Original Article

Safety monitoring of the newer Disease Modifying Therapies in Multiple Sclerosis patients in Mater Dei Hospital

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Abstract

Patients with highly active Multiple Sclerosis can be started on the newer pharmaceutical agents, Dimethyl Fumarate or Fingolimod. Safety monitoring recommended includes regular blood analysis and also ophthalmic tests and MRI scans in the case of Fingolimod.

The aim of this audit is to verify whether timely investigations are being taken, checked and results documented in a database and whether the appropriate action is being taken should safety become a concern.

Method: An Excel document shared by all four Neurology consultants documents the patients' personal details, any baseline investigations or other recommended tests taken and the blood results taken at regular intervals. This data was analysed for accuracy by keeping it up to date. The products' SPC recommendations were used as guidelines and the time-frame modified locally.

Results: After analyzing all the blood tests taken while on Dimethyl fumarate, 39% of patients took their regular blood tests on time; 31% were not taken on time and 30% had no blood tests taken at all. On the other hand, only 59% of patients on Fingolimod took their blood tests on time. 82% of the blood results were documented in their Excel document. A repeat MRI scan 6 months after starting Fingolimod showed that only 53% took it on time.

Conclusion: Using an Excel document was a trial to try and ensure compliance with these recommendations. However, this audit clearly documents that it is not enough to follow patients on a regular basis, highlighting the need for a specialist nurse to monitor such patients.

Keywords

Multiple Sclerosis; medical audit; Dimethyl fumarate; Fingolimod; Malta

Abbreviations

Multiple Sclerosis (MS); Central Nervous System (CNS); Summary of Product Characteristics (SPC); Progressive Multifocal Leukoencephalopathy (PML); Complete Blood Count (CBC); Urea & Electrolytes (U&E); Liver Function Tests (LFT); Magnetic Resonance Imaging (MRI); Disease-Modifying Agents (DMA's); Upper Normal Limit (UNL).

Introduction

Multiple Sclerosis (MS) is a chronic, autoimmune, inflammatory, demyelinating neurological condition of the central nervous system (CNS) whereby the T-cell mediated immune system destroys the myelin and axons in varying degrees. MS is a progressive disorder that has an unpredictable and varied course. Initially, the symptoms are reversible as demyelination heals incompletely; however, prolonged demyelination

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causes axonal loss and clinically progressive symptoms. The trigger is unknown, although it is thought to have a combination of genetic predisposition and environmental factors, such as a viral infection early on in life.[1]

The mean age of onset is usually between 20 to 40 years [2] and women are twice more likely to be affected than men.[3] It has a higher prevalence in Caucasians and in temperate countries such as Northern European countries, possibly linked to low levels of circulating Vitamin D.[1]

There are four major categories of MS based on the course of the disease:[4]

1. *Relapsing-remitting MS* (85% of patients): The most common form, it is characterised by flare-ups (relapses or exacerbations) of symptoms followed by periods of remission.
2. *Secondary progressive MS*: may develop in patients with RRMS as the disease progresses. Periods of remission lessen and symptoms may not disappear completely as disability accumulates.
3. *Primary progressive MS* (10% of patients): There is a steady decline as symptoms continue to worsen from the start of the disease with no relapses/remissions, although there may be occasional plateaus. This is the most challenging type to manage as it is resistant to most drugs used in MS.
4. *Progressive-relapsing MS* (5% of patients): This rare form of MS is progressive from the start with intermittent flare-ups along the course and no periods of remission.

MS has a wide range of symptoms and signs on presentation but it usually presents monosymptomatically.[1] Patients can present with visual symptoms such as diplopia, unilateral optic neuritis; sensory disturbances including dysthaesia (burning and "pins and needles") or paraesthesia (numbness or tingling); motor symptoms such as leg weakness; or also brainstem or cerebellar symptoms including ataxia, vertigo, tremor etc.

Early on, relapses may be followed by remission and full recovery. Since it is a progressive disorder, with time remissions becoming shorter and less frequent and may not return back to normal in between flare-ups as disability accumulates.

At Mater Dei Hospital, the new Disease-Modifying Agents (DMA's) used in highly active relapsing-remitting multiple sclerosis include Dimethyl fumarate and Fingolimod. According to the Summary of Product Characteristics (SPC) of Dimethyl fumarate, one of the precautions mentioned include close monitoring of the patients' blood tests at regular intervals to look out for lymphopenia, changes to the hepatic and renal function, and MRI imaging if at increased risk of Progressive Multifocal Leukoencephalopathy (PML). The SPC of Fingolimod also recommends regular blood tests to look out for lymphopenia and hepatic impairment. In addition, all patients should have an ECG and blood pressure measurement performed prior to and 6 hours after the first dose of Fingolimod in view of the risk of bradyarrythmia, MRI imaging to assess for the risk of PML, and an Ophthalmology review after 3 months of starting treatment to look out for macular oedema. In view of the serious consequences that may arise should any shortcomings occur, the Neurology consultants within Mater Dei Hospital started an Excel document to try and ensure compliance with these safety measurements.

Methods

Approval was sought from the Data Protection Office and University Research Ethics Committee, with endorsements from all four Neurology Consultants. An Excel document shared between the four consultants keeps track of all patients on Dimethyl fumarate and Fingolimod. It documents patients' personal details, starting date of treatments, any baseline investigations or other recommended tests taken, and blood results taken at regular intervals. The products' SPC recommendations are used as guidelines to identify what tests are needed to be taken regularly.

The time-interval was set as bi- or tri-monthly, as agreed between the consultants. The results were either documented as "on time" (i.e. taken within the 30-day period of that month), "not on time" (i.e. outside of the 30-day window), or "not taken" (no blood results taken 1 month before or after the anticipated month were found). All blood tests were taken at Mater Dei Hospital and the results were found on the computer programme iSoft Clinical Manager; thus excluding any tests performed in the private sector. Patients that stopped treatment or were lost to follow-up did not have any further blood tests taken regularly. According to Fingolimod's SPC recommendations,

patients should have a repeat MRI after 6 months of starting medication to ensure there is no relapse/disease progression.

The Excel document was accessed during the first week of January 2016 and any data inputted up to this date was analysed for accuracy, kept up-to-date with the latest blood results, and any documented actions taken, without consulting each patient's personal Medical file.

Results

Dimethyl fumarate

The bar graph in *Figure 1* was created to show how many of the 38 registered patients on Dimethyl Fumarate had their blood tests actually taken on time, how many were not taken on time, how many were not taken at all and how many are still pending at timely intervals (x-axis). No clear pattern is observable, however one can note that over time there were less tests taken (on time and not on time) while there are increasing pending tests in view of new patients being started on Dimethyl fumarate.

Since one cannot assume or predict how the pending tests will behave, as either taken on time or not on time, our existing data needs to be interpreted without taking them into consideration. Therefore, after deducting the pending tests, the pie-chart in *Figure 2* shows that up to 39% of the tests taken so far were done in a timely fashion; whilst, 31% of such tests were not taken on time according to the predetermined timeframe. Moreover, up to 30% of the regular assessments were not taken at all since no results were shown on iSoft. Therefore, altogether up to 70% of tests were taken whilst one-third have lost their opportunity to be adequately monitored for any abnormalities (*Figure 2).*

Fingolimod

From the blood tests actually taken, 68 out of 115 total tests were taken on time, making up just 59% of the total tests. On the other hand, a little less than half of the tests were not taken on time, as 47 tests out of 115 tests, i.e. 41% of them, were taken at an earlier or later date than the predetermined timeframe *(Table 1) (Figure 3).*

If one were to analyse whether blood tests results were chased, acknowledged and documented in their Excel database, one will find that the majority (i.e. 82%) were clearly documented whilst only 18% were found to be not documented in their database. The results were found in iSoft Clinical Manager, indicating that the patient had taken the test but it was unclear whether the result was chased by the firm *(Table 2) (Figure 4).*

Out of 23 patients registered, only 19 had their 6-monthly MRI taken, of which 10 were taken on time, 3 were taken at an *earlier* date whilst 6 had the MRI taken at a *later* date. The MRI date was late by 1 month at the lowest and 4 months by the highest. These would tally up to 53% of the MRI's taken on time, 16% taken at an earlier date and 32% taken late *(Table 3) (Figure 5).*

Figure 1: Blood tests taken at set intervals for Dimethyl Fumarate

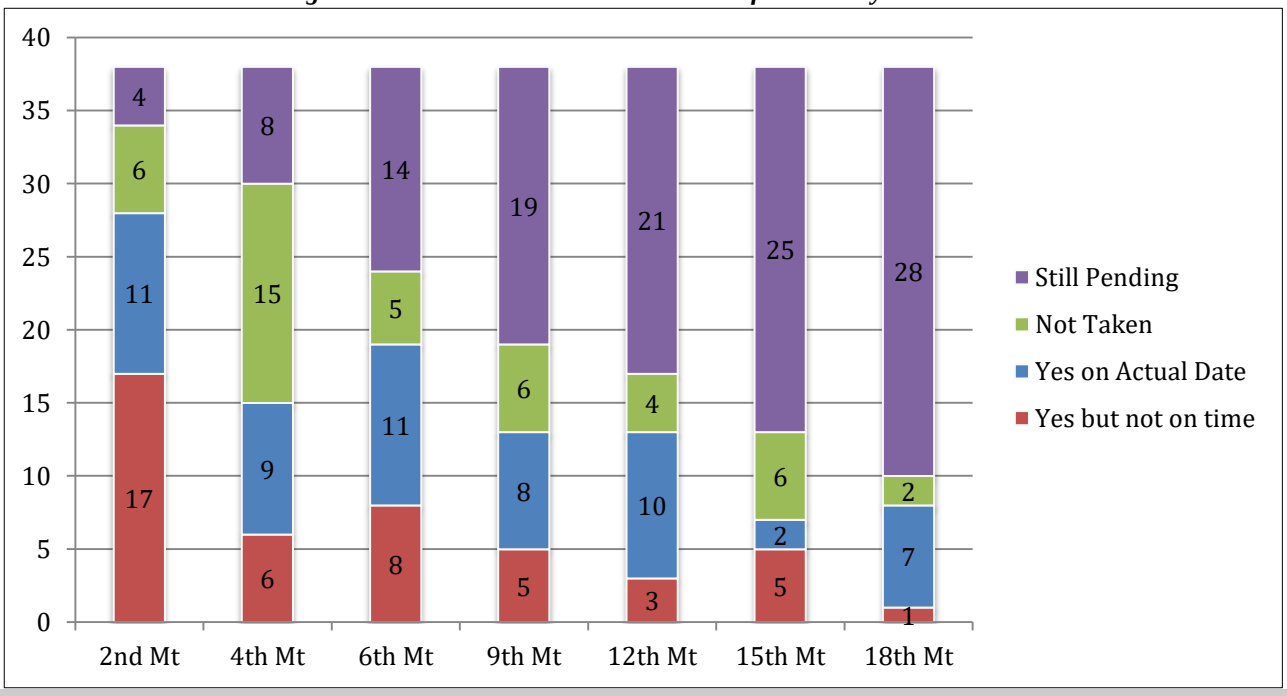


Figure 2: *Percentage for total blood tests booked for Dimethyl Fumarate*

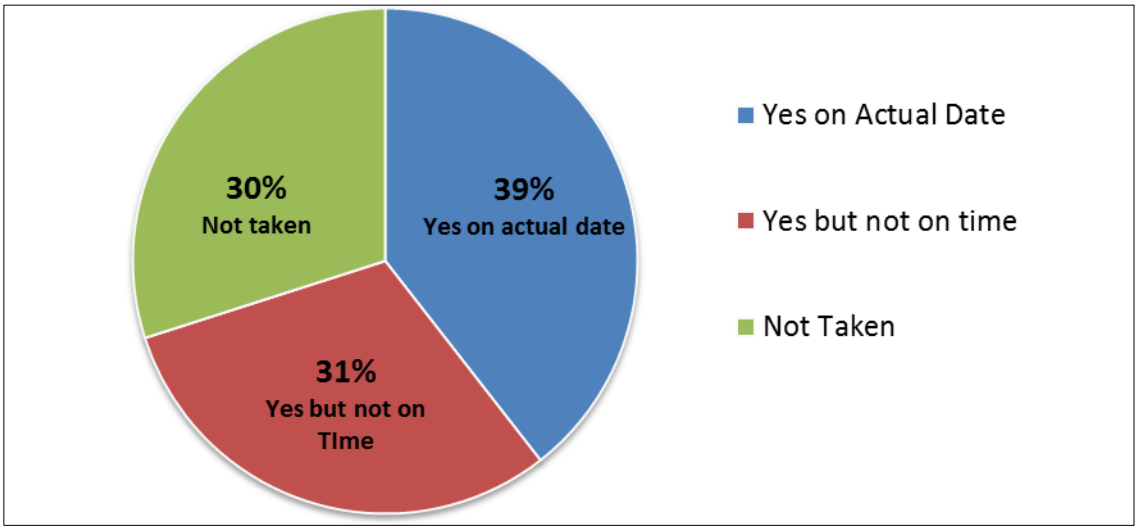


Table 1*: Timely blood tests taken on Fingolimod treatment*

Timely Blood tests		
Blood tests taken on Time	**68**	**59%**
Blood tests NOT taken on time	**47**	**41%**
Total tests performed	**115**	

Figure 3*: Timely blood tests taken for Fingolimod*

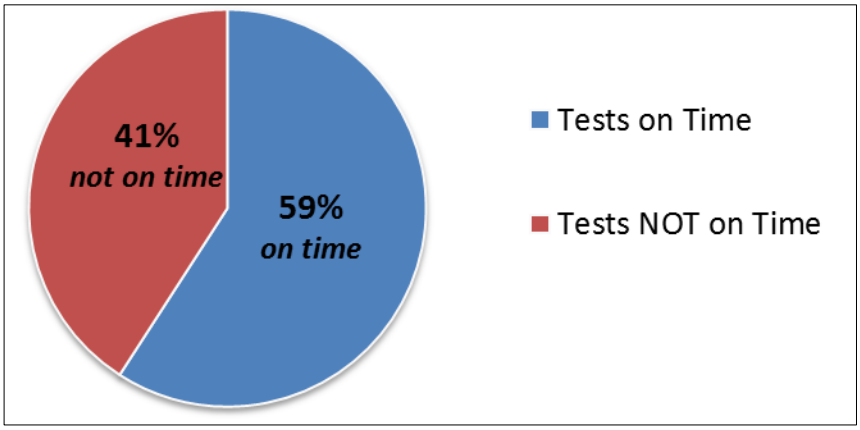


Table 2*: Blood test documentation in Excel database on Fingolimod*

Blood test result documentation in Excel database		
Result documented	**94**	**82%**
Result not documented	**21**	**18%**
Total results available	**115**	

***Figure 4**: Result Documentation in Database for Fingolimod*

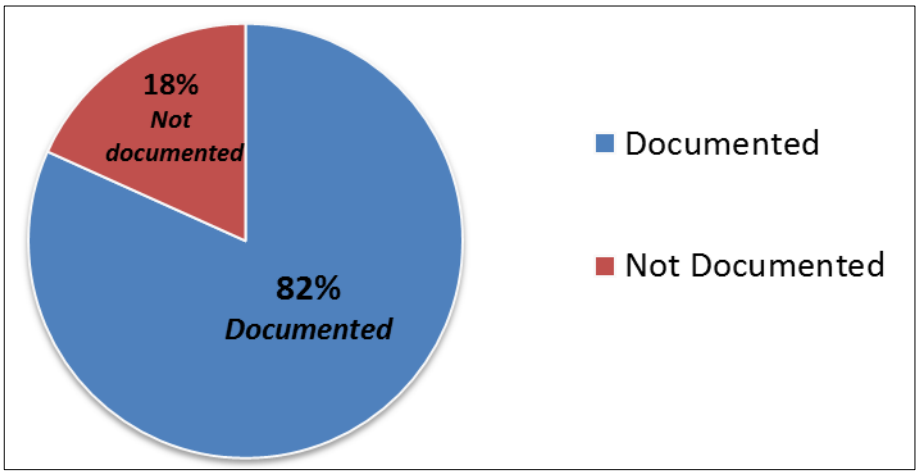
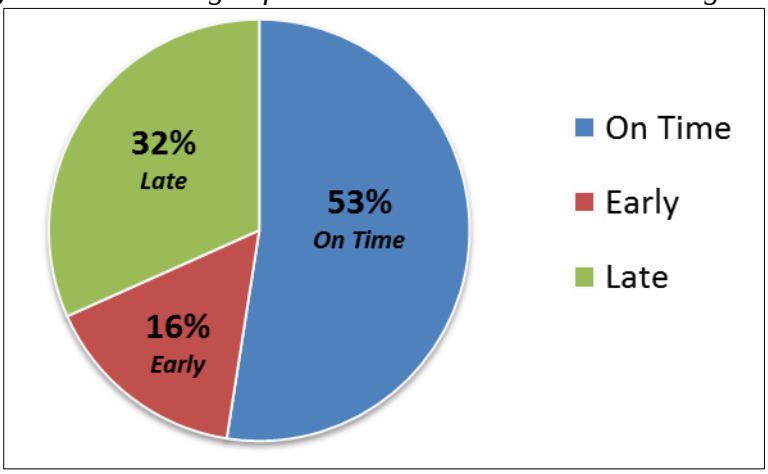


***Table 3**: 6 months MRI surveillance while on Fingolimod*

6 Months MRI surveillance		
Total patients performed	**19**	
MRI taken on time	**10**	**53%**
MRI taken at an earlier date	**3**	**16%**
MRI taken at a later date	**6**	**32%**

***Figure 5**: Percentage of 6-Months MRI scan while on Fingolimod*



Discussion

Dimethyl fumarate - (Tecfidera®)

After collecting and interpreting all the data, a number of observations were noted. In a few cases, not all three blood tests (CBC, U&E, Cr and LFT's) were taken as baseline before starting treatment, taken regularly every month or screened for any abnormalities from their baseline.

While in their database it was stated that baseline bloods were available on a particular date, on three occasions these could not be traced on the iSoft programme, raising the question whether they were actually taken and the source of their claim. In other instances, the starting date of treatment was not stated in the Excel database. There were cases where the predicted timeframe for due tests did not correspond with the starting date of treatment as documented in their database. This made it debatable whether treatment was actually started on the date as stated, or whether the tests were routinely taken 1 month later.

While searching for their regular blood tests on iSoft, it was noted that some of the values were not documented on their Excel database, raising

concerns whether they were chased and acknowledged. Moreover, some lymphocyte results were not documented in the right tab on their Excel database – For example, the 2nd and 4th month results were swapped.

On three occasions, the lymphocyte count was noted to drop below 0.5 $x10^9$/L. Despite this, no action was documented in their Excel sheet as to whether this treatment was temporarily suspended to allow the lymphocyte count to recover, as advised by the product's SPC recommendations.

Some patients had pending blood tests showing on iSoft Manager for the upcoming months, while for the majority they had no upcoming blood tests ordered. This raised concerns on how compliance was monitored and whether checks were made to ensure patients had an appointment set for blood-letting.

Fingolimod - (Gilenya®)

Similarly to Dimethyl fumarate, not all three blood tests (CBC, U&E, Cr and LFT's) were taken as baseline before starting treatment, taken regularly every month or screened for any abnormalities from their baseline. 10 patients out of the total of 23 did not have documentation of their 3-month ophthalmological examination, whether it was performed or the exam's conclusion in the Excel document.

Some MRI tests did not have their results documented in their Excel database, making it uncertain whether they were chased and acknowledged in a timely fashion. 16% of the 6-monthly MRI were taken earlier, possibly performing it during a suspected relapse when the patient exhibited signs and/or symptoms.

Not all patients had blood tests booked on iSoft programme for the upcoming months. This made it difficult to ensure compliance from the patient to take their blood tests on time. On 7 occasions in total, the blood test results documented on their Excel database did not match the true results as taken from the iSoft computer programme. In one case, two sets of results were swapped as the 6th and 9th month result respectively. While searching for patients' regular blood tests on iSoft, it was noted that some of the values were not documented on their Excel database, thus raising concerns whether they were chased and acknowledged.

In two cases, the lymphocyte count had dropped less than 0.2 $x10^9$/L (0.16 and 0.17) with no documented action keyed into their database. On the other hand, two particular patients were documented as "monitoring lymphocyte count and to decide on further management". One of these had discontinued Fingolimod indefinitely in view of recurrent lymphopenia.

After 12 months, according to the consultants' database it states any further blood tests to be taken as "regular follow-up". However, there was no clear pattern as to how often this should have been taken. In fact, some tests were sparsely taken and in other occasions were taken too close to each other to observe for any abnormalities. Only one consultant kept a regular time-frame after the 12th month, which made it easier to keep track of the patient's blood tests and MRIs due.

Conclusion

The use of Dimethyl fumarate and Fingolimod require a number of investigations to be taken before starting treatment to ensure that the right candidate is eligible for these DMA's. In addition, close follow-up of these patients with regular blood tests, MRI scans and an ophthalmological review are necessary to ensure no complications arise. The SPC recommendations are clearly documented and any shortcomings can have serious consequences.
In view of this, the consultants within the Neurology Department felt the need to utilise an Excel document as a trial to try and ensure compliance with these recommendations. However, this audit clearly documents that it is not an easy task as it is quite time-consuming and laborious. As a result, the Excel document was not used appropriately, and clearly it is not enough to follow patients on a regular basis.

Therefore, the suggestions below may help to alleviate the problem and ensure better compliance in the future;

1) A qualified specialist nurse would be highly beneficial to educate, support and advise patients to take regular blood tests and stress the importance of compliance. He/she would work with the professional backup offered by Neurologists should a problem arise.
2) Ensure each patient has a set of baseline blood tests, including **all** three tests (CBC, U&E, LFT's), taken before initiating therapy.
3) **All** three blood tests should be regularly booked and screened for any abnormalities

during their appointment, namely the lymphocyte count and the liver hepatic enzymes.

4) Patient should be provided with set appointments according to the timeframe set in the Excel database and if they do not show up by mid-month, they can be reached via phone/email/SMS and reminded of their appointment.
5) Once the test has been taken, the result should be chased and acknowledged by the nurse and inputted in the Excel database in the correct order.
6) Should there be any concerns, the nurse can discuss the issues with the Neurologist for any action required. These should then be clearly documented in the Excel database for future reference.
7) The specialist nurse would also act as the point of contact should the patient report any symptoms or signs of an infection to check their latest lymphocyte count, concerns about the treatment's side-effects, queries about appointments and any other information required about their condition.
8) Patients on Fingolimod, should have regular Liver Function Tests taken and assessed for any abnormalities. Results should be documented in case there are elevated liver enzymes which if >5 times UNL, would necessitate suspending treatment temporarily as advised by the SPC recommendations.
9) In view of a high rate of patients suffering from Diabetes Mellitus locally, such patients taking Fingolimod would benefit from regular ophthalmological examinations and not just as baseline and at 3-months of therapy. Macular oedema may develop with or without visual disturbances.

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