Drug induced progressive multifocal leukoencephalopathy: a comprehensive analysis of the WHO adverse drug reactions database

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Progressive multifocal leukoencephalopathy (PML) is a rare, serious and progressive demyelinating disease of the central nervous system arising from reactivation of the ubiquitous JC polyomavirus (JCV). JCV is present in 50-60 % of adults aged 20-50 years, and the percentage increases with the age (Major, 2011).
The pathogen remains quiescent in different organs and tissues, and a reactivation leads to an infection of the brain targeting astrocytes and promoting lysis of oligodendrocytes.
It is normally fatal within months if the patient remains immunocompromised and it has been associated to treatment with various drugs.
PML affects nearly 1 out of 200,000 people among the general population over lifetime and causes death in 3-5% of AIDS patients (Bellizzi et al., 2013).
The aim of this study is to evaluate potential safety signal of PML due to drugs indicated by spontaneous pharmacovigilance reporting system worldwide.
All spontaneous reports containing suspected or interacting drugs-PML related, held in VigiBase, the WHO-Adverse Drug Reactions database up to 01/09/2014 were retrieved. We used data from ICSRs containing the Preferred Terms 'Progressive multifocal leukoencephalopathy' or 'Leukoencephalopathy', according to the Medical Dictionary for Regulatory Activities classification system (MedDRA). In order to estimate the strength of association between the suspected/interacting drugs and PML, we used the Reporting Odds Ratio (ROR) as a measure of disproportionality (Bate et al., 2009).
We estimated the ROR with 95% confidence intervals (95% CIs) for each drug-reaction pair considered and identifying a safety signal if a drug was reported more than twice in PML cases with a ROR>2 and a lower 95% CI limit above 1.
We retrieved 2452 reports associated to PML, corresponding to 343 different drugs reported as suspected or interagent. PML was reported similarly for males and females adults (18-64 years). In almost 30% of cases, a fatal outcome was reported. Most ATC groups detected concerned antineoplastic agents (23.5%), antivirals for systemic use (10.1%) or immunostimulants (4.6%).
A significant disproportionality was found for 88 out of 343 total drug, and a new safety signal was identified for 59 cases, as no information on possible risk for PML was indicated in their Summaries of Products Characteristics. Among those ones, we found cytarabine (ROR 6.35, 95% CI 5.16-7.81, p<0.001), doxorubicin (3.38, 2.73-4.18, p<0.001), basiliximab (3.7, 1.54-8.89, p<0.01), bevacizumab (2.69, 2.08-3.48, p<0.001), lamivudine (4.93, 3.71-6.55, p<0.001) and saquinavir (6.39, 3.78-10.81, p<0.001).
Multiple associations in this disproportionality analysis between PML and several drugs have been detected confirming previously reported signal and finding newer ones. On the contrary, these data does not allow any conclusion on causality between exposure and PML. In addition, ROR computing does not allow quantification of the true risk of ADR, but only suggests a statistically significant association between a drug and an adverse event.
Finally, we identified safety signals for drugs that have never been associated to PML, and for which no information were available neither in SPCs nor in literature.
Our analysis highlights a rare but serious ADR that can be detected only after marketing authorization. These safety signals needs follow-up by regulatory authorities, and the corresponding SPCs should be revised.

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