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CENTRAL MACULAR THICKNESS IN FINGOLIMOD TREATED MULTIPLE SCLEROSIS PATIENTS, A LOCAL EXPERIENCE

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ABSTRACT

Background: Multiple sclerosis is a demyelinating disease of the central nervous system and is one of the commonest causes of optic neuritis. Fingolimod is the first United States Food and Drug Administration-approved orally-given agent for the treatment and modification of relapsing-remitting forms of multiple sclerosis. Fingolimod-associated macular edema is a well-recognized risk for its use in a renal indication. **Aim of the Study:** To evaluate the effect of fingolimod on central macular thickness in patients with multiple sclerosis. **Patients & Methods:** a prospective observational cross sectional study was conducted on a sample of Iraqi patients with multiple sclerosis treated with fingolimod during the period from June 2019 to October 2020, in which 156 eyes of 78 patients were assessed and followed up for one year to evaluate the development of macular edema by measuring central macular thickness, using optical coherence tomography. **Results:** 78 patients participated in the study, their mean age was 39 ± 10.6 years, the most frequent age group was 30-<40 years with 26 (33.3%) participants, and 59 (75.6%) of them were females while 19 (24.4%) were males. The central macular thickness increased slightly from baseline after 3-6 months of treatment, and then returned to levels slightly below the baseline readings after one year; however, these changes were not statistically significant and no patient of those who were followed up for one year developed macular edema. **Conclusion:** The recommended, FDA-approved, orally given, daily dose of fingolimod (0.5mg) that is prescribed for a patient with multiple sclerosis is a well-tolerated drug regarding the risk of macular edema.

KEYWORDS: Fingolimod, macular edema, central macular thickness, multiple sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is one of the most common neurologic disorders, affecting approximately 300,000 persons in the United States and its highest incidence is in young adults.[1]

It is defined clinically by the involvement of different parts of the central nervous system at different times, provided that other disorders causing multifocal central dysfunction have been excluded.[1]

Initial symptoms generally commence before the age of 55 years, with a peak incidence between ages 20 and 40 years; women are affected nearly twice as often as men. The cause of multiple sclerosis is unknown, but tissue damage and neurologic symptoms are thought to be triggered by an immune mechanism directed against myelin antigens. Viral infection or other inciting factors may promote the entry of T cells and antibodies into the central nervous system by disrupting the blood-brain barrier.[1,2]

Clinical disease activity in multiple sclerosis can manifest as relapses or insidious progression. According to the occurrence and timing of these features, four main categories of multiple sclerosis were outlined in 1996 in the widely accepted classification of Lublin and Reingold, these include relapsing-remitting multiple sclerosis RRMS (approximately 85% of individuals present with relapses and remission), secondary progressive multiple sclerosis, primary progressive multiple sclerosis, and progressive relapsing multiple sclerosis.[2]

Ocular involvement produces a broad diversity of abnormalities, affecting both the afferent and efferent visual pathways. Essentially every portion of the visual sensory system, including the retina, optic nerve, chiasm, post-chiasmal pathways, and the visual sensory cortices and their connections may be involved.[3,4]

Optic neuritis, as a classic example of afferent visual system involvement, is the most frequent relapsing manifestation and is the most studied complication in the literature. Patients with MS also develop ocular motor disorders leading to diplopia or oscillopsia. The most common ocular motor abnormalities in patients with MS are internuclear ophthalmoplegia, saccadic hypermetria, gaze-evoked nystagmus, and impaired vestibulo-ocular reflex suppression.[5,6]

Although some disorders may be manifestations of acute MS relapses, they more frequently occur in the chronic disease phase, in which they persist over time.[7,8]

Several drugs are used in the treatment of a relapsing form of MS. Fingolimod (Gilenya) is one of ten agents approved by the Food and Drug Administration (FDA).[9,10] It is an oral immune-modulator agent derived from the fungal metabolite myriocin[2] also approved by the National Institute for Health and Care Excellence, for use in patients with highly active relapsing-remitting multiple sclerosis (RRMS) after recent clinical trials demonstrated its efficacy in reducing the frequency of relapses and disability progression on long-term follow-up of patients with multiple sclerosis when compared with placebo.[11,12]

The therapeutic effects in multiple sclerosis therapy are thought to be due to the action of fingolimod on preventing the egression of lymphocytes from lymphoid tissue into the circulation, thereby sparing the central nervous system from attack by myelin-reactive lymphocytes,[13,14] by inducing aberrant internalization of the sphingosine 1-phosphate (S1P) receptor and, thereby, reduces recirculation of auto aggressive lymphocytes to the central nervous system.[15]

Adverse events upon the use of fingolimod include transient bradyarrhythmias on the initiation of treatment, non-fatal herpes virus infections, macular edema, mild hypertension, elevated liver enzyme levels, and lymphopenia. Skin cancers did occur, but the incidence of malignancies was not significantly raised.[2] Since initial authorization, unexplained death in a patient within 24 hours of taking fingolimod has led to further regulatory advice on cardiovascular safety.[2] Fingolimod is not recommended for patients with a history of a cardiovascular or cerebral-vascular disease or who take heart-rate lowering medication. On initiation of treatment, the electrocardiogram should be monitored before receiving the first dose and for at least 6 hours after. Vaccination against the varicella-zoster virus is recommended in antibody-negative patients before treatment.

Monitoring of full blood count and liver function on treatment and ophthalmological review for macular edema are also recommended.[2]

The mechanism for fingolimod-associated macular edema (FAME) is unclear. In addition to its function as described, S1P and its receptors also play an important role in the regulation and maintenance of vascular endothelial and epithelial barriers.[16] given this role, it is likely that this may underlie the development of FAME. Coexisting conditions such as diabetes mellitus, uveitis, retinal vascular disease, or recent ophthalmic surgery are associated with an increased risk of macular edema (ME).[17] Pre-existing inflammation of the vascular endothelium may be exacerbated by fingolimod-induced S1P-receptor agonist and breakdown of the inner blood-retinal barrier, making FAME is more likely to occur.[18]

To date, the efficacy of fingolimod in relapsing-remitting multiple sclerosis (RRMS) has been demonstrated in four large phases III double-masked randomized trials: Freedoms, Freedoms 2, Transforms, and Informs.[10,11,19.20]

FAME was first noted incidentally in renal transplant trials, where fingolimod was used at approximately 5–10 times the dose that is currently approved for the treatment of MS. In renal transplant patients, doses of 2.5 mg to 5 mg were used and FAME incidence ranged between 0 and 12.5%, the follow-up in these studies was 12 months.[21 to 25]

Subsequent trials in patients with MS have shown that the risk of FAME is dose-dependent and the follow-up period of these trials, including extensions, was 24 to 60 months.[26,27,28]

Pooled data from the FREEDOMS and TRANSFORMS trials observed that FAME typically occurred during the first four months of fingolimod use and caused visual symptoms in approximately half the cases.[17]

Clinically, the diagnosis of ME is based on a fundoscopic examination, an inspection of OCT images, as well as the retinal thickness measurements reported with the OCT segmentation software.

OCT test has vastly augmented the ability to diagnose ME non-invasively providing a higher resolution, quantitative, cross-sectional images of the retina OCT analyzes infrared light reflected from the interfaces within the retina, with newer generation spectral-domain OCT (SD-OCT) devices providing retinal images at an axial resolution greater than 4µm. SD-OCT unit shaves

canning speeds 40 times faster than traditional time-domain OCT units.[29]

In normal individuals, the retinal thickness at the central point of the macula (central foveal thickness) is approximately 182 ± 23 μm, and mean foveal thickness (measuring the circular region 1 mm in diameter centered on the foveola) is approximately 212 ± 20 μm (as tested with Stratus OCT 3, Carl Zeiss Meditec, Dublin, CA).[29]

Currently, the only licensed dose of oral fingolimod is 0.5 mg, after use of 1.25 mg fingolimod was halted in all MS clinical studies in November 2009. This was following the unblinding of the FREEDOMS trial, which revealed higher discontinuation rates due to adverse events and little additional efficacy associated with the 1.25 mg dose compared with the 0.5 mg dose.[11]

To evaluate the effect of fingolimod on central macular thickness in a sample of Iraqi patients with multiple sclerosis receiving 0.5 mg fingolimod we conducted this study.

Methodology
A prospective observational cross sectional study was conducted at Baghdad medical city and Ghazi Al-Hariri Hospital for Surgical Specialities from June 2019 to October 2020.

The necessary official approvals and consents were obtained before the initiation of data collection, which include:
- The approval of the scientific committee of Baghdad Teaching Hospital / MS clinic from which data were collected.
- The approval of the scientific committee of Ghazi Al-Hariri Hospital for Surgical Specialties/ ophthalmology clinic where patients were examined.
- Verbal consents from all the patients to participate in the study after explaining to them the aim of the study.

Total of 135 patients who were about to start fingolimod 0.5 mg per day for their RRMS, attending MS clinic in Baghdad medical city were included in the study.Exclusion criteria include any condition that might increase the risk of macular edema namely, diabetes mellitus,retinal vein occlusion, age-related macular degeneration, chronic use of drugs causing macular edema (like prostaglandin analogue), uveitis , cataract surgery or other intra-ocular intervention (within 1 yr) , retinitis pigmentosa, intra-ocular malignancy.

The 270 eyes of 135 patients using fingolimod were included in the study, but only 78 patients completed it because some patients did not attend their scheduled visits or develop systemic complications of fingolimod and excluded from the study.

A full history was taken from the patients at MS clinic then ophthalmological examination was done at the eye clinic in Ghazi Al-Hariri Hospital, which include visual acuity (VA), slit-lamp examination , fundus examination with indirect non-contact lens after pupillary dilation. Then all patients were examined by optical coherence tomography (OCT) imaging to measure the central macular thickness (CMT). OCT was done by trained technicians at Ghazi Al-Hariri Hospital using optovue OCT machine.

Examination was repeated at baseline, after 3-6 month, and after one year from using fingolimod in addition to asking the patients about their general conditions, compliance with treatment, and any new symptoms.

Analysis of data was carried out using IBM© SPSS© (Statistical Package for the Social Sciences) Statistics Version 25.

Normal distribution of numerical variables was tested by Anderson–Darling test, and the variables that did not follow normal distribution were tested by Mann-Whitney U test (compare between two variables), and Kruskal Wallis test (compare between more than two variables). While independent sample T-test(compare between two variables) and Univariate ANOVA (compare between more than two variables) for variables that followed the normal distribution. A p-value less than 0.05 was considered significant throughout data analysis

RESULTS

The mean age of the study participants was 39± 10.6 years, the most frequent age group was 30-<40 years with 26(33.3%) participants, and 59 (75.6%) of them were females. Table-1.

Table-1: Basic characteristics of the study group.

Variable	Number	%
Age groups (years)		
20-<30	14	17.9
30-<40	26	33.3
40-<50	23	29.5
50-<60	12	15.4
60-<70	3	3.8
Gender		
Male	19	24.4
Female	59	75.6
Total	78	100.0

The CMT increased slightly from baseline after 3-6 months, and then returned to levels slightly below the baseline readings after one year; however, these changes were not statistically significant, as shown in Table (2).

There were no statistically significant differences in CMT between age groups at baseline, 3-6 months, or after one year, as shown in Table-3.

**Table-2: Distribution of CMT in µm according to date of measurement.**

Variable	CMT	
	Mean	SD
Baseline	241.65	16.72
"3-6 months"	243.74	16.99
"After one year"	239.28	18.24
P-value	.277	
Univariate ANOVA		

Table-3: Distribution of CMT in µm according to age groups.

Variable, age group		CMT		P-value
		Mean	SD	
Baseline	20-<30	243.21	14.54	.051
	30-<40	237.37	11.55	
	40-<50	239.09	18.24	
	50-<60	251.53	20.70	
"3-6 months"	20-<30	244.64	13.35	.107
	30-<40	241.56	11.26	
	40-<50	239.72	17.98	
	50-<60	252.83	23.73	
"After one year"	20-<30	238.89	14.59	.471
	30-<40	239.31	10.88	
	40-<50	235.59	19.04	
	50-<60	245.27	28.12	
Univariate ANOVA				

Comparison between age groups showed no statistically significant differences in percent changes of CMT after 3-6 months, as shown in figure-1. However, changes of

CMT after one year was significantly higher only among patients aged 30-<40 years compared to patients aged 40-<50 years, as illustrated in Figure (2).
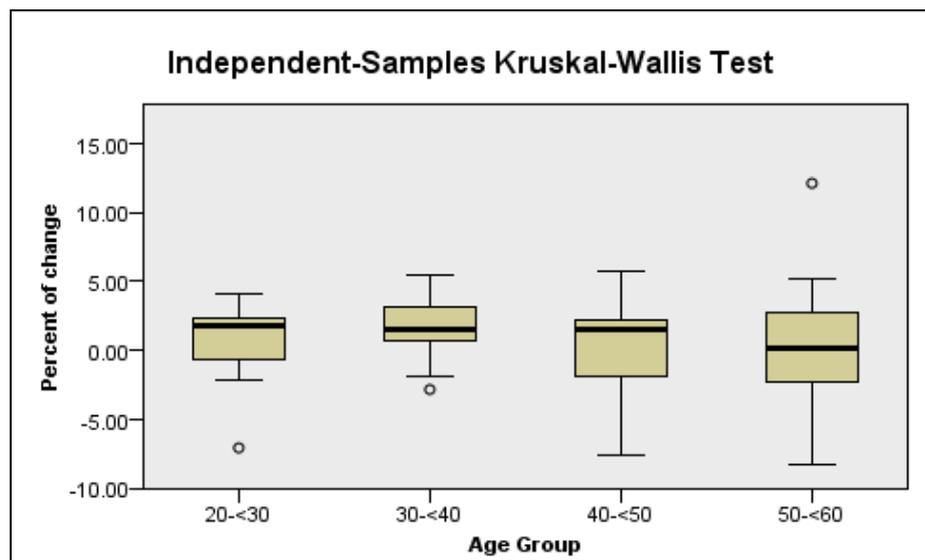
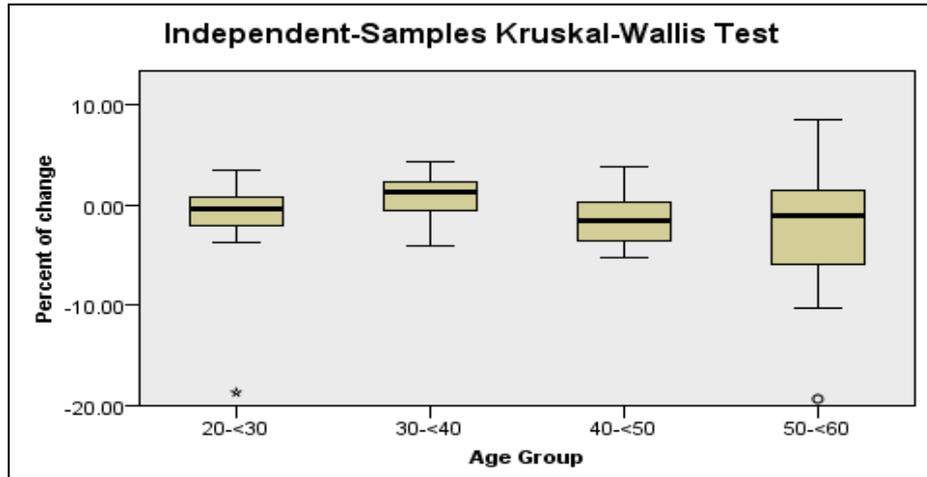**Figure-1: Percent change of CMT after 3-6 months from treatment (P-value= .319).**

Figure-2: Percent change of CMT after one year from treatment (P-value= .011) (30-<40) > (40-<50).

Comparisons of CMT between genders showed no statistically significant differences in CMT at baseline and 3-6 months, however, after one year, males have statistically significant higher CMT than females, as mean CMT of male eyes was 247.92±16.90μm which was higher than mean CMT of female eyes (236.50± 17.91). As shown in Table-4.

Table-4: Distribution of CMT according to genders.

Variable		CMT	
		Mean	**SD**
Baseline	Male	247.11	16.33
	Female	239.89	16.60
	P-value	.101	
"3-6 months"	Male	249.45	16.22
	Female	241.90	16.96
	P-value	0.092	
"After one year"	Male	247.92	16.90
	Female	236.50	17.91
	P-value	.017*	
Independent samples T-test, *: significant <.05			

Figures 3 illustrates the percent changes of CMT after 3-6 months and Figure 4 illustrates the percent changes of CMT after one year and in both there were no statistically significant differences in the percent changes between males and females.
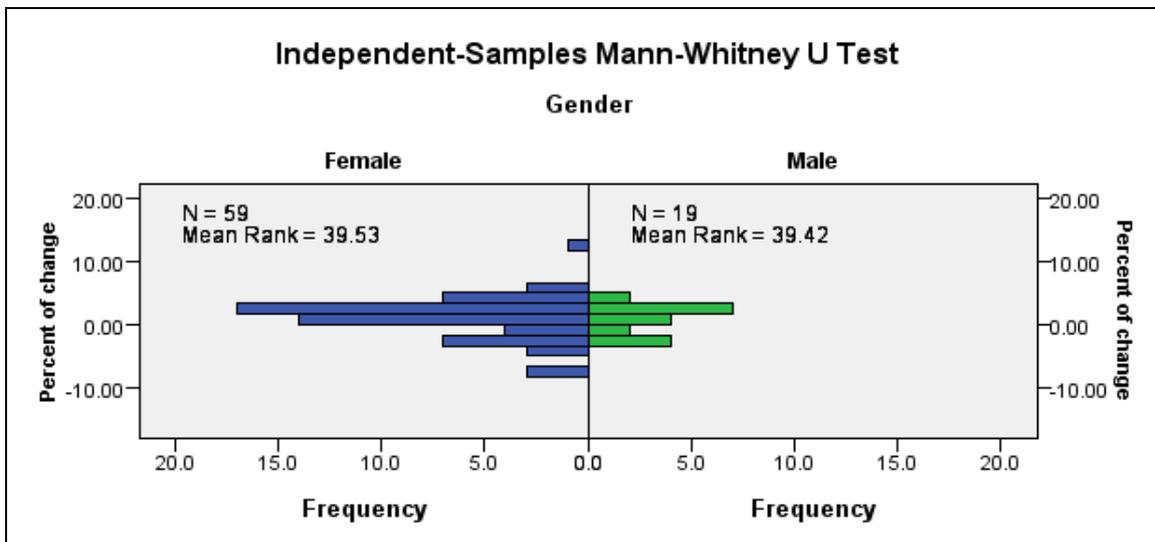

Figure-3: Percent change of CMT after 3-6 months from treatment according to gender (P-value= .986).
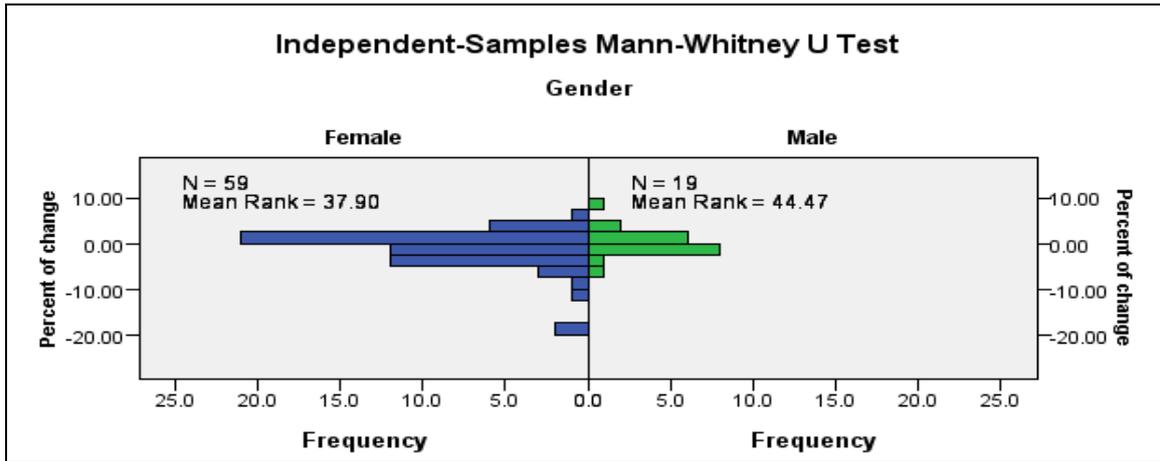
Figure-4: Percent change of CMT after one year from treatment according to gender (P-value= .271)

The duration of disease before starting fingolimod did not have significant impact on CMT, in all the timelines of the study (baseline, 3-6 months and after one year). It can be noticed that patients who had initiated fingolimod 6 months and below before enrollment, had highest mean CMT after 3-6 months (247.04± 12.74μm) and after one year (241.75± 12.93μm), as show in Table-5.

Table-5: Distribution of CMT in μm according to duration of disease before starting fingolimod.

Variable		No.	CMT		P-value
			Mean	SD	
Baseline	≤6 month	24	241.50	13.48	.629
	7-12 months	17	238.24	15.37	
	13 month- years-4	17	240.82	12.50	
	>4 years	20	245.43	23.59	
"3-6 months"	≤6 month	24	247.04	12.74	.682
	7-12 months	17	242.62	14.68	
	13 month- years-4	17	240.71	11.82	
	>4 years	20	243.30	25.51	
"After one year"	≤6 month	24	241.75	12.93	.881
	7-12 months	17	238.32	16.28	
	13 month- years-4	17	238.85	11.91	
	>4 years	20	237.50	28.13	
Univariate ANOVA					

After 3-6 months; the percent change of CMT was significantly higher in patients with disease duration of ≤6 months and 7-12 months, compared to those with disease duration > 4 years, i.e. shorter disease duration was correlated with higher CMT changes.Figure (5)
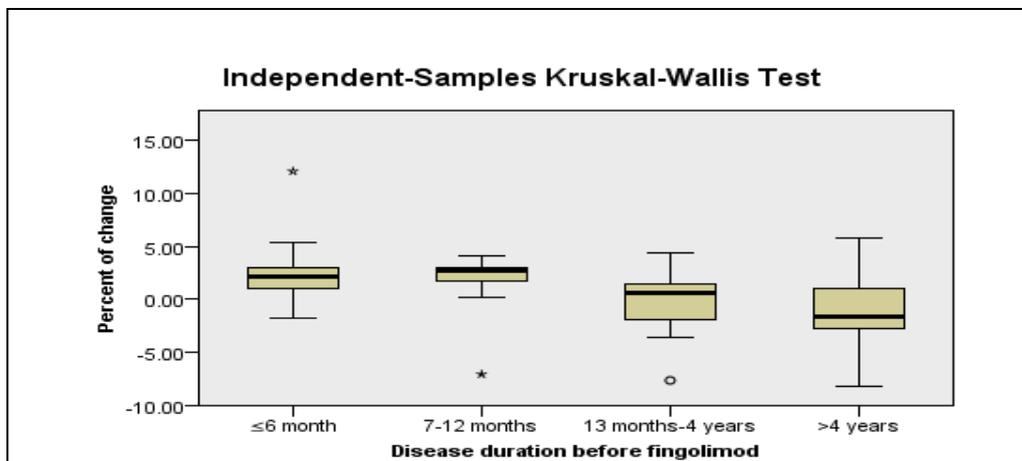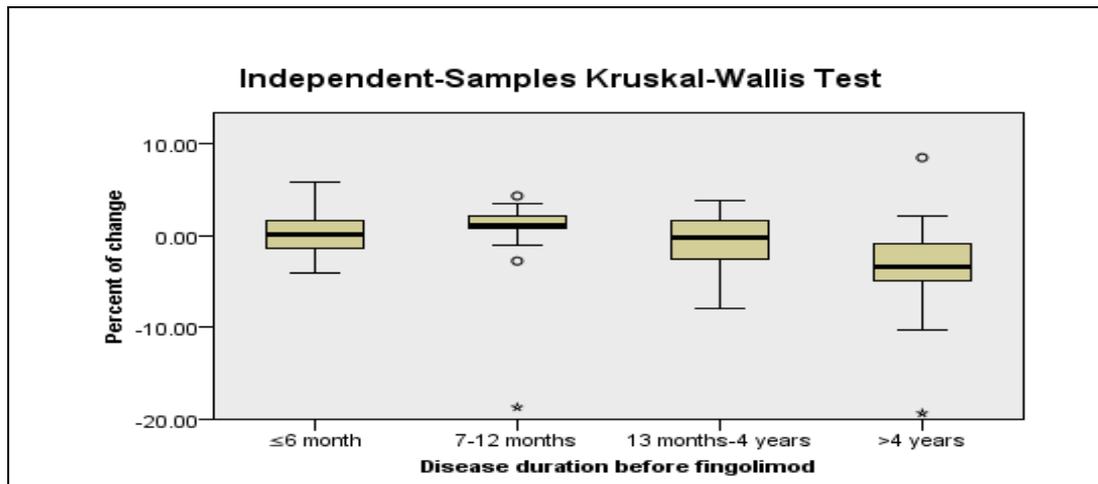

Figure-5: Percent change of CMT after 3-6 months from treatment according to disease duration prior to fingolimod (P-value= <.001).

After one year; the percent change of CMT was significantly higher in patients with disease duration of ≤6 months and 7-12 months, compared to those with disease duration > 4 years. Figure (6)

Figure-6: Percent change of CMT after one year from treatment according to disease duration prior to fingolimod (P-value= .003).

DISCUSSION

The majority of patients in this study were females (59 of 78 patients) that represent 75.6% while males contribute 24.4% (19 of 78 patients). The mean age of the study participants was 39 ± 10.6 years, the most frequent age group was 30-<40 years with 26 (33.3%) participants, and these findings are approximately the same as general epidemiology of MS which showed that the peak incidence is between 20-40 years of age and females are affected nearly twice as often as males.[1]

In the current study, The CMT increased slightly from baseline after 3-6 months, and after one year the CMT decreased to baseline or slightly lower levels ˈhowever; these changes were not statistically significant. These results did not agree with Lublin et al., Kappos et al., and Cohen et al. which showed that FAME typically occurred during the first 4 months of starting fingolimod use which may be due to the anti-inflammatory effect of fingolimod and enhanced astrocytes function. [15]

Regarding the age of patients, there were no statistically significant differences in CMT between age groups at baseline, 3-6 months, or after one year in and this coincided with INFORMS study which showed that age has no significant effects.[19]

The percent of changes in CMT after one year was significantly higher only among patients aged 30-<40 years compared to patients aged 40-<50 years and this result differs from Zarbin et al. which showed that FAME was more likely to occur among patients aged ≥ 41 years and this attributed to a higher incidence of diabetes mellitus in older aged groups.[17] These differences in results may be related to the exclusion criteria in which we exclude diabetes mellitus and other diseases that may be associated with macular edema from our study.

Comparisons of CMT between the genders showed no statistically significant differences in CMT at the baseline and 3-6 months and these results are the same as results of INFORMS study which showed that in the subgroup analysis of sex in the first 6 months after commencing fingolimod to patients with primary progressive MS, the gender of patients did not affect the results.[19] However, after one year, males have statistically significantly higher CMT than females, these results can`t be explained and there were limited data globally.

The duration of the disease before starting fingolimod did not have a significant impact on CMT in all the timelines of the study (baseline, 3-6 months, and after one year). However, it can be noticed that patients who had initiated fingolimod with a duration of MS ≤ 6 months before enrollment, had the highest mean CMT after 3-6 months and after one year; the percent change of CMT was significantly higher in patients with a disease duration of ≤ 6 months and 7-12 months, compared to those with a disease duration > 4 years, i.e. shorter disease duration was correlated with higher CMT changes. However, no difference in the percent-change of CMT after one year concerning the disease duration before the initiation of fingolimod; these results may be related to the recurrent attacks of optic neuritis and its resultant degenerative changes including thinning of the retina, neuronal loss, and reduced

macular volume particularly in patients with long-standing or severe MS. [32]

At the end of this study, no patients of those followed up for one year after starting fingolimod developed FAME within this year. This result is different from initial and extension MS trials: FREEDOMS, FREEDOMS 2, TRANSFORMS, and INFORMS as well as a Japanese trial, which showed that the incidence of FAME ranged from 0 to 2.08%.[33]

This zero-result may be related to many factors including
1.Small number of patients as compared to other studies; in FREEDOMS study, 1033 of 1272 patients completed the study [11]; in TRANSFORMS study, 1153 of 1573 patients completed the study [10]; while in our study, only 78 of 135 patients completed it.

2.The incidence appears to be dose-dependent; The FREEDOMS study was a phase III multicentre, 24-month, double-blind randomized study comparing 0.5mg (n=425) and 1.25 mg (n=429) fingolimod oral daily treatment with placebo (n=418) in patients with RRMS. No one of the 425 patients receiving 0.5 mg fingolimod developed macular edema; seven out of 429 (1.6%) patients receiving 1.25mg fingolimod developed macular edema and three of these were reported as serious FAME. [32] The dose-dependent nature of this adverse event may also explain why ME occurred more commonly in studies of renal transplant recipients, where study doses were five-(2.5 mg/day) to ten-fold (5.0mg/day) higher than the FDA-approved dose for the treatment of relapsing-remitting multiple sclerosis (0.5 mg/day)[34]. While in our study, we use only the lowest dose of fingolimod as recommended by the neurologist.

3.The incidence of FAME in the MS trials may be limited by the inclusion and exclusion criteria; a history of uveitis was not an exclusion criterion for either the FREEDOMS or TRANSFORMS studies; Patients with MS have an increased risk of developing uveitis, in particular the intermediate uveitis subtype in which ME is a well-characterized feature [34], while in our study, we exclude most of the conditions that may be associated and\or increase risk of macular edema, including uveitis.
4.There are other factors that may affect the incidence of FAME, like drug metabolism, receptor density, genetic differences, or unrecognized drug-drug interactions.[17]

Fingolimod 0.5 mg administered orally once daily is an FDA-approved disease-modifying therapy for the treatment of relapsing-remitting MS. In clinical trials, fingolimod therapy has resulted in a significant reduction in the number of relapses, disability progression, and inflammatory lesion activities on magnetic resonance imaging. Besides, fingolimod therapy significantly reduced the rate of brain volume loss compared with placebo; these treatment benefits outweigh the low risk of ME that is almost universally reversible with a low impact on the quality of life of the patients. The approved dose of fingolimod 0.5 mg is associated with an incidence of ME of $\leq$ 1% in MS clinical studies, including long-term observation trials. The ME generally resolved with or without treatment after drug discontinuation. Few patients had residual VA loss even after resolution of FAME. [17]

As a conclusion to this work we found that the recommended, FDA-approved, orally given, daily dose (0.5mg) of fingolimod that is prescribed for a patient with RRMS is a well-tolerated drug regarding the risk of macular edema as per our patients and the follow up period we chose. To strengthen our results, further studies with a larger number of patients is recommended with a comparison between fingolimod and other drugs used in the treatment of MS regarding ophthalmological complications (conducting a cohort study).

It is important to emphasize that regarding follow up of patients starting fingolimod, a baseline VA with fundus examination and OCT in booking visit is mandatary and then only VA with fundus exam would be sufficient in follow up visits. OCT is recommended for those with high-risk factors (diabetes mellitus, uveitis, history of intraocular surgery, etc.) or patients with suspicious features of macular edema on fundus examination specially if we consider that multiple extra OCT examination time-consuming with extra-financial burden.

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