# Fingolimod Titration is an Option to Manage Side Effects Effectively, Reduce Patient Treatment Withdrawal and Achieve a Full Therapeutic Dose Regime

*Susanne Baker, Meena Sharma*

MS Clinic, Liverpool Hospital, Sydney, Australia

## INTRODUCTION

Multiple Sclerosis (MS) is a chronic progressive inflammatory demyelinating disease of the central nervous system.[1] Fingolimod was the first oral disease modifying therapy (DMT), approved for the treatment of relapsing remitting multiple sclerosis (RRMS).[2] A major Australian tertiary teaching hospital with a large MS clinic anticipated that patients commencing on Fingolimod, and experiencing poor drug tolerability would soon request, or simply decide to cease their medication. Historical experience with interferon promoted discussions with the neurologist and the MS nursing staff. Through consultation in relation to dosing alternatives it was identified that there was an opportunity to explore individualised oral drug titration. Select patients whose quality of life was being disrupted by an unwanted side effect profile would then be offered a titration and monitoring opportunity. The goal of the "go slow" approach[3] was to achieve the full recommended daily dose regime and establish self-confidence with a nonexistent or minimal acceptable side effect profile

## BACKGROUND

The paradigm shifts of MS treatment therapies, along with their accessibility, are rapidly evolving, thus necessitating more than ever the need for tailoring individualized treatments.[4] Some of the discussion contained herein is derived from evidence-based studies, whilst the other is contingent upon the MS clinic, collective clinical experience.

Fingolimod is the first oral immunomodulating medication, approved for treating relapsing remitting multiple sclerosis.[2] It is a sphingosine 1-phosphate receptor modulator and amongst other potential actions works in a way which sequesters lymphocytes into the lymph nodes. This interruption of lymphocyte transmigration ultimately prevents the ability of these blocked cells to contribute to an autoimmune reaction.[5,6,7]

The recommended Fingolimod dose is 0.5mg which is reported to have a predictable pharmacokinetics profile that allows effective once-daily oral dosing.[6] Studies indicate that for many, this drug dosing and frequency, can delay disability progression and reduce the rate of relapses by over half.[5,6]

Fingolimod is reported to have an acceptable safety profile however unwanted side effects result in a portion of patients withdrawing from treatment. An MS clinic located in a major Australian teaching hospital identified that patients who commenced Fingolimod and experienced poor drug tolerability would soon request to cease their medication. Through a process of consultation and historical experience with other DMTs, it was identified by the neurologist and MS nursing expertise that there was an opportunity to explore individualised oral drug titration.

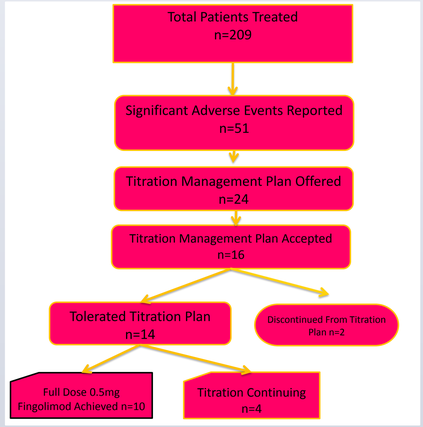
## OBJECTIVE

To reduce and eliminate treatment side effects, reduce patient treatment withdrawal, and achieve the full therapeutic dose regime.

## METHODS

In collaboration with the neurologist, MS Nurses were engaged to manage side effects, and titrate the Fingolimod dose according to side effects experienced. Patients who chose to withdraw from Fingolimod were given the option of a personalised management plan. No clinical assessment tool was used to grade severity of the adverse event. All supportive care given was based on the patients reported perception of discomfort. The program offered regular monitoring and side effect management for Lymphopenia, Gastrointestinal Disturbance, Headache and a feeling of being generally unwell. Ongoing consultation with the neurologist by the MS nursing staff was maintained along with Fingolimod dose adjustments. A variety of supportive medication, although not limited to Paracetamol, Ibuprofen, Ranitidine, Metoclopramide, and Loperamide were used. Services were delivered via phone consultation, email, fax, mail, clinic visits and the patient's general physician. Although the MS clinic provided a comprehensive management service, many patients chose their local pathology facility for blood collection due to location convenience, and travel cost efficiency.

**Figure 1**




## DATA COLLECTION

This was not a clinical study. All information provided is through retrospective clinical experience and implementing currently accepted standard practice medications along with reduced dosing strategies. All patients commencing Fingolimod were placed onto a tracking spreadsheet (Figure 1). Pre-screening tests,[8] side effects experienced and patient withdrawal was notated.

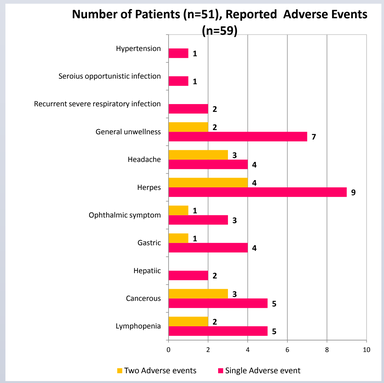
Patients, who experienced clinically significant side effects such as malignancy, serious infection, and ophthalmic symptoms (Figure 2), were not considered suitable for the titration management program. Fingolimod dosing was variable to the individual with most requiring 2nd or 3rd daily administration. A few patients require several dose adjustments over weeks before reaching the desired endpoint.

The crude form of data collection provided valuable information and an insight into treatment barriers. All Serious Adverse Events (SAEs) and Medical Events of Interest (MEOIs) were officially reported to Novartis locally

## RESULTS

In total 209 patients were treated with Fingolimod (Figure 1). A few patients experienced multiple side effects which contribute to the reporting incidence of 59 (Figure 2). Clinically significant adverse events such as Lymphopenia, Herpes Zoster, Malignancy, Headache, Ophthalmic symptoms, Gastrointestinal disturbance and a feeling of being generally unwell were reported by n=51 (24.4%), From this patient group n=24( 47%) were offered a side effect management and drug titration plan. Resulting from the invitation n=16 (66.7%) chose to participate in the innovative treatment approach. Hence, n=10 (62.5%) were able to reach the full dose and remain on treatment (Figure 3), n=2 (12.5%) patients discontinued treatment due to poor tolerance and n=4 (25%) continue to remain on drug titration. Nil relapses were observed or reported during the titration period (Figure1).

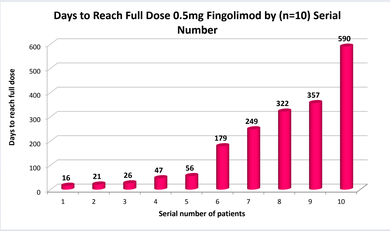
**Figure 2**




## LIMITATIONS

There was no protocol or treatment plan structured as each patient had personalised prescription recommendations, and time to reach Fingolimod full dose or withdrawal was anticipated to vary. Analysis of the individual data revealed some patients were not always prompt with instructions issued such as blood sampling, and dose escalation. Reasons given were social events, delays in filling supportive side effect prescriptions and holidays. Unfortunately one patient was intermittently lost to follow up due to a holiday lasting several months, however during the period of absence, continued low dose Fingolimod. On return the patient reinitiated contact with the MS nursing service and full dose prescription was eventually achieved. This occurrence has impacted significantly on the mean data of 186.3 days (Figure 3). Hence, social and economic variables are acknowledged to influence medication management prescribed, and time to full dose prescription.

**Figure 3**




## DISCUSSION

Historically approved MS treatments offered have been self injectable DMT's.[9] Although individualised dose adjustment regimes when using numerous types of medication is not a new concept,[5] flu type symptoms that were induced by using the interferon's encouraged lateral thinking by clinicians and titration doses were introduced.[3,10] Essentially incremental dosing facilitated acceptable side effect management.[3,10,11] By employing this strategy, research reports that the majority of patients could achieve the full dose prescription.[3]

Furthermore, pharmacokinetic investigations of Fingolimod reveal no clinical relevance that is associated with age, sex or ethnicity.[6] However, a small Japanese study of three patients hypothesised that women with small body surface areas may experience a variation in plasma concentration and alternative treatment schedules may be required.[12] Although Fingolimod has been shown to have a low to moderate inter-subject variability in relation to the absorption, and clearance rate,[6] post marketing discussions have included dialog regarding the exploration of minimal dose effectiveness of 0.25mg/day,[2] especially when there is a definite relationship between exposure and side effects experienced.[5,12]

Again it could be hypothesised that a "Right dose" approach is required, and that a lower dose Fingolimod exposure of 0.25mg/day, could be as effective as 0.5mg/day.[13] Often the MS management and treatment plan requires a team approach. As MS therapies continue to evolve so will the increasing demand on the MS nursing services which identifies gaps, coordinates other relevant services and essentially brings supportive disciplines together.[4,16] Research indicates that if the patient can be offered a high quality interventional relationship with the MS nurse, and treatment team, the benefits of tolerance and adherence may result in a better quality of life, lower the risk of relapse, impact on disability progression, and result in fewer hospitalizations and emergency room visits.[13,14,16]

## CONCLUSION

Long term data which demonstrates the success of interferon titration[17] is encouraging and the same approach should be effective for a select group of patients who struggle tolerating the initial recommended 0.5mg daily therapeutic Fingolimod dose. There may be a role for Fingolimod 0.25mg/day, however the optimal recommended therapeutic dose of 0.5mg daily is achievable for many individuals if side effects and Fingolimod titration is efficiently and effectively managed.

## REFERENCES

1. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372:1502–1517. doi: 10.1016/S0140-6736(08)61620-7
2. Jeauserdo G, O'Connor P., Montalbon X, et al. Five-year results from a phase study of oral fingolimod in relapsing multiple sclerosis. *Mult Scler*. 2013; 0(0): 1-5. doi: 10.1177/1352458513513059
3. graneri G, Filini G, Farrell A, et al. Fingolimod modulates peripheral effector and regulatory T cells in MS patients. *J Neuroimmune Pharmacol*. 2013; 8(5):1106-13. doi: 10.1007/s11481-013-9465-5
4. Therese B, Dishon S, McEwan L, Smrtka J. The evolving role of the multiple sclerosis nurse: An international perspective. *Int J MS Care*. 2011;13:105-112.
5. Huang SM, Bhattaram A, Mehrotra N, Wang Y. Is this the dose for you?: the role of modeling. *Clin Pharmacol Ther*. 2013; 93(2):159-162. doi: 10.1038/clpt.2012.228
6. David JD, Kovarik J M, Schmouder RL. Clinical pharmacokinetics of fingolimod. *Clin Pharmacokinet*. 2012; 51(1):15-28.
7. Filho ML, Bouvie J, Brillante RT, et al. Perspective on approaches to limit flu-like symptoms during interferon therapy for multiple sclerosis. *Int J MS Care*. 2014;16(1):55–60. doi:10.7224/1537-2073.2013-006
8. You and Gilenya. *Booklet, Novartis*. 2013.
9. Jrodsman L, Phillips T, Kokel K, et al. Disease-modifying therapy in multiple sclerosis: strategies for optimizing management. *Neurologist*. 2002;8(4):227-236.
10. Brandes DW, Callender T, Lathi E, O'Leary S. A review of disease-modifying therapies for MS: maximizing adherence and minimizing adverse events. *Curr Med Res Opin*. 2009;25(1):77-92.
11. Bubalo J, Clark RX, Jling SS, et al. Medication adherence: Pharma-cist perspective. *J Am Pharm Assoc*. 2010;50:394–406.
12. Tanaka M, Park K, Tanaka K. Reduced fingolimod dosage treatment for patients with multiple sclerosis and lymphopenia or neutropenia. *Mult Scler*. 2013;19:1244-1245. doi: 10.1177/1352458512472750
13. alonde RL, Kowalski KG, Hutmacher MM, et al. Model-based drug development state of the art. *Clin Pharmacol Ther*. 2007;82: 21-32. doi:10.1038/sj.clpt.6100235
14. emington G, Rodriguez Y, Logan D, Williamson C, Treadaway K. Facilitating medication adherence in patients with multiple sclerosis. *Int J MS Care*. 2013;15:36-45.
15. Devonshire V, Lapierre Y, Macdonell R, et al. The Global Adherence Project (GAP): A multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2011; 18(1):69-77. doi:10.1111/j.1468-1331.2010.03110.x
16. Ward-Abel N, Vernon K, Warner R. An exciting era of treatments for relapsing-remitting multiple sclerosis. *Brit J Neurosci Nurs*. 2014;10(1):21-28.
17. inger B, Lucas S, Kresa-Reahl K, Ross AP, Blake P. Optimizing adherence to multiple sclerosis therapies managing tolerability and monitoring safety. *Int J MS Care*. 2008;10:113-126.

## ACKNOWLEDGEMENT

The authors would like to thank Dr Suzanne Hodgkinson, founder and director of the MS clinic Liverpool Hospital; who contributed and supported the MS nursing personalised management titration plan.

## DISCLOSURE

There is no known conflict of interests to be disclosed.

RESEARCH POSTER PRESENTATION DESIGN © 2012
www.PosterPresentations.com