Fulminant Multiple Sclerosis After Fingolimod Cessation

Susan Agland[1], Matthew Rowlandson[2], Joanne Sy[3] and Jeannette Lechner-Scott[1]

1. Neurology Department, John Hunter Hospital, Newcastle, Australia 2. John Hunter Hospital, Newcastle, Australia
3. Department of Neuropathology, Royal Prince Alfred Hospital, Sydney, Australia

Introduction

Multiple Sclerosis (MS) is a complex neurological disorder, frequently diagnosed in young adults. Immune modulating therapy is often recommended shortly after diagnosis to prevent long term disability accumulation. As therapy will be ongoing for decades, interruptions to therapy due to family planning, adverse events or other reasons are probable.

The outcome of therapy interruption is not well understood. We report a case of fulminant disease recurrence three months after ceasing fingolimod, resulting in fatality. We review the available literature to assess the risk of treatment cessation to help guide clinicians to prevent such an outcome.

Case Study

A 37 year old female, had relapsing remitting MS (RRMS) for 11 years. She was treated with fingolimod for a total of 4 years and 9 months, over two periods separated by a planned pregnancy.

Treatment was suspended after a period of 34 months of relative stability (EDSS 3.5) due to severe necrotising pneumonia, lymphocyte count was 0.3 10x9/L. Four months after ceasing fingolimod the subject presented to clinic with increasing confusion, difficulty walking and inability to coordinate tasks. On examination she had significant cognitive impairment and was emotionally labile. She had bilateral dysmetria in upper and lower limbs and decreased sensation on the left side with associated 3/5 weakness of the left lower limb. Her gait was ataxic with tendency to fall towards the left. Her EDSS was 6.0 at this time and lymphocyte count was 2.4 10x9/L.

Examination of her cerebrospinal fluid showed a white cell count of 45 (100% mononuclear), red cell count of 19. Other biochemistry markers included glucose 2.9 (mmol/L), protein 1.16 (g/L), lactate 1.7 (mmol/L), lactate dehydrogenase <30 (U/L). Enterovirus, toxoplasmosis, cryptoccocal antigen, cytomegaly virus, tuberculous, herpes, varicella, HHV 6 and John Cunningham virus PCR were negative. No clear infective process was evident.

Her MRI showed multiple new T2 hyperintense lesions with significant oedema, several lesions were contrast enhancing on T1 throughout the cerebral hemispheres. Interval MRIs over the next month showed increasing size and number of lesions despite treatment.

Outcome

The subject was treated with high dose methyl prednisone pulse therapy, followed by plasmapheresis but her neurological function continued to deteriorate. Natalizumab was initiated in an effort to salvage her condition. Interval MRI images showed ongoing inflammation and active lesions involving her brainstem. She was given also one gram of rituximab without effect. She was managed in ICU with ongoing neurological deterioration including persistent abnormal decerebrate posturing and bilateral up-going plantar reflexes. She opened her eyes spontaneously but with no eye tracking and left gaze deviation. Electroencephalogram (EEG) showed generalised slowing but absence of epileptic activity.

Shortly after the subject developed autonomic dysfunction with increased heart and respiratory rates and diaphoresis. She became septic with Enterobacter bacteraemia which was treated with meropenem and required inotropic support. Despite these efforts there was no change in subject's neurology and with her family's counsel the focus of care shifted to comfort measures. The subject passed away peacefully. Limited brain autopsy was performed which confirmed aggressive MS as the cause of death.

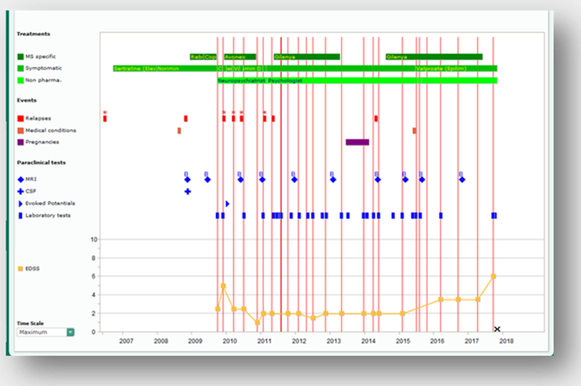

Figure A: iMED entry, capturing subject MS details including diagnosis, therapy, investigations and EDSS over time.

Literature

Reactivation of disease is a well-known consequence when stopping natalizumab but has not received the same attention after fingolimod cessation. Both agents reduce central nervous system (CNS) inflammation by altering lymphocyte trafficking either at the interface of blood brain barrier (Baumgartner, et al 2012) or at the lymph nodes (Kappos, et al 2010). Uygunoglu (et al, 2018) observed that the severe disease reactivation after cessation of fingolimod was similar to what is observed after cessation or interruption of natalizumab.

A growing number of case reports have described MS recrudescence associated with the cessation of fingolimod therapy (Havla et al 2012; Hakiki et al, 2012; La Mantia et al, 2014; Beran et al, 2013; Faissner et al, 2015; Salam et al, 2016. The commonalities of these case reports include onset relatively soon after cessation (6-14weeks), severe clinical presentations and considerable radiological disease activity.

Frau (2018) characterised reactivation and rebound in a large case series of 100 patients taking fingolimod and described severe reactivation as relapse with ≥ 2.0 points EDSS increase or ≥ 2 relapses in the 6 months after stopping fingolimod. Fingolimod reactivation was reported in 26% of the population group within 6 months of stopping, with 10% experiencing severe reactivation. Of this group half were considered to have fingolimod rebound. Frau concluded that rebound might be differentiated from reactivation by its return within a short time frame post fingolimod cessation and its poor response to rescue immunosuppression.

While no factors, including clinical factors or pseudo biomarkers have been robustly linked to rebound, it is more common in younger age and disease activity before treatment (Frau et al, 2018). Lower total lymphocyte count at cessation may also be associated (Sato et al, 2018).

Hatcher (et al 2016) carried out a review which found severe clinical neurological disease and highly active disease on MRI post fingolimod were the criteria for rebound. Of the total cohort (N=46) 10.9% experienced clinical rebound along with a significant increase in lesions on MRI occurring between four- 16 weeks post fingolimod cessation. Hatcher hypothesised that peripheral lymphocytes return within 4-8 weeks of cessation, and, like Uygunoglu, proposed lymphocyte re-entry into the central nervous system may act as a catalyst for the rebound syndrome.

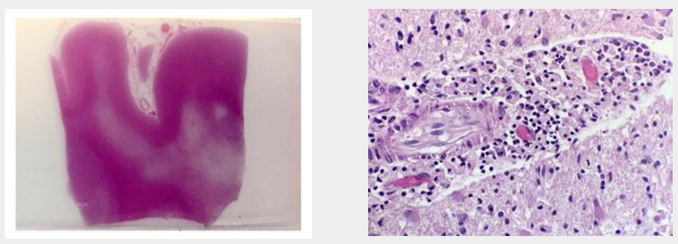

Figure D: Pathology, cerebral images of recently active MS lesions

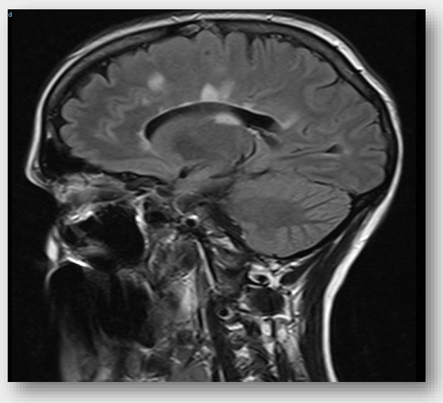

Figure B: MRI, Sagittal T2 FLAIR brain, prior to fingolimod cessation.

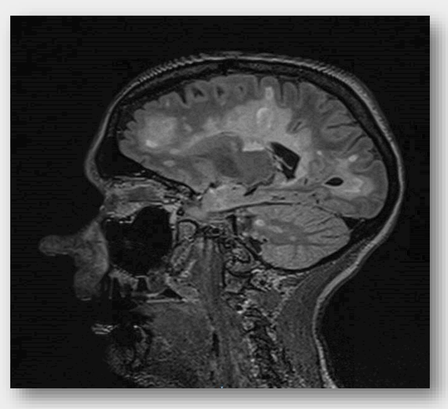

Figure C: MRI, Sagittal T2 brain, 4 months post fingolimod cessation

Conclusion

Fingolimod rebound is underestimated amongst general physicians and neurologists. This is a rare case of mortality associated fingolimod withdrawal in a patient with highly active disease prior to treatment with fingolimod. It highlights the need for a better predictive method to identify those patients at risk and the importance of aggressive post cessation monitoring, early recognition of disease activity and retreatment.

References

Baumgartner A, Stich O, Rauer S. Clinical and radiological disease reactivation after cessation of long-term therapy with natalizumab. International Journal of Neuroscience. 2012 Jan 1;122(1):35-9

Kappos L, Radue EW, O'connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, Agoropoulou C, Leyk M, Zhang-Auberson L, Burtin P. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. New England Journal of Medicine. 2010 Feb 4; 362(5):387-401.

Uygunoglu U, Tutuncu M, Altintas A, Saip S, Siva A. Factors Predictive of Severe Multiple Sclerosis Disease Reactivation After Fingolimod Cessation. The neurologist. 2018 Jan 1; 23(1):12-6.

Havla JB, Pellkofer HL, Meinl I, Gerdes LA, Hohlfeld R, Kümpfel T. Rebound of disease activity after withdrawal of fingolimod (FTY720) treatment. Archives of neurology. 2012 Feb 13;69(2):262-4.

Hakiki B, Portaccio E, Giannini M, Razzolini L, Pastò L, Amato MP. Withdrawal of fingolimod treatment for relapsing–remitting multiple sclerosis: report of six cases. Multiple Sclerosis Journal. 2012 Nov;18(11):1636-9.

La Mantia L, Prone V, Marazzi MR, Erminio C, Protti A. Multiple sclerosis rebound after fingolimod discontinuation for lymphopenia. Neurological Sciences. 2014 Sep 1;35(9):1485.

Beran RG, Hegazi Y, Schwartz RS, Cordato DJ. Rebound exacerbation multiple sclerosis following cessation of oral treatment. Multiple sclerosis and related disorders. 2013 Jul 1;2(3):252-5.

Faissner S, Hoepner R, Lukas C, Chan A, Gold R, Ellrichmann G. Tumefactive multiple sclerosis lesions in two patients after cessation of fingolimod treatment. Therapeutic advances in neurological disorders. 2015 Sep;8(5):233-8.

Salam S, Mihalova T, Siripurapu R. Severe tumefactive rebound of multiple sclerosis following fingolimod cessation. BMJ case reports. 2016 Jun 3;2016.

Frau J, Sormani MP, Signori A, Realmuto S, Baroncini D, Annovazzi P, Signoriello E, Maniscalco G, La Gioia S, Cordioli C, Frigeni B. Clinical activity after fingolimod cessation: disease reactivation or rebound?. European journal of neurology. 2018 May 31

Sato, K., Niino, M., Kawashima, A., Yamada, M., Miyazaki, Y., & Fukazawa, T. (2018). Disease exacerbation after the cessation of fingolimod treatment in Japanese patients with multiple sclerosis. *Internal Medicine*, 0793-18.

Hatcher SE, Waubant E, Nourbakhsh B, Crabtree-Hartman E, Graves JS. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. JAMA neurology. 2016 Jul 1; 73(7):790-4.

NSW GOVERNMENT