

Evaluation of CYP2D6 Phenotype-Guided Tamoxifen Dosing in European Female Breast Cancer Patients using a PBPK-Model

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Objectives

Tamoxifen is a first-line agent in the treatment of estrogen receptor-positive breast cancer. Endoxifen is a secondary metabolite of tamoxifen and regarded as a major contributor to its anti-tumoral activity [1-3].

Patients with the intermediate or poor metabolizer (IM, PM) phenotype of cytochrome P450 2D6 (CYP2D6), one major enzyme involved in biotransformation of tamoxifen to endoxifen, exert a gene-dose dependent decrease in endoxifen steady-state plasma concentrations [4; figure 1].

The impact of reduced CYP2D6 activity and decreased endoxifen steady-state plasma concentration on treatment outcome remains to be elucidated. However, there is concerning evidence that IM and PM may not fully benefit from regular tamoxifen therapy [5,6].

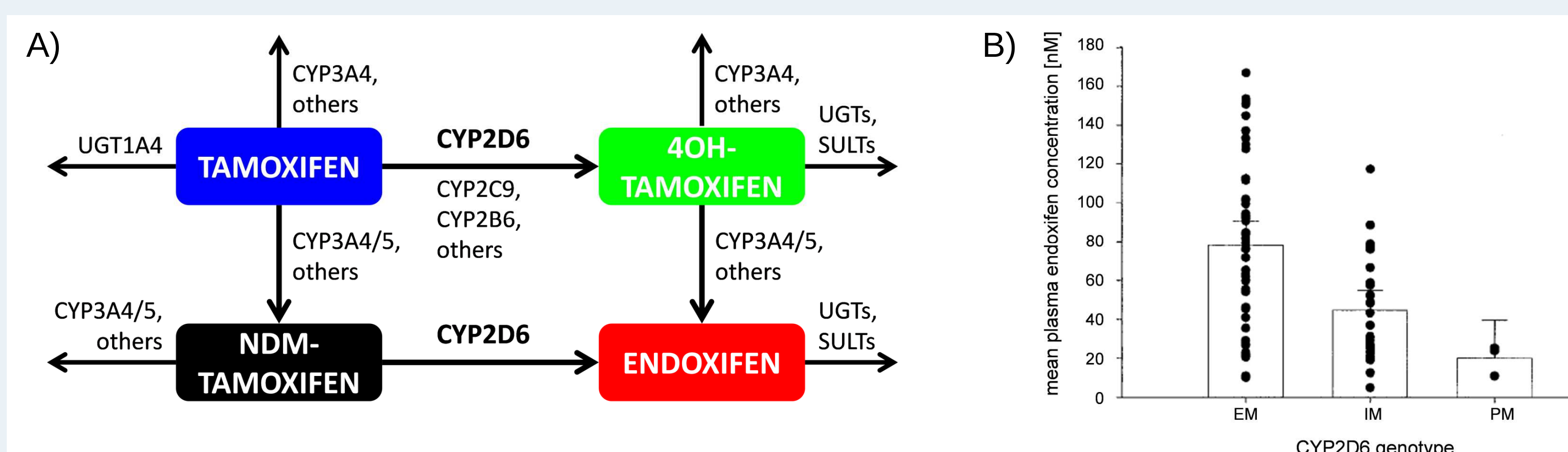


Figure 1: A) Simplified biotransformation scheme of tamoxifen in man. Tamoxifen is mainly N-demethylated to N-desmethyltamoxifen (NDM-tamoxifen) and subsequently 4-hydroxylated to endoxifen. A minor pathway proceeds via 4-hydroxylation to 4-hydroxytamoxifen (4OH-tamoxifen) followed by N-demethylation to endoxifen. The polymorphic CYP2D6 is involved in crucial steps of endoxifen formation [7-10]. **B)** Endoxifen steady-state plasma concentration in patients with two, one, or no functional CYP2D6 allele (EM, IM, PM). Figure taken and adapted from Jin et al (2005) [4].
Abbreviations: CYP (cytochrome P450); SULT (sulfonyltransferase); UGT (uridine-5'-diphosphoglucuronyltransferase); EM (extensive metabolizer); IM (intermediate metabolizer); PM (poor metabolizer)

Thus, a currently discussed possible new treatment strategy for IM and PM patients might be phenotype-guided dose escalation of tamoxifen to achieve endoxifen steady-state plasma concentrations comparable to extensive metabolizers (EM) [11].

This work presents a PBPK-model-based evaluation of CYP2D6 phenotype-guided tamoxifen dose escalation in European breast cancer patients of IM and PM phenotype.

Materials & Methods

A physiologically-based pharmacokinetics (PBPK)-model of endoxifen formation out of tamoxifen was developed for populations of European female individuals of EM, IM, and PM phenotype [12] comprising physiological variability [13] and using prior knowledge of CYP2D6 activity [8].

The populations of PM and IM were then adapted to a dose regimen of 4 months of standard 20 mg tamoxifen once daily followed by 4 months of 20 mg tamoxifen twice daily [11]. Additionally, 4 months of standard 20 mg tamoxifen once daily followed by 4 months of 40 mg tamoxifen once daily (IMs, PMs) or 4 months of 60 mg tamoxifen once daily (PMs) were simulated [figure 2].

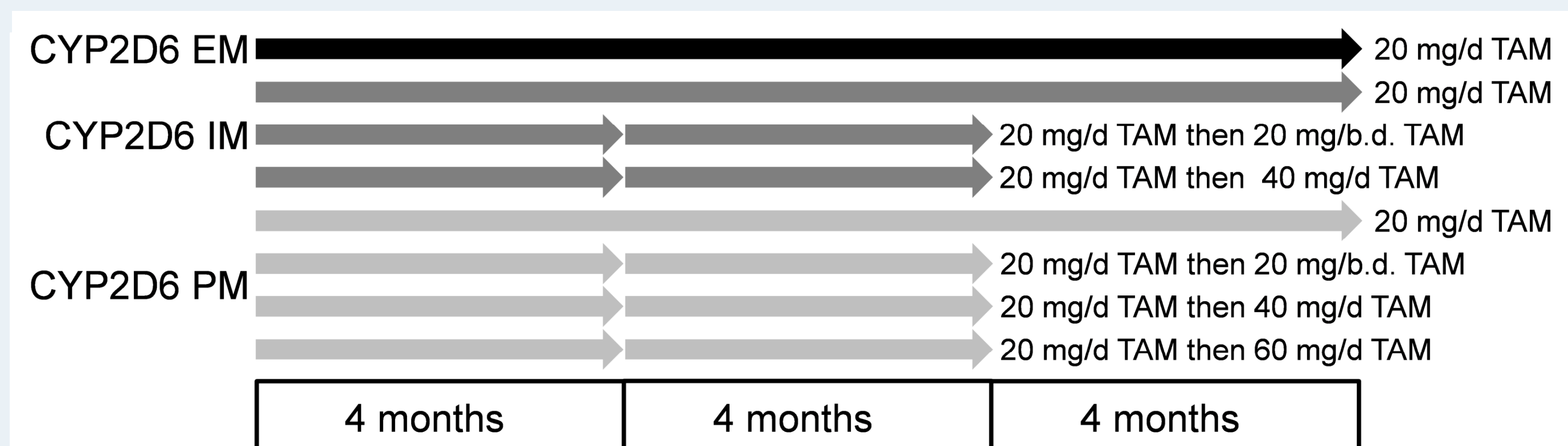


Figure 2: Simulated dose regimens of tamoxifen in populations (N=1000) of CYP2D6 EM, IM, and PM phenotypes to give a PBPK-model-based evaluation of CYP2D6 phenotype-guided tamoxifen dose escalation.
Abbreviations used in figure: TAM (tamoxifen); mg/d (mg dosed once daily); mg/b.d. (mg dosed twice daily)

Simulation results of the presented dose regimens in EMs, IMs, and PMs were compared to corresponding data taken from the literature [11, 14-17]. Dose escalation of tamoxifen in IMs and PMs was additionally assessed in terms of endoxifen steady-state plasma concentration increase compared to median endoxifen steady-state plasma concentrations reported in EMs [11, 14-17].

Results I

Simulation results of standard 20 mg tamoxifen once daily over a period of twelve months in EMs, IMs, and PMs were compared to corresponding experimental data taken from the literature to assess model accuracy in terms of describing the steady-state plasma concentrations of tamoxifen, N-desmethyltamoxifen, 4-hydroxytamoxifen, and endoxifen in all three phenotypes [11, 14-17; figure 3].

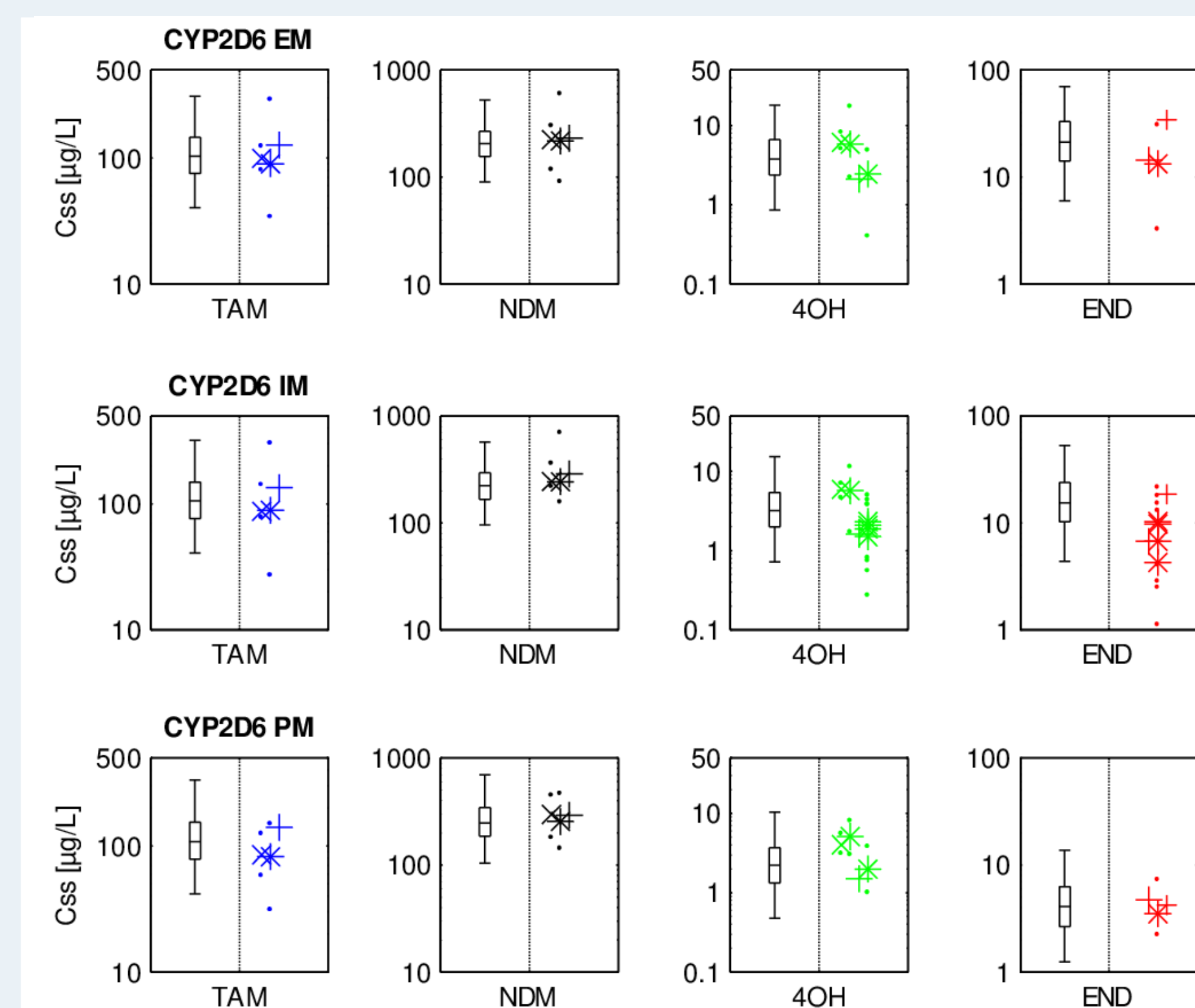


Figure 3: Trough steady-state plasma concentrations (C_{ss}) of tamoxifen (TAM), N-desmethyltamoxifen (NDM), 4-hydroxytamoxifen (4OH), and endoxifen (END) in populations of CYP2D6 EM, IM, and PM phenotypes (N=1000).

Box-whisker-plots indicate the percentiles 5, 25, 50, 75, and 95 of the population simulations.

Symbols represent experimental data used for model validation (from left to right: Gjerde et al (2010), median +/- 25th/75th percentile (x +/- dots); Gjerde et al (2008), median +/- range (* +/- dots); Madlensky et al (2011), median (+); Mürdter et al (2011), median +/- range (* +/- dots); Irvin et al (2011); median (+)) [15,14,16,17,11].

Results II

Dose escalation from standard 20 mg tamoxifen once daily to 20 mg tamoxifen twice daily led to increased endoxifen steady-state plasma concentrations in both populations, IMs and PMs [11, figure 4,5].

The IM population reached median endoxifen steady-state plasma concentration levels similar to reported EM median endoxifen steady-state plasma concentrations (13.3 -34.3 µg/L) [11, 14-17] as shown by both, model (23.5 µg/L) and experimental data (21.8 µg/L) [11].

Simulation experiments show that 40 mg tamoxifen once daily achieved results regarding C_{ss} of tamoxifen and metabolites comparable to 20 mg tamoxifen twice daily in both populations, IMs and PMs.

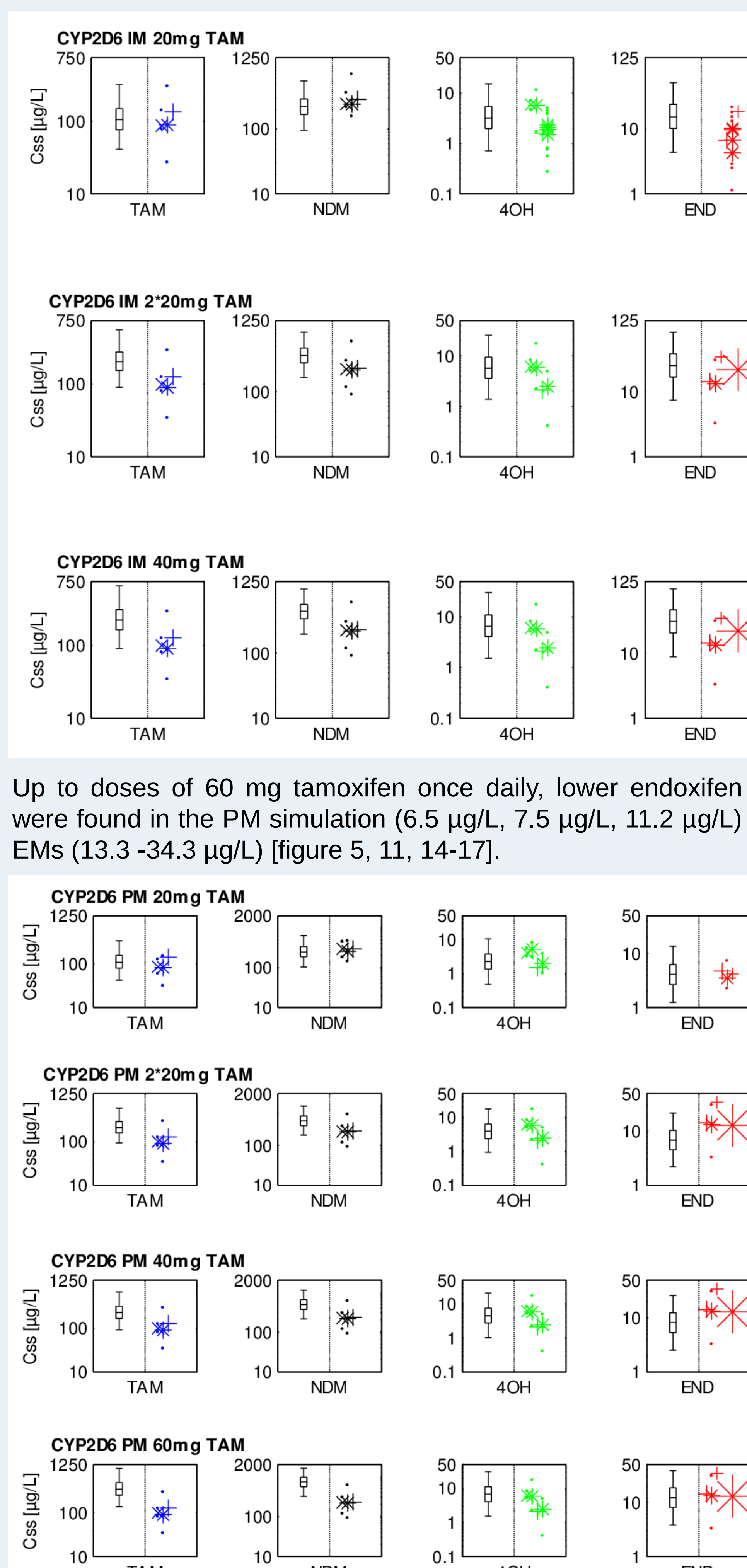


Figure 4: Trough steady-state plasma concentrations of TAM, NDM, 4OH, and END in populations of CYP2D6 IM phenotype (N=1000) following CYP2D6 IM dosing schemes I-III [figure 2].

Box-whisker-plots indicate the percentiles 5, 25, 50, 75, and 95 of the population simulations. Symbols represent experimental data from CYP2D6 IMs in case of 20 mg TAM once daily and from CYP2D6 EMs receiving 20 mg/d TAM in case of TAM dose escalation in CYP2D6 IMs (from left to right: Gjerde et al (2010), median +/- 25th/75th percentile (x +/- dots); Gjerde et al (2008), median +/- range (* +/- dots); Madlensky et al (2011), median (+); Mürdter et al (2011), median +/- range (* +/- dots); Irvin et al (2011); median (+)) [15,14,16,17,11].

The median endoxifen steady-state plasma concentration following TAM dose escalation in CYP2D6 IMs taken from the literature is presented as a big red star [11].

Up to doses of 60 mg tamoxifen once daily, lower endoxifen steady-state plasma concentrations were found in the PM simulation (6.5 µg/L, 7.5 µg/L, 11.2 µg/L) in comparison to the levels found for EMs (13.3 -34.3 µg/L) [figure 5, 11, 14-17].

Figure 5: Trough steady-state plasma concentrations of TAM, NDM, 4OH, and END in populations of CYP2D6 PM phenotype (N=1000) following CYP2D6 PM dosing schemes I-IV [figure 2].

Box-whisker-plots indicate the percentiles 5, 25, 50, 75, and 95 of the population simulations. Symbols represent experimental data from CYP2D6 PMs in case of 20 mg TAM once daily and from CYP2D6 EMs receiving 20 mg/d TAM in case of TAM dose escalation in CYP2D6 PMs (from left to right: Gjerde et al (2010), median +/- 25th/75th percentile (x +/- dots); Gjerde et al (2008), median +/- range (* +/- dots); Madlensky et al (2011), median (+); Mürdter et al (2011), median +/- range (* +/- dots); Irvin et al (2011); median (+)) [15,14,16,17,11].

The median endoxifen steady-state plasma concentration following TAM dose escalation in CYP2D6 PMs taken from the literature is presented as a big red star [11].

Conclusions

Dose escalation of tamoxifen could prove a preferable new treatment strategy for IM breast cancer patients, as model and experimental data both indicate comparable median endoxifen steady-state plasma concentrations to EMs undergoing regular tamoxifen treatment.

In terms of patient compliance, once daily 40 mg tamoxifen can be regarded superior to twice daily 20 mg tamoxifen.

Nevertheless, phenotype-guided dose escalation of tamoxifen does not achieve standard endoxifen EM levels (13.3 -34.3 µg/L) for PMs up to doses of 60 mg daily (11.2 µg/L) and may therefore not be regarded as a better alternative for these patients.

Possibly, direct endoxifen dosing to CYP2D6 PMs could be a suitable option for breast cancer treatment in these patients. First-in-man studies have already been published [3].

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Acknowledgements

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