Letter to the Editors

Minimum quality criteria are needed in the assessment and communication of unexpected drug safety findings of marketed products from randomized controlled trials

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Michel and colleagues described a randomized, controlled trial (RCT) with the well established analgesic flupirtine (F) that aimed to demonstrate efficacy in a new indication [1]. The main purpose of the article, however, was to alert about an unexpected high frequency of liver test abnormalities (particularly in ALT) observed with F treatment. The authors concluded that established safety profiles of drugs may not be comparable across different target populations or therapeutic indications.

Safety findings from RCTs can be a valuable source of relevant information with possible impact on patient care. Respective reports should provide transparent, comprehensive and relevant information concerning design, conduct, analysis and generalizability of the trial, thereby allowing informed judgements regarding the internal and external validity. For RCTs with already marketed products to benefit ultimately patient care, published reports should be of the highest possible standard [2].

In light of the ongoing interest in the hepatic safety of F [3], recognition of liver test abnormalities in a RCT would have been a formidable opportunity for a careful characterization of the apparent involvement of F in hepatic adverse reactions in certain patients, possibly allowing deeper mechanistic insights. Unfortunately this opportunity was missed, and the article appears to provide just another piece of 'anecdotal evidence' with the potential to cause uncertainty in the medical community and among license holders, regulators and patients, as the overall presentation and interpretation of the trial data are flawed in many aspects.

First, incomplete description of important study details does not allow firm conclusions on whether the trial results actually reflect true effects of the interventions rather than artificial ones. The authors did not share important information on potential bias, thereby not allowing judgement

on whether the randomization and blinding procedures were indeed effective (e.g. no information provided on allocation concealment, masking/blinding, potential country or centre effects).

The study was prematurely terminated based on an observed dysbalance in liver test abnormalities on single occasions in a very small number of patients ($n = 8$, $n = 7$ on F and $n = 1$ on placebo), but the authors did not discuss the limited robustness of this small sample along with the respective possibility of randomness for the observed dysbalance, despite randomization.

Very basic information is lacking on the demographic characteristics (e.g. gender and age) and the exact number of the patients affected after ≥ 6 weeks of treatment, although the reported incidence of 31% referred to this group. Also hepatic baseline laboratory parameters were neither reported for the randomized patient groups nor for the F subgroups with and without liver test abnormalities.

The authors did not provide full information on the identity (i.e. trade name) and source (i.e. manufacturer) of the employed study medication. The authors just indicated that an extended release formulation of F was used. The employed 'forced titration' posology to 600 mg once daily deviates in important aspects from the registered F use i.e. it was not in line with the approved labelling (maximum of 400 mg once daily). The authors did not discuss the role of this posology as a possibly relevant factor, the adequacy of their fairly aggressive dosing strategy and the possible impact of intrinsic factors in the context of the specific demographic characteristics of their study population (average age about 60 years, 83.6% females). The authors also did not comment that F dose increments from 400 to 600 mg were associated with a three-fold exposure increase in one subgroup between week 8 (540 ± 404 ng ml⁻¹) and week 12 (1520 ± 987 ng ml⁻¹) possibly

signifying a non-linear, over-proportional F exposure increase beyond registered doses.

The authors did not acknowledge in the interpretation of their findings that transient and asymptomatic liver test abnormalities are commonly seen in clinical trials [5, 6], especially for ALT, and that a low threshold for the definition of drug induced liver injury (DILI = ALT/AST increases $\geq 3 \times$ upper limit of normal) and reliance on single observations rather than repeat measurements may lead to false conclusions. Also, the authors did not discuss the clinical relevance of their findings, as they did not acknowledge that alterations in liver parameters, even if drug induced, may be transient and mild in nature and revert to baseline even when therapy is continued ('adaptation', e.g. as with tuberculostatic and statin therapy) [4–6]. Also the terminology used for the description of the findings seems inadequate, as the observed liver test abnormalities did not constitute 'liver damage', 'liver dysfunction' or 'liver impairment'.

Most importantly, the authors did not acknowledge that the suspect of DILI requires a thorough exclusion of the manifold other conceivable causes of liver disease, and failed to provide a structured causality assessment to establish probability estimates for the assumed link between drug intake and the observed liver test abnormalities. Hence, the report does not meet current minimum requirements for the diagnostic assessment of suspected cases of DILI [4–7].

About two-thirds of study patients took concomitant medications, but the authors did not provide details in that regard, although analysis of concomitant medications (prescription drugs as well as over the counter products, herbal medicines and supplements) is an essential part of the causality assessment [7]. A recent evaluation of 226 case reports of apparently F-related hepatic adverse drug reactions (ADRs) in Germany (reported to BfArM from 1992 to 2008) indicated that only about 20% of the reported cases were probably or likely related to F treatment, but that in about two-thirds of cases (151/226) patients received an average of three co-medications with labelled hepatic ADR profiles [3]. Hence, there is a reasonable plausibility that complex co-medications with hepatotoxic drugs may be important contributors in the majority of F-related hepatic ADR reports. As nitrofurantoin and trimethoprim-sulfamethoxazole, two antibiotics commonly used in predominantly female urological patient populations, are among the most commonly reported suspect drugs for DILI [4], it would have been indeed important in the context of the present study to present the exposure to concomitant medications in detail to allow for analysis of possible differences in the concomitant medication pattern in different indications and patient populations.

Competing Interests

JM and PC are employees of MEDA Pharma, a Marketing Authorisation Holder of flupirtine. RH has received speaker fees and fees for consulting by MEDA Pharma.

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