Numerous studies have reported a prevalence of headache (HA) in multiple sclerosis (MS) patients ranging from 4% to 64%; moreover, the prevalence of migraine (in particular migraine without aura) in MS patients is more than twice than in general population (1). Whether HA is a risk-factor, a comorbidity or a symptom of MS, it remains unclear. Disease modifying therapies (DMTs) used to treat MS may play a role in causing or exacerbating HA: in particular, several studies confirmed that beta-interferon (βIFN) may worsen pre-existing HA or trigger a de novo HA (2). On the contrary, glatiramer acetate (GA) and natalizumab (NTZ) do not appear to aggravate comorbid HA (3-4). Fingolimod (FTY720) is the first oral DMT approved for Relapsing-Remitting (RR) MS. It acts as a sphingosine-1-phosphate (S1P) receptor modulator that interferes with T and B cells traffic between lymphoid organs and blood. HA is reported as a common side effect of FTY720 in randomized clinical trials: a long-term safety analysis, integrating data of phase 2 and 3 and extension phase studies, showed a non significant, slightly higher frequency of HA in FTY720-treated patients. Moreover, in an observational study, HA resulting to be the most frequent adverse event leading to discontinuation of FTY720 during the first three months of therapy (5). However, despite the wide use of FTY720 in clinical practice, definite data regarding the impact of this drug on comorbid primary HA are still lacking.

**PURPOSE**

The goal of our analysis was therefore to investigate the influence of FTY720 on HA frequency and severity in a cohort of consecutive RR-MS patients.

**METHODS**

In our Centres (MS Centre of the City of Health and Science University Hospital of Turin, the MS Centre of Catania and MS Centre of Genoa ASL3), the presence of a comorbid primary HA, HA subtype and frequency of attacks is systematically investigated during serial routine neurological evaluations. All patients who started fingolimod from April 2011 to April 2015 were considered for this analysis, which focused on:

1. presence of a comorbid primary HA (or changes to pre-existing HA / onset of de novo HA)
2. HA subtype
3. frequency /intensity of HA attacks during the 12 months before and after fingolimod starting. Occurrence of a status migrainosus was also recorded.

**RESULTS**

We evaluated 289 consecutive, FTY720-treated patients (66% females).

Population characteristics were:

- mean age 42.4 years (SD 9.5);
- mean disease duration 13.14 years (SD 7.6);
- median EDSS 3

Previous DMTs, before receiving FTY720 were:

- βIFN in 126 patients (90 βIFN-1a; 36 βIFN-1b)
- GA in 39 patients
- NTZ in 61 patients
- immunosuppressive treatments in 17 patients

In 38 cases FTY720 represented the first DMT. 61% of our population (176/289 patients) suffered from a primary HA; HA subtypes are described in Table 1.

**CONCLUSIONS**

Impact of fingolimod on HA frequency and characteristics still represents an open question. Our data show that fingolimod might exert a positive influence on pre-existing HA, especially in patients suffering from TTH. Most of these improving TTH patients (48%) were switching from βIFN; therefore improvement may reflect the withdrawal of a therapeutic agent which is not neutral towards HA (2).

In the subgroup of migraine patients, 23.5% reported a “worsening” in frequency/intensity of attacks, in some cases with the need of a prophylactic therapy. An abnormal prevalence of status migrainosus (3.8%) was recorded as well, in 2 cases leading to treatment discontinuation.

The neurobiological mechanisms underlying the possible effects of fingolimod on HA remain to be elucidated.

FTY720 can exert its action directly on S1P receptors in the central nervous system (in oligodendrocytes, astrocytes, microglial cells and neurons). In addition, the drug interacts with endothelial cells expressing S1P receptors (type 1,3) inducing an activation of endothelial nitric oxide synthase and producing vasodilatation (6). On the basis of our results, we conclude that aggravation of pre-existing primary HA or the occurrence of de novo HA must be taken into account among the side-effects of fingolimod. The presence of HA should be prospectively monitored during fingolimod therapy in order to improve the impact on treatment tolerability and adherence.

**REFERENCES**