Does hepatic impairment affect the exposure of mAbs?

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Background and Objective

➢ Increased efforts to evaluate mAbs to treat different diseases, including viral infections

➢ No FDA guidance or EMA guidance on hepatic impairment (HI) effect on exposure of mAbs

➢ FDA 2013 paper (~ 90 therapeutic proteins (TPs) approved through 2013):
  7 TPs (only 3 mAbs) with HI information
  results inconclusive due to limited data
  Clin Ther. 2013, 35, 1444

➢ Patients with HI included in target population for many mAbs
  Patients may develop hepatic dysfunction as diseases progress

➢ Knowledge essential for dosing strategy in patients with HI
Methods and Results

➢ New available HI data for TPs, especially for mAbs:
  TPs approved between Jan 2013 and Mar 2018 (n=45, 31 mAbs)
  TPs approved before 2013 with updated information (n=~90)

➢ TPs with new HI data:
  18 mAbs, 4 ADCs, other TPs (2 fusion proteins, 1 growth factor, 1 hormone)
  Almost no data for severe HI (n=0 or 1 for all)
  Limited data for moderate HI (4 mAbs and 2 ADCs with n≥5)
  Sufficient data for mild HI (~ 20 mAbs with n=tens to hundreds)

➢ Sig. exposure decrease for several mAbs and ADCs (not small molecule part):
  Ado-trastuzumab emtansine ADC: ↓ 40%/70% in mild/moderate HI
  Evolocumab: ↓ 40%/50% in mild/moderate HI
  Brentuximab vedotin ADC: ↓ 35% moderate HI

Trend for AUC decrease: bezlotoxumab, alirocumab etc.
Lower albumin level associated with lower exposure for additional mAbs and ADCs

Poster #: 15
Discussion and Conclusions

➢ Potential mechanisms:

**FcRn binding:** HI → increased endogenous IgG → competitive FcRn binding → decreased exposure of mAbs or ADCs

*endogenous IgG level inversely related to mAb t1/2 in different diseases*

**TMDD:** breast/other cancers → liver metastases → hepatic dysfunction (higher tumor burden for cancer patients w/ HI) → higher TMDD (if involved) for certain mAbs or ADCs

**FcγR binding:** HI → increased cytokines → increased FcγR-mediated elimination (with soluble immune complexes/effecter functions/increased FcγR binding)

➢ Conclusions:

**HI may impact the disposition of mAbs (or ADCs due to mAb part)**

Additional data are needed, particularly for moderate and severe HI to inform drug development and dose strategies