Disease activity and lymphocyte dynamics in patients switching to alemtuzumab from fingolimod

Thomas Williams[1], Ann Donnelly[2], Mariana Enriquez-Larrondo[2], Wallace J Brownlee[1,2], Jeremy Chataway[1,2]

[1] Queen Square MS Centre, Department of Neuroinflammation, UCL Institute of Neurology, London, UK
[2] National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

UCL

Background:
The expanding arsenal of immunotherapies for multiple sclerosis (MS) has resulted in new questions regarding the personalisation of treatment strategies and optimum drug sequencing. Previous reports have highlighted high rates of disease activity in patients switching from fingolimod to alemtuzumab (Bernard-Valnet et al., 2018; Wehrum et al., 2018; Willis et al., 2017). It has been suggested that prolonged sequestration of lymphocytes after fingolimod withdrawal may limit alemtuzumab efficacy, with subsequent delayed lymphocyte egress driving recurrent disease activity.

Aims:
To investigate the relationship between disease activity and lymphocyte dynamics in patients switching to alemtuzumab from fingolimod and injectable disease-modifying therapies (DMTs).

Methods and patients
Pharmacy records were reviewed to identify all patients treated with alemtuzumab at the National Hospital for Neurology and Neurosurgery from 2015 to Feb. 2018. Case records were reviewed, and disease activity was defined as clinical relapse or new radiological activity.

Results:

Table 1. Patient characteristics

	Injectable (n=28)	Fingolimod (n=20)
Age (y)	34	38.5
Disease duration (y)	6.6	10.9
Fingolimod washout (m)	NA	4.0 (1-11)
Follow-up post-alemtuzumab first cycle (m)	15.5	17.0

Durations reported as median (range), where applicable

Patients previously treated with fingolimod tended to be older and had a longer disease duration than the injectable group (table 1). Patients previously treated with fingolimod experienced a higher rate of disease activity in the first year following alemtuzumab compared to the injectable group (table 2).

Table 2. Disease activity in first year following alemtuzumab (first cycle)

	Injectable (n=28)	Fingolimod (n=20)	p*
Activity in 1st year	2/28 (7%)	6/20 (30%)	0.036
Time from first cycle to activity (m)	5.5	6.0	NA

*Cross-tabulation, Pearson Chi-Squared.

Baseline lymphocyte counts were lower in the fingolimod group (p=0.003, figure) on day 1 of alemtuzumab. The fingolimod group tended towards a higher lymphocyte count at all time points during the first 11 months after alemtuzumab.

Age, MS duration, fingolimod treatment duration and washout duration did not significantly correlate with lymphocyte counts. There was, however, a trend towards fingolimod duration negatively correlating with baseline lymphocyte count (r = -0.441, p = 0.059), and this was stronger than the relationship between washout duration and baseline lymphocyte counts (r = 0.265, p = 0.272).

Table 3. Comparison of patient characteristics by disease activity group, fingolimod patients

	Disease activity in first year		
	No (n=14)	Yes (n=6)	p
Age (y)	38.3	42.0	0.183[1]
MS duration (m)	118.0	140.3	0.654[1]
Fingolimod duration (m)	24.5	19.0	0.444[1]
Washout duration (m)	5.4	3.2	0.163[2]

1 via ANOVA; 2 via Kruskal-Wallis

Categorised by disease activity, no significant differences were identified in patient characteristics or rates of lymphocyte reconstitution (table 3). The active disease group tended to have a shorter washout period. Logistic regression demonstrated that no variable contributed significantly to predicting disease activity, and the overall model was poorly predictive.

Key messages:

1. We replicate previous findings of unexpectedly high rates of disease activity following alemtuzumab in those previous treated with fingolimod

2. Compared to injectable therapies, those with previous fingolimod treatment have lower baseline lymphocyte counts, and a tendency to faster lymphocyte reconstitution

3. Replication in larger cohorts is required, but neurologists should be aware of this phenomena and consider the role of prolonged washout +/- bridging therapy before treating fingolimod patients with alemtuzumab

Lymphocyte reconstitution following first Alemtuzumab cycle
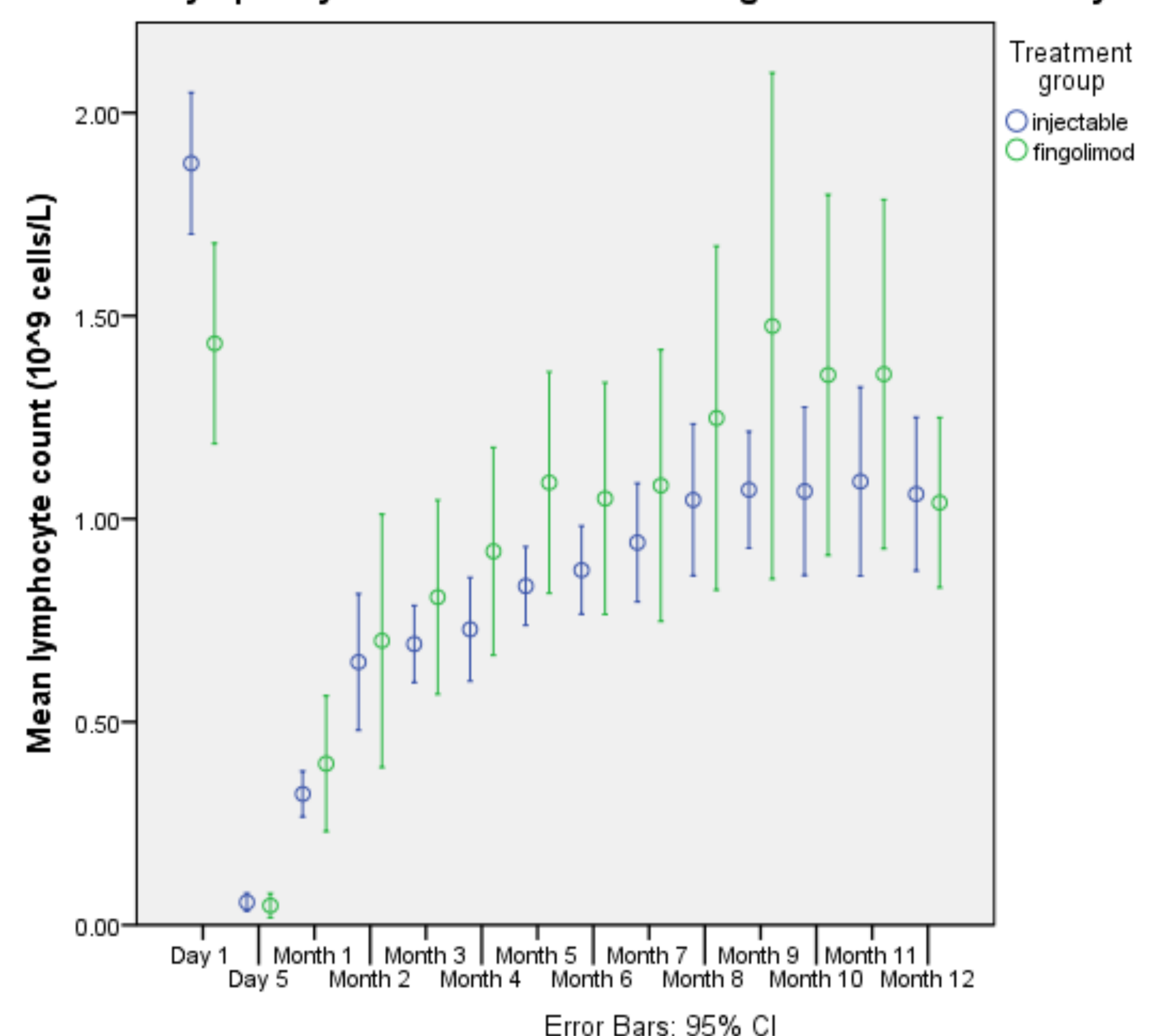
Conclusions:
Following alemtuzumab, those previously treated with fingolimod experienced a higher rate of disease activity. This may be related to difference between the injectable and fingolimod cohorts. Alternatively, the high rate of disease activity in the fingolimod group may be related to the previous treatment modulating alemtuzumab efficacy, as has been previously suggested.

Our observed disease activity rate of 30% is similar to that reported in a previous cohort (Willis et al., 2017). We also demonstrate differences in lymphocyte dynamics – the fingolimod cohort had a lower lymphocyte count at alemtuzumab baseline, and a trend towards faster lymphocyte reconstitution during the first year. Both observations could be in keeping with the hypothesis of prolonged lymphocyte sequestration due to previous fingolimod resulting in reduced lymphocyte clearance by alemtuzumab, with subsequent delayed lymphocyte egress from lymph nodes driving recurrent disease activity.

Our data is in contrast to another cohort of fingolimod-alemtuzumab switchers that demonstrated low levels of disease activity (Huhn et al., 2018). This cohort, however, had a longer washout period, which may be in keeping with our observation of a non-significant tendency towards shorter washout in those with disease activity.

This work needs repeating in larger cohorts. Neurologists, however, should be aware of this phenomena and consider the role of prolonged washout +/- bridging therapy before treating fingolimod patients with alemtuzumab.

References
Bernard-Valnet, R., et al. (2018). Unexpected high multiple sclerosis activity after switching from fingolimod to alemtuzumab. Multiple Sclerosis and Related Disorders, 25(August), 216–218.
Huhn, K., et al. (2018). Alemtuzumab as rescue therapy in a cohort of 50 relapsing–remitting MS patients with breakthrough disease on fingolimod: a multi-center observational study. Journal of Neurology, 265(7), 1521–1527.
Wehrum, T., et al. (2018). Activation of disease during therapy with alemtuzumab in 3 patients with multiple sclerosis. Neurology, 10.1212/WNL.0000000000004950.
Willis, M., et al. (2017). An observational study of alemtuzumab following fingolimod for multiple sclerosis. Neurology: Neuroimmunology and NeuroInflammation, 4(2), 1–7.

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