QSP modeling shows efficacy of an NK3R antagonist to reduce treatment-induced vasomotor symptoms

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Introduction

Background:
- Vasomotor symptoms (VMS, hot flashes) are common in cancer patients treated with hormone-deprivation therapy
  - 84% of women treated with tamoxifen¹
  - 80% of men treated with leuprolide²
- NK3 receptor (NK3R) antagonists reduce VMS in postmenopausal women without added estrogen
- ACER-801, an NK3R antagonist, is being evaluated to reduce frequency and severity of therapy-induced VMS

Objectives:
- Use a quantitative systems pharmacology (QSP) model of the hypothalamic-pituitary-gonadal (HPG) axis to evaluate ACER-801 for treatment of induced VMS
- Verify ACER-801 efficacy when co-administered with tamoxifen or leuprolide
- Identify optimal dosing strategies

Results:
- Co-administered ACER-801 reduces tamoxifen-induced VMS frequency and severity
- Co-administered ACER-801 reduces leuprolide-induced VMS frequency and severity
- Twice daily dosing decreased VMS more than once daily dosing

Conclusions

Research using the HPG QSP model demonstrates:
- ACER-801 is predicted to be efficacious in reducing NKB binding and vasomotor symptoms due to menopause or tamoxifen- or leuprolide-induced hormone deprivation
- Twice daily dosing was superior in lowering VMS compared to once daily dosing

Model simulations match published data

Comparison of model simulation to clinical data. Induced VMS are often measured as a combined score.
In women, tamoxifen therapy increases VMS³.

ACER-801 treatment should not interfere with hormone deprivation therapy in cancer patients

Leuprolide treatment in a male VP decreases testosterone to castration levels of <50 ng/dL. ACER-801 co-administration does not increase the testosterone concentrations.

Tamoxifen treatment in a female virtual patient (VP) increases hormone concentrations

In post-menopausal women, treatment with tamoxifen should not cause large increases in estradiol, but could result in changes in GnRH and NKB.

References
5. Bioinformatics 22, 514-5

For more information, see:
QSP modeling shows efficacy of an NK3R antagonist to reduce treatment-induced vasomotor symptoms: Handout with more information. Link to handout

The model incorporates the HPG axis and hormone feedback to evaluate the effect of drug treatment on induced VMS (iVMS)

• Decreased estradiol causes decreased dynorphin and increased NKB, which trigger hot flashes in the vasomotor center
• Tamoxifen blocks the E2 receptor, mimicking loss of estradiol
• Leuprolide (GnRH agonist) decreases all sex hormone production
• ACER-801 blocks NKB receptor signals

Co-administered ACER-801 reduces tamoxifen-induced VMS frequency and severity

In a female VP, co-administration of ACER-801 and tamoxifen reduces both VMS frequency and severity.

Co-administered ACER-801 decreases VMS frequency in a leuprolide-treated male VP

Leuprolide treatment increases VMS in a male VP. Co-administration of ACER-801 with leuprolide reduces VMS to near 0 in this VP.

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