Summary of Study report - EUPAS 19610

Title

Prospective Cohort Study of Long-Term Safety of Teriflunomide in Multiple Sclerosis Patients in Europe.

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Main author: Philippe Autier, MD, PhD

International Prevention Research Institute (iPRI, www.i-pri.org), Lyon (France)

Keywords

PASS, cohort, teriflunomide, Europe, real-life setting, adverse events

Rationale and background

Teriflunomide (also known as HMR1726, Aubagio®) is an immunomodulator with both anti-proliferative and anti-inflammatory activity that has shown to be effective in remitting-relapsing forms of Multiple Sclerosis (MS). In order to further evaluate the long-term risks of teriflunomide, a five-year post-approval observational study was conducted to investigate the incidence of Adverse Events of Special Interest (AESI) in European MS patients treated with teriflunomide in a real-life setting.

Research question and objectives

Research question: What is the long-term safety profile of teriflunomide in real-life European MS patients?

Primary Objective: To characterize the long-term safety profile of teriflunomide and determine the incidence and risk of AESI in a real-life setting. AESI include acute liver injuries, serious infections, serious opportunistic infections (including Progressive Multifocal Leukoencephalopathy (PML)), interstitial lung disease, pancreatitis, malignancies, peripheral neuropathy, psoriasis, renal failure and cardiovascular events.

Secondary Objectives:

- To describe the patient characteristics and utilization patterns of teriflunomide in real-life setting.
- To evaluate whether the teriflunomide treatment is associated with an increased risk of any of the selected AESIs compared to other approved MS Disease Modifying Therapy (DMT).

Study design

Prospective active comparator five-year study of MS patients treated with teriflunomide or treated with another DMT included in Multiple Sclerosis registries or in administrative data sources.

Setting

Secondary use of data from two MS registries, (the Belgian Treatments in Multiple Sclerosis Registry (BELTRIMS) in Belgium and the Danish Multiple Sclerosis Registry (DMSR) in Denmark) and two administrative databases (Agence Inter Mutualiste- Inter Mutualistic Agency (AIM-IMA) in Belgium and the Système National des Données de Santé (SNDS) in France). Because of Covid-19 pandemic, there were substantial delays in data gathering and analysis in the Belgian data sources (BELTRIMS and AIM-IMA). The available data for this study spanned from 2013-2014 to 2018-2021 (variable between data sources).

Patients and study size, including dropouts

All patients who were treated with at least one DMT between the date of teriflunomide reimbursement in their respective country and the end of data collection were selected. This represented 83,604 patients. Of them, 1,984 were excluded (mostly patients aged < 18 years at cohort entry and patients with unknown history of DMT exposure). In total, 81,620 patients remained for analyses, with 6,624 from the DMSR, 59,663 from the SNDS, 1,686 from the BELTRIMS, and 13,647 from the AIM-IMA.

Variables and data sources

Variables on patient characteristics, characteristics of multiple sclerosis, prescription and dispensing of DMT and AESI were retrieved in each data source.

Statistical analyses

Risks were assessed by comparing AESI occurrence in the group of patients being treated with teriflunomide to AESI occurrence in the group of patients treated with another platform DMT. Risks were computed as hazard ratios (HR) derived from Cox models with time-dependent exposures. HR were adjusted for confounding, including gender, age, new user or prevalent user status, history of major comorbidities in years preceding inclusion in the cohort, and when available, the EDSS.

Results

Overall, 81,620 patients were included in the study, 72% of which were women. The median age and interquartile range (IQR) were 42 years (33-49) in the DMSR, 43 years (34-51) in the SNDS, 40 years (31-49) in the BELTRIMS, and 43 (34-53) in the AIM-IMA. In total, 27% of patients were

ever treated with teriflunomide. The percentage of patients ever treated with teriflunomide ranged from 19% (AIM-IMA) to 46% (DMSR). Patients ever treated with teriflunomide were slightly older than patients never treated with teriflunomide. The entire study cohort included 36% of patients who were newly treated with a DMT after the date of teriflunomide reimbursement (new users), and 64% of patients who were already treated with a DMT at the date of teriflunomide reimbursement (prevalent users). New users of DMT ranged from 34% (SNDS) to 52% (BELTRIMS). The percentage of new users of DMT was higher among patients who were ever treated with teriflunomide than among patients who were never treated with teriflunomide. The median follow-up of patients was 4.1 years and 287,879 person-years (PY) of follow-up were accumulated in the four data sources.

Among patients ever treated with teriflunomide, age-standardised rates (ASR) per 1,000 PY of all-cause mortality were 1.90 in the DMSR, 2.87 in the SNDS, 1.91 in the BELTRIMS and 2.61 in the AIM-IMA. For pneumonia, age-standardised rates were 4.38 in the DMSR, 2.77 in the SNDS and 0.00 in the BELTRIMS. For the composite outcome myocardial infraction and stroke, age-standardised incidence rates were 2.32 and 3.08 in the DMSR and the SNDS, respectively. For malignancies, ASR were 4.50 in the DMSR, 2.90 in the SNDS and 0.87 in the BELTRIMS. For opportunistic infections, the ASR was 0.36 in the SNDS. For renal failure, it was 0.65 in the DMSR and 0.37 in the SNDS.

Compared to patients treated with platform DMT other than teriflunomide, treatment with teriflunomide was not associated with raised risk of all-cause mortality, acute liver injuries (leading to hospitalisation), serious infections, interstitial lung disease, pancreatitis, malignancies, and cardiovascular events. No case of PML was reported for patients treated with teriflunomide.

In the SNDS, an adjusted HR of 2.41 (95% CI: 1.22, 4.78) for opportunistic infections was found for teriflunomide vs. other platform DMT treatment. The risk of opportunistic infection was not bound to a particular type of opportunistic infectious agent. Few cases of tuberculosis were reported (12 in SNDS, 32 in AIM-IMA, and zero in DMSR and BELTRIMS), precluding meaningful analysis.

In the SNDS, renal failures were reported for 52 patients, with an adjusted HR of 1.99 (95% CI: 1.08, 3.69). On the other hand, there was no increased risk of haemodialysis associated with teriflunomide treatment (n=61 patients; adjusted HR: 1.61 (95% CI: 0.66, 3.92)). A history of renal failure or of dialysis before cohort entry was reported 187 patients. None of the 38 patients subsequently treated with teriflunomide had a new episode of dialysis or renal failure during the study period, whereas 19 of the 149 other patients experienced another episode of renal failure.

In the BELTRIMS, no association was found between abnormally high serum concentrations of creatinine and urea with teriflunomide treatment. In the

DMSR, incidence rates did not suggest an increased risk of renal failure. In the AIM-IMA, no analysis could be conducted because of a small cell.

A small number of cases of peripheral neuropathies were reported (16 in the DMSR and six in the BELTRIMS). In these two data sources, incidence rates were five to ten times higher in the teriflunomide group than in the group of patients treated with another DMT. No further analysis could be carried out.

In the AIM-IMA, an increased risk of psoriasis (adjusted HR = 1.59 (95% CI: 1.02, 2.47)) was detected. No analysis was possible for psoriasis in other data sources because of small numbers of cases.

Discussion

There were some differences in terms of patient characteristics between data sources. The proportion of patients over 60 years of age was larger in the AIM-IMA (12%) than in other data sources (4% to 8%). The proportion of patients treated with teriflunomide was higher in the DMSR than in other data sources. A reason is that use of teriflunomide is recommended as first treatment for MS in Denmark, while no such recommendation exists in France and Belgium.

Limitations in data (e.g. paucity of cases for rare AESI, possible unmeasured confounders) call for cautious interpretation of results. Nonetheless, overall results are in line with the known long-term safety profile of teriflunomide and mostly consistent between the four data sources.

Regarding renal failure, the adjusted HR of 1.99 (95% CI: 1.08, 3.69) observed in the SNDS for renal failure among patients being treated with teriflunomide as compared to patient treated with STF was isolated and difficult to interpret for several reasons. First, no episode of renal failure was reported among SNDS patients treated with teriflunomide who had a history of renal failure. Second, there was no increased risk of dialyses in the SNDS. Third, results from other data sources (DMSR, BELTRIMS and AIM-IMA) did not suggest renal damage associated with teriflunomide treatment. Hence, results on renal disorders were inconsistent across analyses and data sources, which does not support the possibility of increased risk of renal damage associated with teriflunomide treatment.