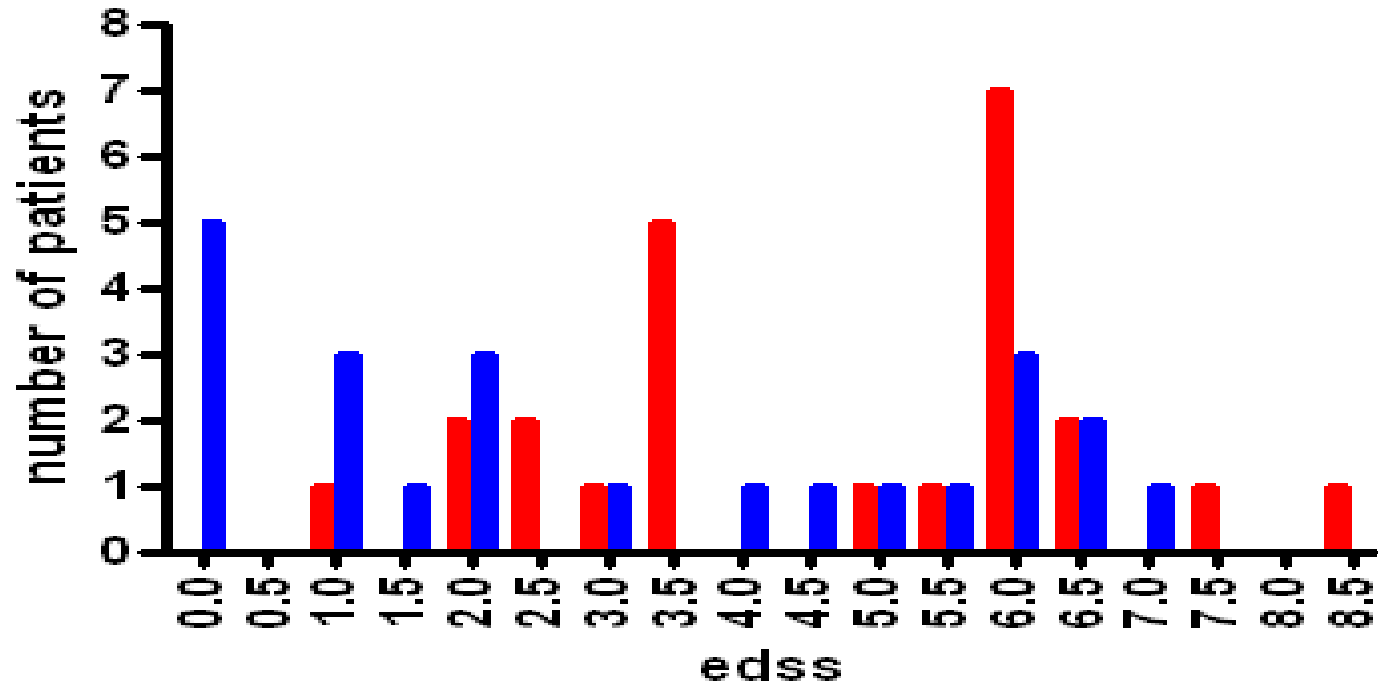
Compared pre and post treatment EDSS and relapse rates.

- 3 significant improvement
- 1 secondary progression
- 2 off to be pregnant ,one had significant relapse while off tx
- 1 further relapses on Mitoxantone now
- 1 further relapses on Copoxone now

24 Patients on 12-23 months on Tysabri relapse comparison

	Pre TX	ON TX
MIMINUM	2	0
MEDIAN	3	0
MAXIMUM	5	5





EDSS comparison in pre treatment and while on Natalizumab for 12 months to 23 months

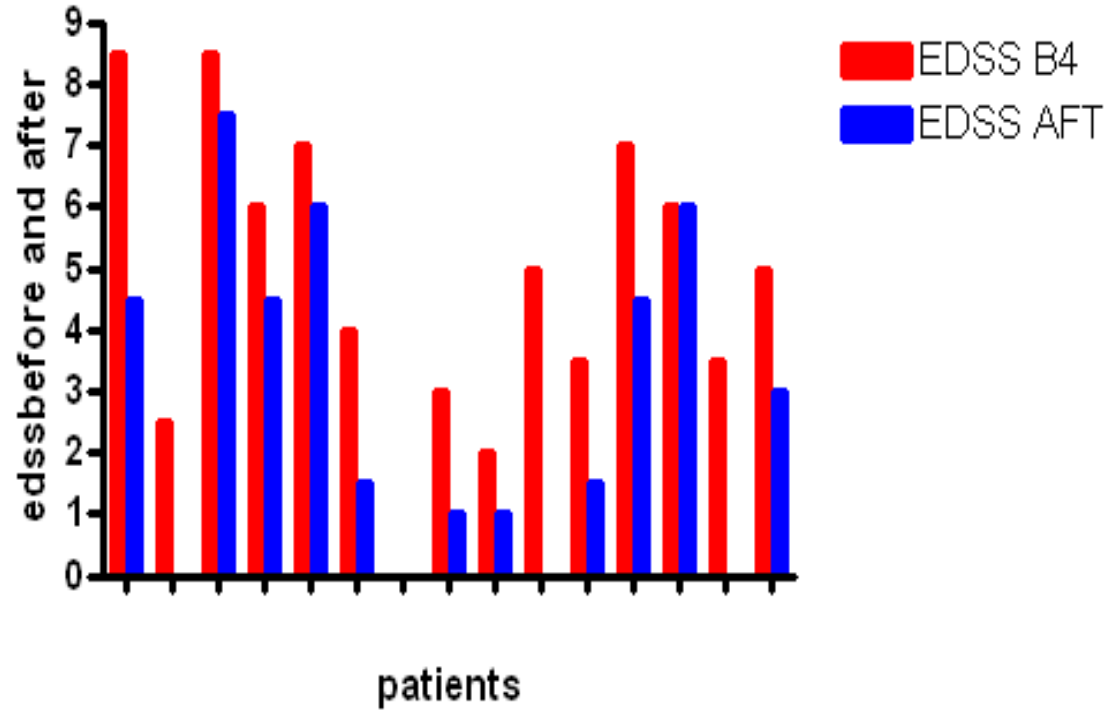
	EDSS B4 TX	EDSS after TX
Minimum	1	0
Median	5.2	2
Maximum	8.5	7.5

38 Patients showing improvement with Natalizumab

- **15** patients have significant improvement on treatment showed reduced relapse rate and drop in EDSS.
- **23** patients continue treatment and have shown good disease control.

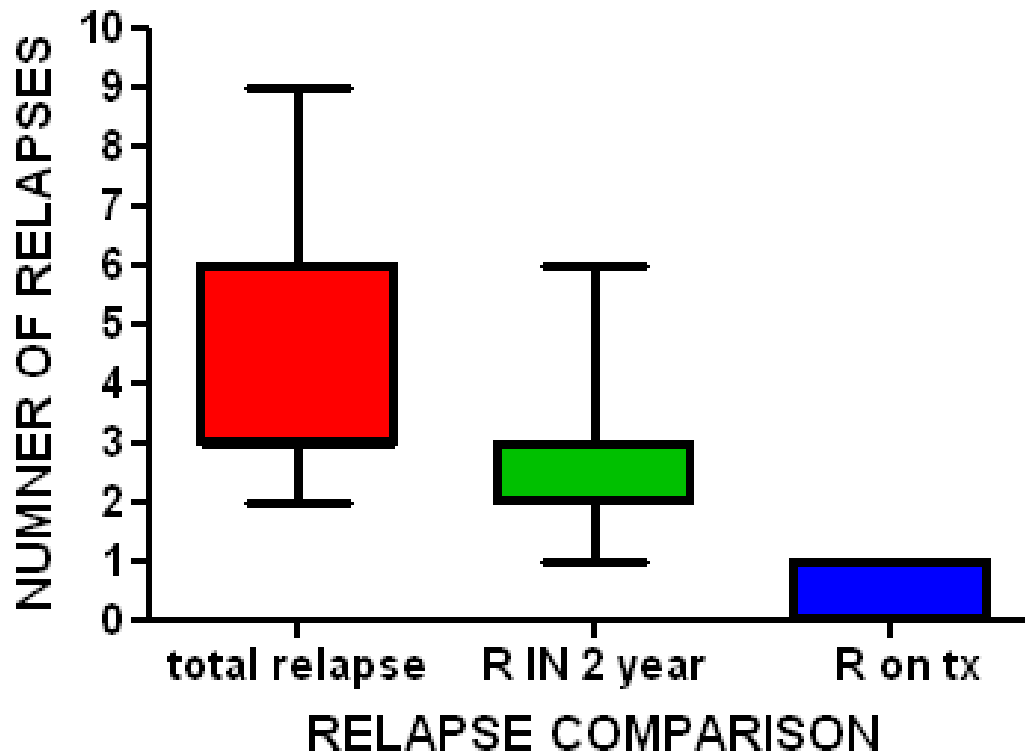
15 patients with significant improvement

Pre dose EDSS		Post dose EDSS	
Max	8.5	Max	7.5
Minimum	2	Minimum	0
Median	5	Median	1.5



15 Patients showing improvement on treatment

	total relapses	relapse 2 year b4	on tx relapses	no of doses
1.	2.	2.	0.	16.
2.	7.	5.	1.	36
3	5.	5.	0.	17.
4	2.	1.	0.	25.
5	3.	3.	1.	26.
6	7.	2.	0.	24.
7	3.	3.	0.	32.
8	3.	3.	0.	33.
9	3.	3.	0.	24.
10	5.	2.	0.	14.
11	3.	3.	0.	34.
12	3.	3.	1.	20.
13	6.	6.	0.	9.
14	9.	3.	1.	19.
15	2.	2.	0.	17.



15 patient with significant improvement

	Relapse since diagnosis	relapse in last 2 years	relapse on tx
Minimum	2	1	0
Median	3	3	0
Maximum	9	6	1

- **23** patients continued on treatment with stable EDSS and good disease control.
- Few of these want to take a drug holiday b/c of Different reason , 2 patients in stopped treatment and had significant relapse so had to restart.

23 patients off Natalizumab

- **5** off Natalizumab , now on Copoxone 3 because of sever relapse , one had anti Tysabri anti bodies , one have rising anti JV virus antibodies titers.
- **5** in Sec progressive phase so off Natalizumab
- **1** decided to stop b/c of depression
- **2** stopped to get pregnant , one had relapse while off
- **1** person stopped had good control and had 2 relapse so restarted
- **3** on Campath b/c of relapse
- **1** person had reaction to Tysabri so off

Side effect from Natalizumab

- **1** person had significant allergic reaction leading to discontinuation of drug.
- **7** people had mild problem like ,rash ,headache, depression worsening and rigors.
- Rest tolerated treatment with out problem