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LETTER TO THE EDITOR

Is there a link between amyotrophic lateral sclerosis and treatment with TNF-alpha inhibitors?

A. BÖRJESSON[1], B. GRUNDMARK[1,2], H. OLAISSON[1] & L. WALDENLIND[1]

[1]*Department of Pharmacovigilance, Medical Products Agency, Uppsala, Sweden, and* [2]*Department of Surgical Sciences, Uppsala University, Uppsala, Sweden*

The pan-European database EudraVigilance database (EVD) contains all serious adverse drug reaction (ADR) reports for all drugs approved within the European Union. In our routine signal detection in EVD, we have observed a cluster of reports of amyotrophic lateral sclerosis (ALS) in relation to treatment with TNF-alpha inhibitors, mainly used in rheumatoid arthritis (RA). The number of reported cases on 15 December 2012 was established to be between 58 and 73 (Table I). The uncertainty in exact numbers is due to possible duplicate reporting. In five of the reports more than one TNF-alpha blocker were reported as suspected drug. The cases originated from 14 different countries. In comparison, the highest number of reported ALS cases in EVD, in relation to any other drug indicated for the use in RA, was found for methotrexate with three cases. In literature three cases of ALS during TNF-alpha blockade treatment have been described (1-3).

Biological substances including the TNF-alpha blockers are less frequently used (~ 20% of patients) in RA treatment compared with methotrexate (86%), prednisone (72%), sulfasalazine (46%), and chloroquine phosphate/hydroxychloroquine (42%) (4-6). If the spontaneously reported ALS cases in relation to TNF-alpha inhibitor treatment were a result of confounding by indication, age, severity of suspected adverse drug reaction, or by novelty and special attention to biological substances, the number of cases for other RA-indicated substances including other biological substances would be expected to be similar in size to that of TNF-alpha inhibitors, taking into account their respective level of use. In other studies it has been found that ALS is not over-represented in active or past arthritic disease when compared with an age-matched general population (7), which contradicts the suspicion of confounding by indication. Furthermore, for other biological substances without an approved indication for RA, the highest number of reports of ALS as a suspected ADR was found for interferon-beta-1A with five reported cases, also speaking against a special attention to the novelty of biological products. Thus, it seems to be a consistent imbalance of suspected ALS cases between TNF-alpha inhibitors and other RA-indicated products including biological substances, as well as other biological substances.

Under-reporting of ADRs is extensive, and estimation of the true incidence of a particular ADR in association with a certain drug is not possible from spontaneous reporting. It has been estimated that on average only 1 of every 20 occurring ADRs is being reported (8,9). The incidence of ALS associated with the TNF-alpha blockers was estimated from the number of cases and available drug exposure data. It was found to be close to the background incidence of approximately 2 cases per 100,000 individuals annually (10). Consequently, the true incidence of ALS with TNF-alpha inhibitory treatment would reach a level above the background incidence. ALS affects the central nervous system, and diagnosis in the reported cases was based on clinical symptoms of progressive motor neuron degeneration confirmed by electrophysiological or neuropathological findings. It is invariably fatal.

TNF-alpha is a major regulator of complex physiological processes within the central nervous system

Correspondence: H. Olaisson, Department of Pharmacovigilance, Medical Products Agency, PO Box 26, SE-751 03 Uppsala, Sweden. Fax: +46 18 54 85 66. E-mail: hans.olaisson@mpa.se

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Table I. Cases of ALS reported to EudraVigilance per 15 December 2012.

Substance	ALS cases per substance
Adalimumab	13–18
Etanercept	25–31
Infliximab	20–24
Other RA-indicated chemical substance	≤ 3
Other RA-indicated biological substance	≤ 2
Other biological substance	≤ 5

(11). Acknowledged ADRs of TNF-alpha inhibitor therapy already include nervous system disorders such as onset of or exacerbation of central nervous system demyelization disorders, including multiple sclerosis, and peripheral demyelization disorders. Two types of TNF-alpha receptors have been described in the literature. Depending on the context, TNF-alpha receptor activation is associated with neuro-protection, stimulation of neurogenesis, axonogenesis and synaptic plasticity (12,13), with associated protection of neurons from neurotoxic milieus such as oxidative stress (14) and glutamate or nitric oxide overload (15,16). Thus, a physiologically plausible mechanism exists in the reported cases explaining why ALS may have been caused by loss of or decreased neuronal protection by TNF-alpha activation.

This pharmacovigilance signal of disproportionate reporting in a public database of ALS in relation to treatment with TNF-alpha inhibitors merits further investigation for a causal relation to be confirmed or refuted.

Results and views of the presented study represent the authors and not necessarily any official views of the Swedish Medical Products Agency where the authors are (partly) employed.

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