

Extended interval dosing of Natalizumab in MS; a New Zealand experience

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Introduction

- Natalizumab is a humanized monoclonal antibody directed against the α 4 β 1 subunit of Very Late Antigen-4 (VLA4). VLA4 is expressed on the membrane of leucocytes and is involved in leucocyte migration to the CNS.
- Natalizumab is highly efficacious and the FDA approved its use in relapsing-remitting multiple sclerosis (RRMS) after interim analysis of 1 year results from the AFFRIM¹ and SENTINEL² studies.
- Natalizumab use is with strict surveillance due to its association with progressive multifocal leukoencephalopathy (PML) from reactivation of the John Cunningham Virus. Extended interval dosing (EID) has been proposed as a strategy to reduce the risk of PML.
- Sheremata et al³ and Plavina et al⁴, through retrospective analysis of data from the SENTINEL and AFFRIM study, have shown there is 80% saturation of the α 4 β 1 subunit up to 4 weeks after a single dose of 300mg of Natalizumab IV. A dramatic reduction in binding of the α 4 β 1 subunit, after a single dose, is observed from >70% at 8 week post dose to less than 40% at 12 weeks.
- EID has been evaluated retrospectively by Ryerson et al⁵ and Bomprezzi et al⁶ with both studies showing that EID does not lead to an increased risk of clinical relapses and MRI detectable lesions.
- Recent data suggests EID of Natalizumab at 300mg IV results in a lower risk of PML⁷. No efficacy data was presented.
- Waikato District Health Board has a catchment of more than 390,000 within a 21,000km² geographic range of the North Island of New Zealand. Since August 2012, the standard treatment of RRMS with Natalizumab is 300mg IV infusions at 6 week intervals.

Objective

To present the prospectively collected data of patients treated with six weekly dosing of Natalizumab at Waikato District Health Board.

Methods

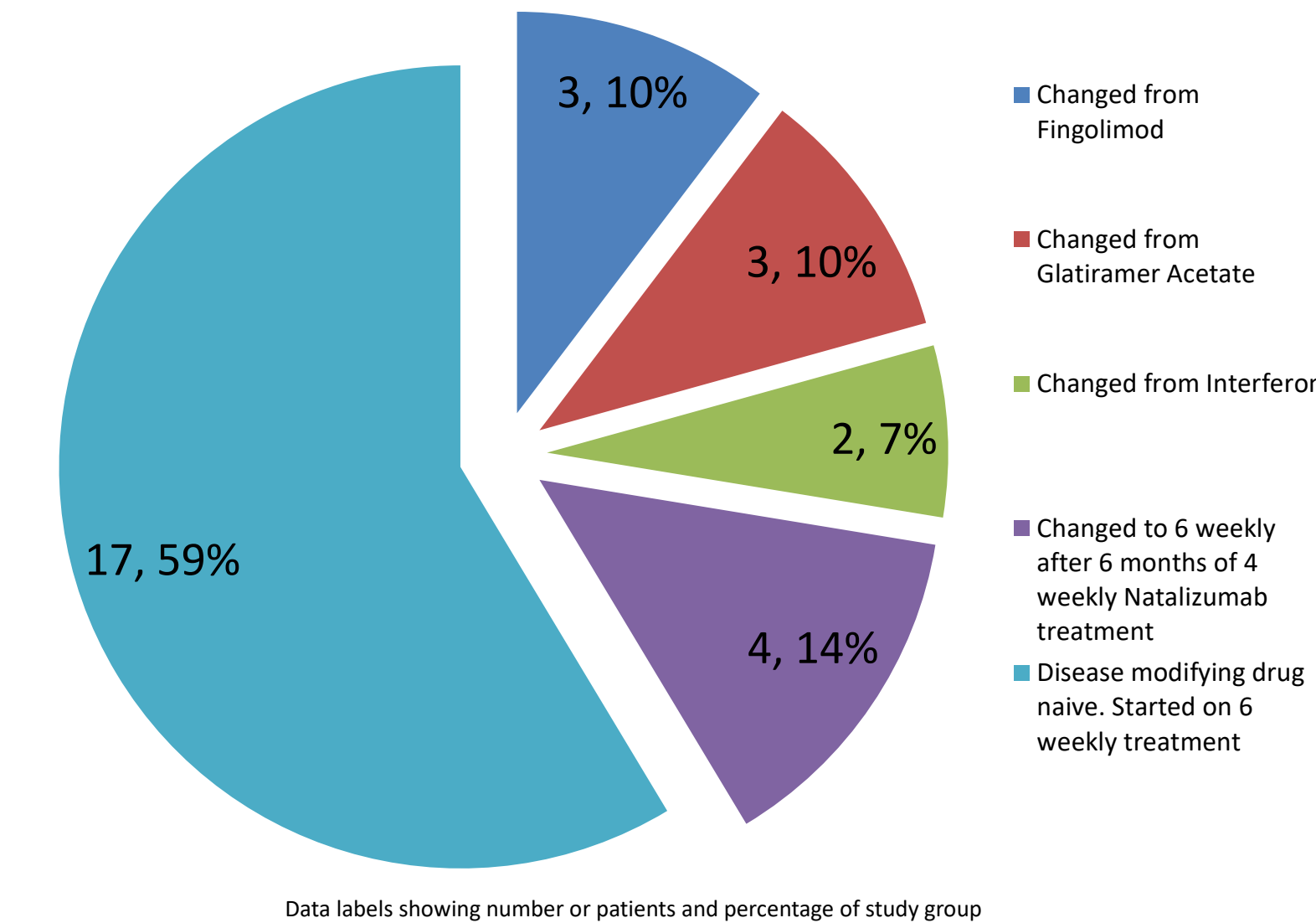
- This is an ongoing prospective observational study conducted by the Department of Neurology at Waikato Hospital, New Zealand.
- Patients were recruited from August 2012. The data presented reflects patients recruited up to the end of February 2017.
- Data was collected from August 2012 to the end of February 2018.
- Patients were prospectively recruited at the time of consent for treatment with Natalizumab. Patients are informed that six weekly dosing of Natalizumab is not the recommended dosing interval in the treatment of RRMS at the time of consent and are offered the option of treatment at four weekly intervals.
- EDSS assessment and clinical follow ups were performed by Dr Jan Schepel (Neurologist).
- Relapses were recorded on electronic regional clinical records.
- Magnetic Resonance Imaging from 2012 to 2015 were acquired on either a GE MRT50 3T or a GE Sigma HDrt 1.5T. From 2015, MRI was acquired on either a GE MRT50 3T or a Siemens Skyra 3T. Imaging was read by the radiology department of Waikato hospital and reviewed by Dr Jan Schepel (Neurologist) and Dr Nick Mellsop (Neuro-Radiologist).
- OCT were acquired on a Zeiss Cirrus HD OCT 5000.

Baseline Characteristics comparing with Tysabri Observation Program

	Waikato DHB	TOP 2014
Total participants	29	4821
Age (range)	22-57	(SD) 27.51 - 46.89
Average Age	40.7	37.2
Female	26 (93.1%)	3466 (72%)
Treatment duration	11 months - 4.7 years, Avg 2.24 years	SD 0.39 - 7.81, Avg 4.1
Baseline EDSS (range)	1.5-4	SD- 1.53 - 4.77
Average baseline EDSS	2.98	3.15
JC +ve	10 (34.5%)	227 (5.1%)
JC titre (range)	0.22 - 3.35	N/A
JC +ve 0.2 - 0.4	N=3	
JC +ve >0.4	N=7	

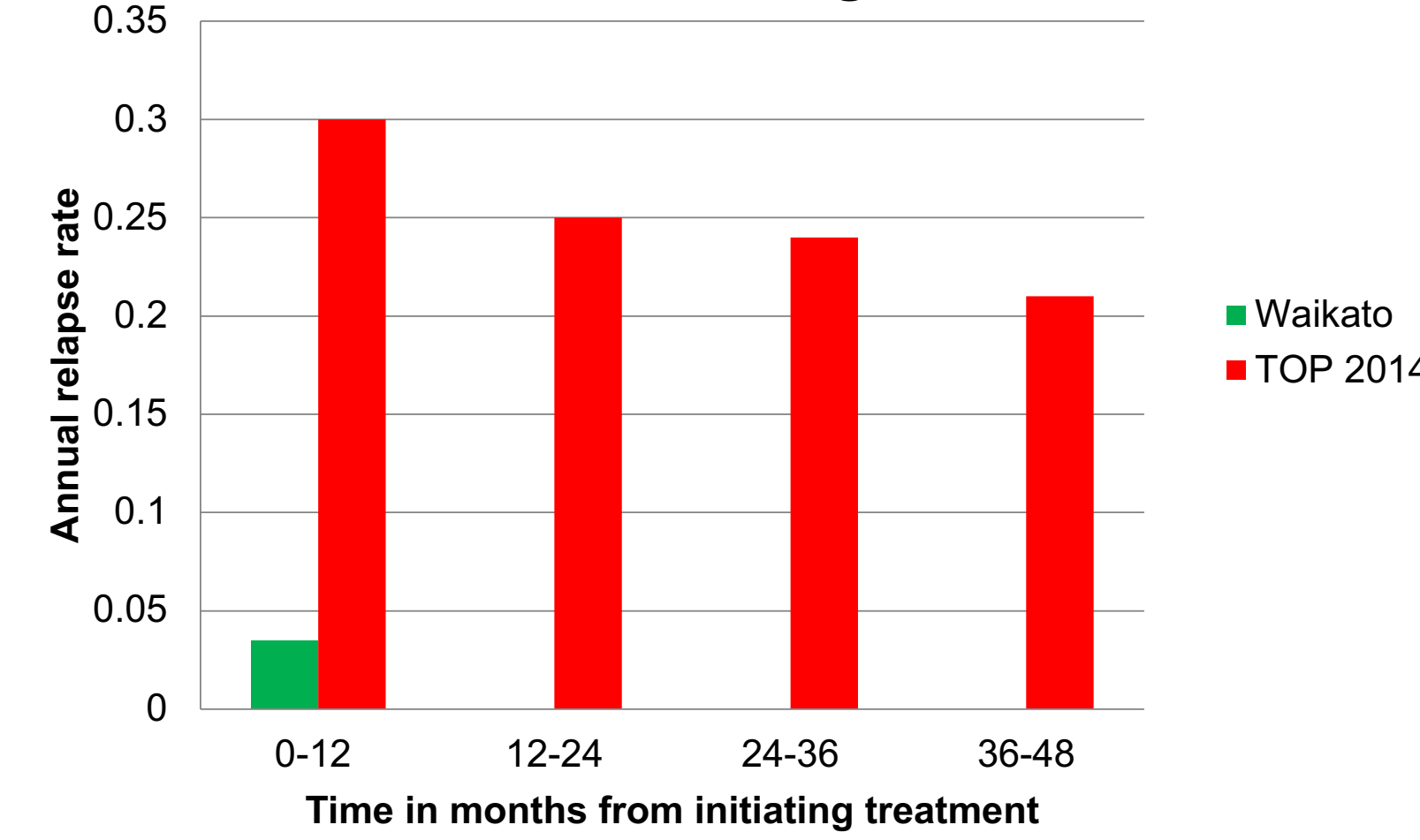
Efficacy and safety of Natalizumab in Multiple Sclerosis: interim observational programme results. Butzkueven H, Kappos L, Pellegrini F, et al. J Neurol Neurosurg Psychiatry Published Online 14 Feb 2014

Immune therapy history prior to start of 6 weekly Natalizumab treatment



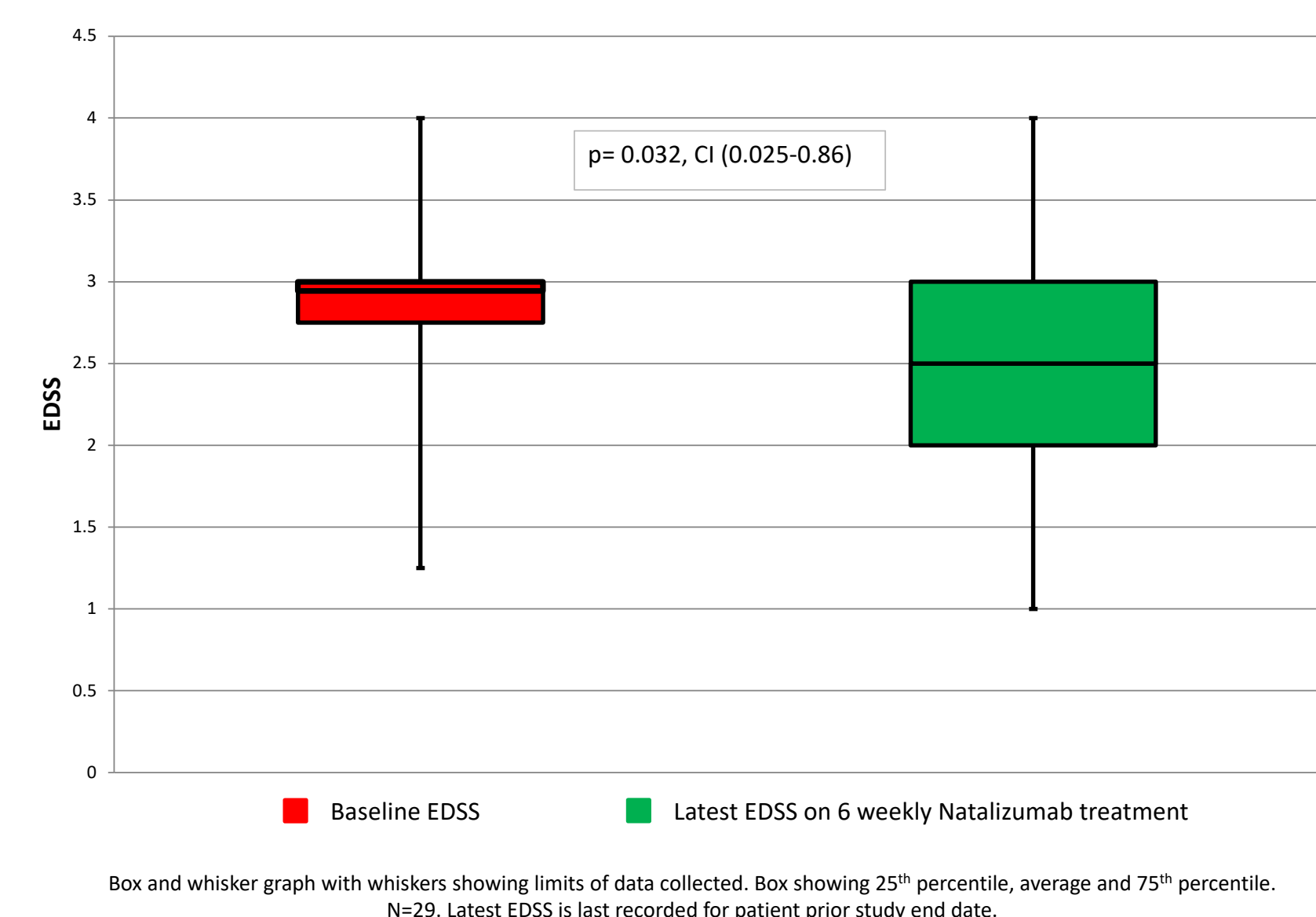
Data labels showing number of patients and percentage of study group

Clinical relapse rate comparing 6 weekly Natalizumab treatment and data from the Tysabri Observation Program*

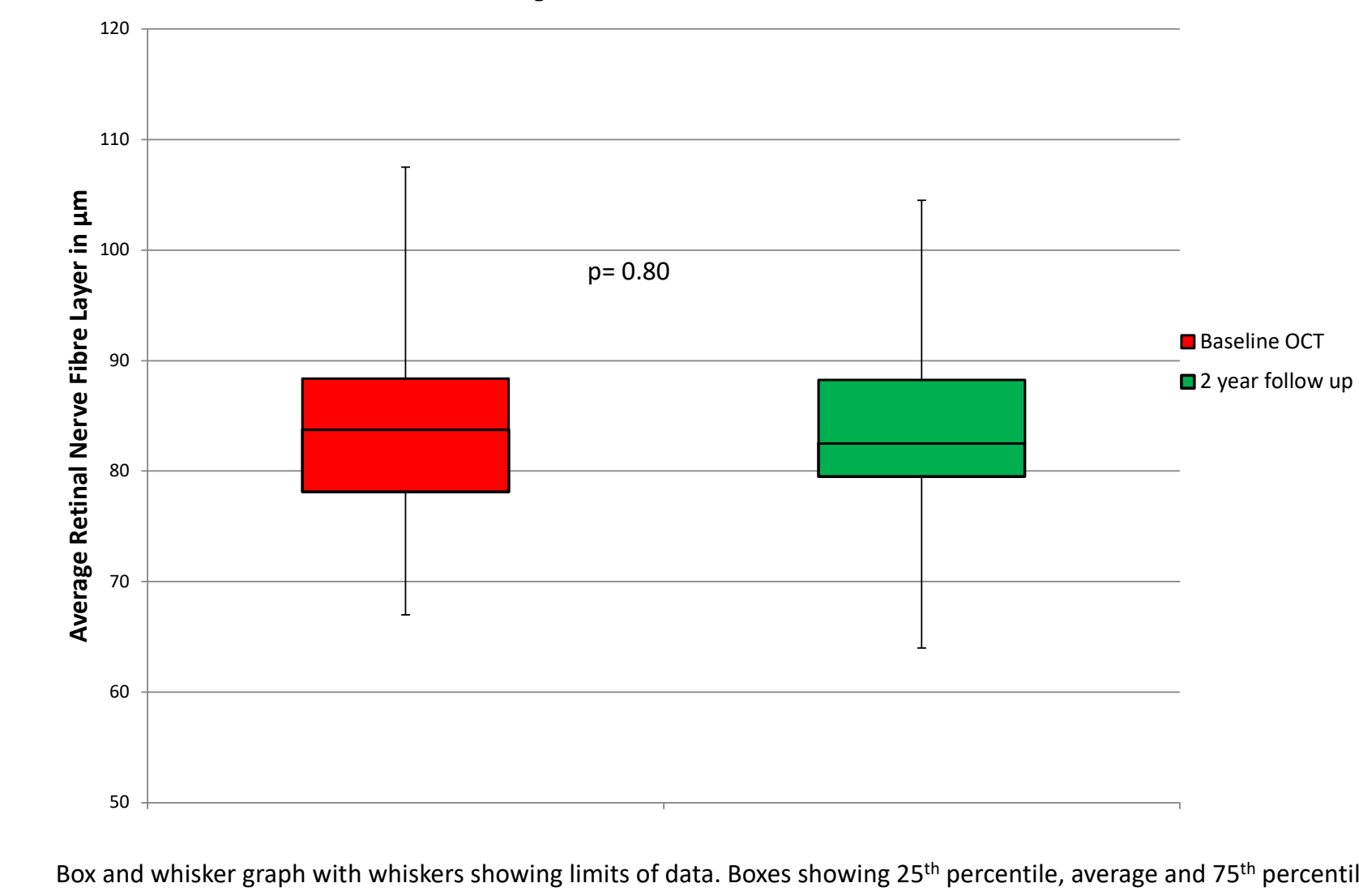


* Efficacy and safety of Natalizumab in Multiple Sclerosis: interim observational programme results. Butzkueven H, Kappos L, Pellegrini F, et al. J Neurol Neurosurg Psychiatry Published Online 14 Feb 2014

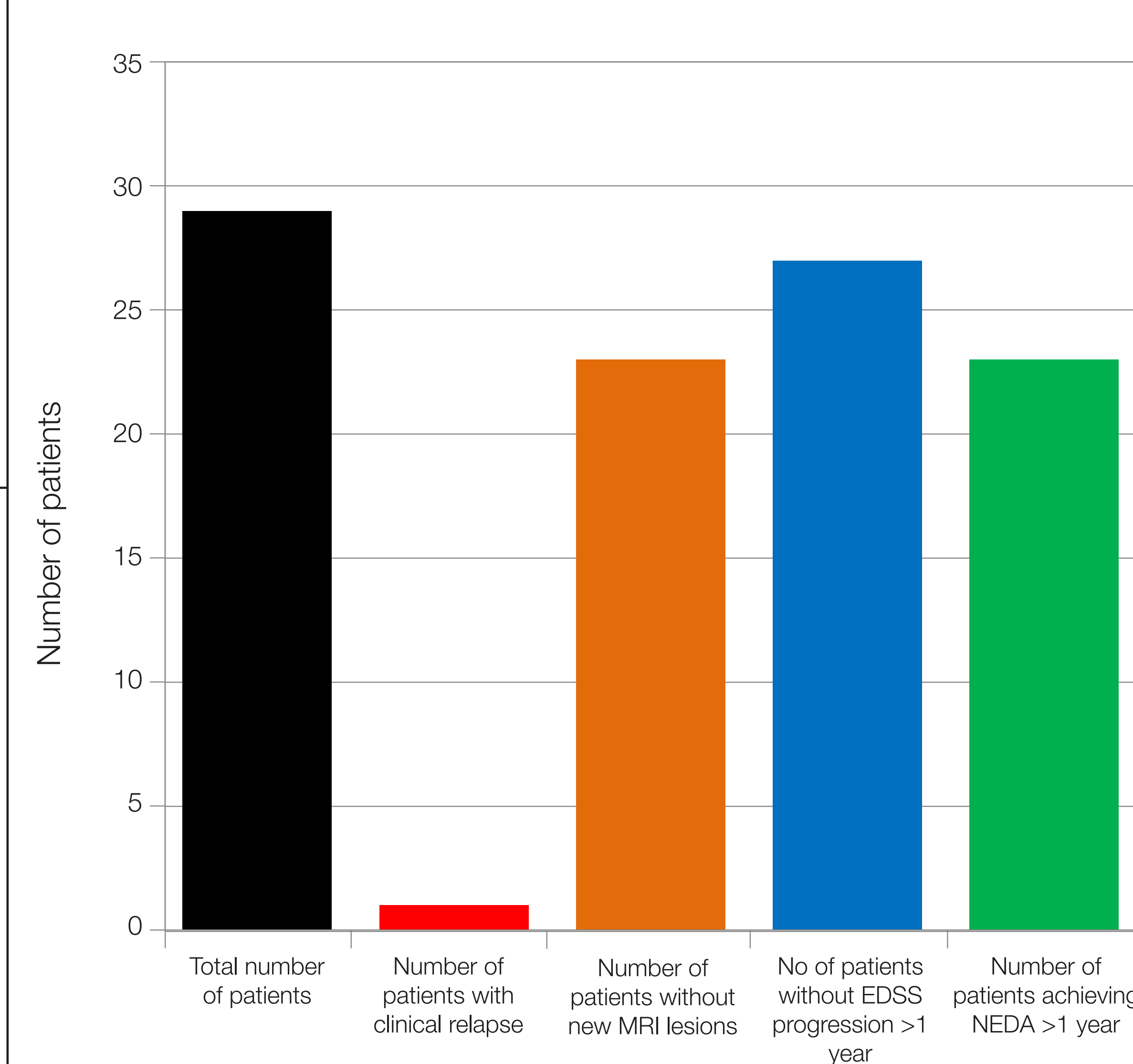
Change in Expanded Disability Status Scale (EDSS)



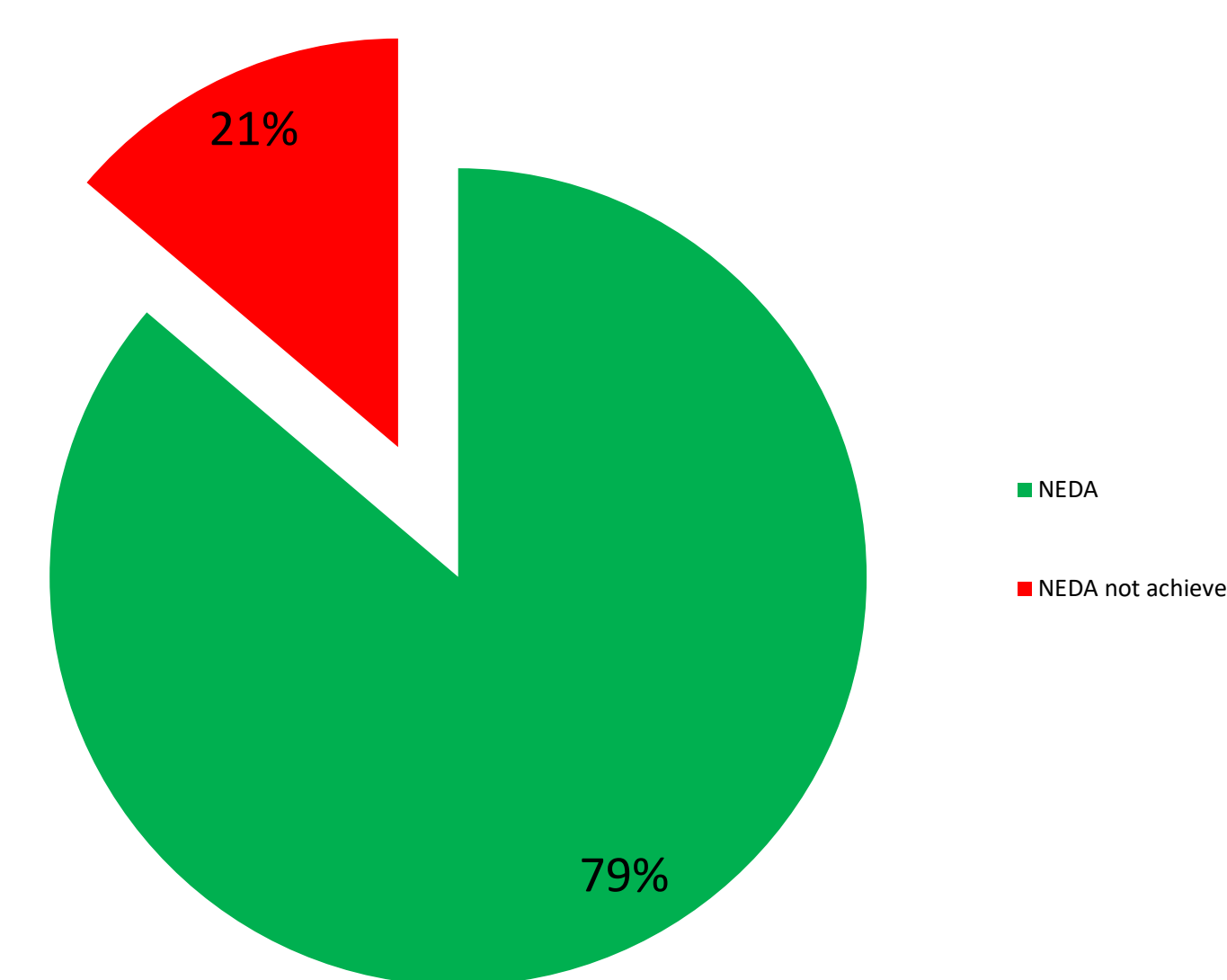
Optical Coherence Tomography (OCT) follow up in 6 weekly treated Natalizumab



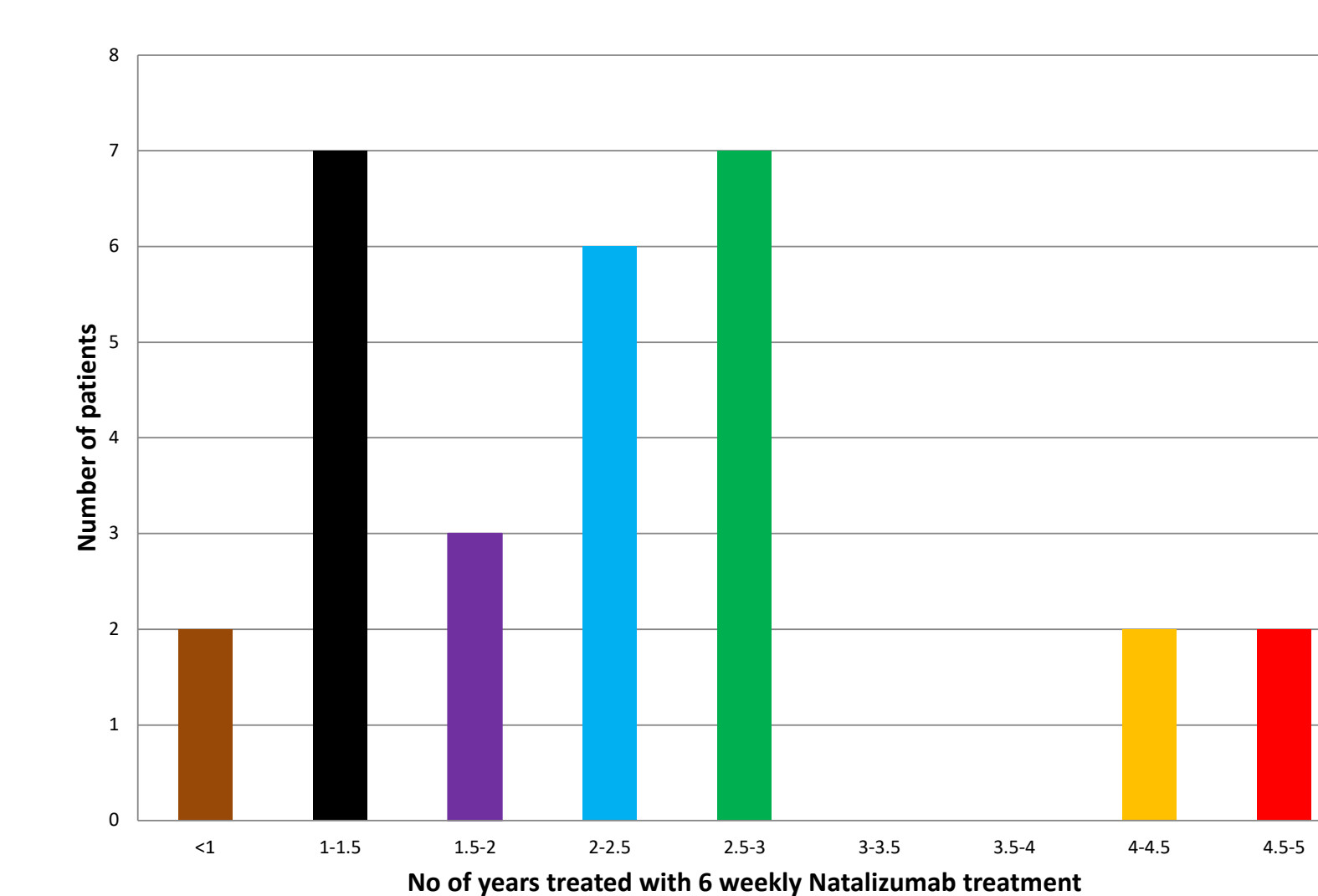
Multiple Sclerosis activity on 6 weekly Natalizumab treatment



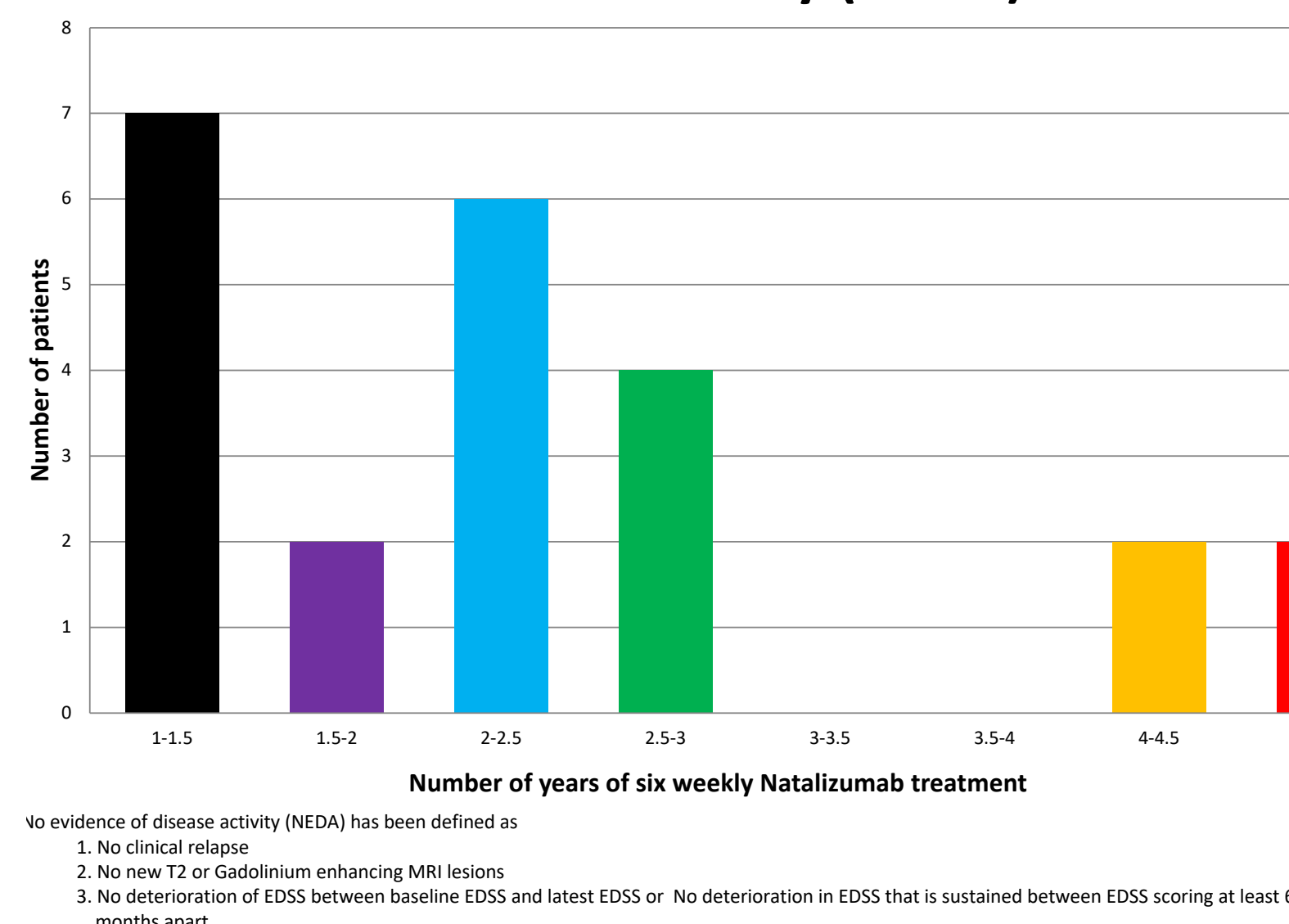
Proportion achieving No Evidence of Disease Activity (NEDA) \geq 1 year



Distribution of patients and treatment period with 6 weekly Natalizumab



Number of patients achieving No Evidence of Disease Activity (NEDA)



Conclusions

From the limited patient group at Waikato District Health Board we conclude:

- There is not an increase in clinical relapses in patients treated with 6 weekly Extended Interval Dosing of Natalizumab when compared to conventional 4 weekly dosing⁸.
- There was no overall deterioration of Expanded Disability Status Scale (EDSS) scoring in patients treated with 6 weekly dosing of Natalizumab. Statistical analysis suggests the improvement in EDSS observed is of significance. However, the study is limited by the small study group and was not designed to be powered to confirm this finding.
- No patients in this study group had progression of their EDSS score from baseline or EDSS score deterioration sustained between EDSS scoring greater than 6 months apart.
- 6 patients (21%) had one or more new MRI lesions while on 6 weekly Natalizumab treatment. This is comparable to the rate observed in international observational studies with 4 weekly treatment with Natalizumab of 19-57%⁹.
- 79% of patients on 6 weekly Natalizumab treatment achieved NEDA of 1 or more years in duration. This is greater than the rate observed in international observational studies with 4 weekly treatment with Natalizumab of 33-63%⁹. However this finding is limited by the small sample group.
- Patients on 6 weekly extended interval dosing are able to achieve 'No evidence of disease activity' (NEDA) as defined as
 - No clinical relapse
 - No new T2 or Gadolinium enhancing MRI lesions
 - No deterioration of EDSS that is sustained between EDSS scoring at least 6 months apart.
- There was no overall deterioration of the average Retinal Nerve Fibre Layer (RNFL) thickness between 2 years in patients treated with 6 weekly Natalizumab. This finding contrasts to Pisa et al¹⁰ who found a 1.25 μ m reduction in RNFL in patients with 'No evidence of disease activity'.

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Disclosures

Dr Jan Schepel has been compensated to speak on advisory committees for Biogen and Roche. He has had travel expenses for congresses paid by Merck, Bayer, Biogen and Roche. The other authors have no disclosures.