Letter in Reply
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Pharmacogenomics

Should *CYP2D6* be genotyped when treating with tamoxifen?

Letter in regards to: Del Re M, Rofi E, Citi V, Fidilio L, Danesi R. Should *CYP2D6* be genotyped when treating with tamoxifen? *Pharmacogenomics* 17(18), 1967–1969 (2016).

In response to: Damkier P. Don't think twice it's all right: tamoxifen and *CYP2D6* genotyping in the treatment of breast cancer patients. *Pharmacogenomics* 18(8), (2017).

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Dear Editor,

We thank the Editor of *Pharmacogenomics* for giving us the opportunity to reply to the letter by Dr Damkier.

For this reason, we would like to engage in a respectful and constructive scientific debate, thus avoiding the aggressive wording which is sometimes typical of poor judgment distorted by personal feelings or convictions.

As a matter of fact, we were quite surprised of the tone of the letter, notwithstanding the politeness dynamics of the academic community. Still, we appreciate the opportunity to clarify some of the comments related to our paper.

First of all, we agree that "*several meta-analyses have been performed none of which are referenced or discussed*" in our editorial, which, however, was not aimed to cover comprehensively the scientific literature regarding *CYP2D6* and tamoxifen, being exclusively an editorial. Indeed, the meta-analysis by Jung *et al.* [1] concludes that "[.] *genetic polymorphisms in CYP2D6 may be important predictors of breast cancer recurrence risk of tamoxifen as a postoperative adjuvant therapy for patients with breast cancer*." Also, Province *et al.* [2] concludes that "[…] *women who meet criterion 1* [.] *should be counseled regarding the potential impact of CYP2D6 on the effectiveness of adjuvant tamoxifen, and potent CYP2D6 inhibitors should be avoided in these patients*."

Regarding the issue of Hardy–Weinberg equilibrium and loss of heterozygosity, discussed by Johnson *et al.* [3], that article supports our point of view because, by citing the work of Goetz *et al.* [4], it concludes that: "*the chromosomal instability in the CYP2D6 locus in breast tumor tissue means that DNA from this source is not reflecting germline DNA in many patients and in particular is not reflecting the CYP2D6 genotype in the liver.* [.] *CYP2D6 genotyping should not be done on breast tumor samples, but rather on adjacent normal tissue, or preferably a traditional germline DNA source*" [3]. Moreover, in the article by Province *et al.* [2] it is said that "*CYP2D6 genotypes from tumor-derived DNA may be subject to error due to somatic mutation by LOH* [.]. *This form of genotyping error is revealed by HWE testing, as was observed in the Breast International Group 1–98 study, in which strong departures from HWE* […] *were observed leading to a call for retraction of this article*." Finally, Goetz *et al.* [4] highlight that "*Tumor DNA should not be used to determine germline CYP2D6 genotype without sensitive techniques to detect low frequency alleles and quality control procedures appropriate for somatic DNA*." Despite these strong opinions, the article by Rae *et al.* [5] reports that results obtained from tumor and germinal *CYP2D6* DNA are the same – but do we really need to manipulate tissue samples to perform germline pharmacogenetics?

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All these data confirm our position and weaken the arguments of the letter by Dr Damkier.

Although we do realize that data about drug–drug interactions are difficult to substantiate because of several factors (i.e., variations in both drug-prescribing patterns during long period of times and modality of data collection), we believe that the risk associated with an unfavorable interaction is clearly high in CYP2D6 poor metabolizers. Our position is in agreement with Ratain *et al.* [6] who conclude that: "*Because the positive association studies are consistent with our understanding of tamoxifen's pharmacokinetics and pharmacodynamics, we recommend that CYP2D6 genotyping be utilized to exclude poor metabolizers from receiving tamoxifen*."

Finally, we cannot but agree with the position of Johnson *et al.* [3] that "*The CYP2D6-tamoxifen story is not closed.* [.] *It is unacceptable that a woman might be placed on 10 years of therapy with a drug for which her genotype predisposes her to reduced efficacy and poor outcomes. She deserves an evidence base that can truly guide the most appropriate treatment for her.*"

On the basis of all the above mentioned counterclaims, we believe that our editorial highlights the meaningfulness of *CYP2D6* analysis, which will hopefully encourage further investigation in this field. As a final note, clinical pharmacologist is a worldwide recognized professional and, by definition, she/he is an expert in clinical pharmacokinetics and pharmacogenetics. Her/his input is invaluable for the management of patients receiving chronic, multi-drug regimens potentially affected by the metabolizer status.

We finally thank Dr Damkier for the letter, which has given us the opportunity to reconfirm our position and, at the same time, mindfully argue the relevant issues concerning this topic.

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