Experiences with development of antibody-based antiviral drugs

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- from molecule to patient

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Agenda

- **Background:** viral infections
- **Antiviral mAbs:**
  - approved
  - under development *(based on publicly available data and not a complete list)*
- **Clinical pharmacology related opportunities and challenges**
  - Fc-based $t_{1/2}$ enhancing strategy: in vitro and in vivo
  - mAb PK in patients with organ impairment
- **Conclusions**

Background: viral infections

- **CMV** (cytomegalovirus): causes serious disease in immunocompromised patients; some anti-CMV small molecules (SMs) associated with neutropenia or nephrotoxicity
- **HBV** (hepatitis B virus): no functional cure; multiple SMs approved
- **HCV**: virologic cure after treatment with direct-acting antivirals for 8 to 12 weeks
- **HDV**: higher rate of progression than other hepatitis and only occurs in HBV co-infected patients; no approved drug
- **HIV-1** (human immunodeficiency virus-1): no functional cure; ibalizumab and SMs: NRTI (nucleoside reverse transcriptase inhibitor), NNRTI, PI (protease inhibitor), INI (integrase inhibitor), EI (entry inhibitor)

Background: viral infections

- **Influenza**: influenza A involved in pandemics; no approved drug for hospitalized patients with influenza infections
- **RSV** (respiratory syncytial virus): aerosolized ribavirin approved for treatment but not widely used; palivizumab for prevention of RSV in children at high risk
- **Others** (clinical efficacy studies challenging, not possible for Smallpox):

  - Ebola, Zika, Dengue, Smallpox, Rabies, etc.

  - If clinical efficacy studies are not ethical/feasible, approval may rely on animal efficacy models.

  - Guidance for Industry: Product Development Under the Animal Rule

Note: not a complete list for all viral infections

Antiviral mAbs: approved

➢ Synagis® (palivizumab)

- Approval year: 1998
- MOA (mechanism of action): RSV F protein inhibitor
- Indication: prevention of RSV in pediatric patients at high risk
- Dose regimen (intramuscular): 15 mg/kg monthly throughout the RSV season (5 doses)

➢ Trogarzo® (ibalizumab)

- Approval year: 2018
- MOA: CD4-directed post-attachment HIV-1 inhibitor
- Indication: treatment of HIV-1 infection in adults with multidrug resistance, in combination with other antiretrovirals
- Dose regimen (intravenous): a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks

Antiviral mAbs: under development

- **publicly available data and not a complete list**
- **does not include products discontinued from development**

Indication	mAb	MOA	Development Status
HIV-1	3BNC117/3BNC117LS	CD4 binding site of gp120	Phase II/Phase I
	VRC01/VRC01LS	CD4 binding site of gp120	Phase II
	VRC07-523LS	CD4 binding site of gp120	Phase I
	PGDM1400	V1V2 site of gp120	Phase I
	10-1074	V3 site of gp120	Phase I
	PGT121	V3 site of gp120	Phase I/II
	10E8V/10E8VLS	membrane proximal external region (MPER) of gp120	Phase I
	PRO140	**host** CCR5 receptor	**Phase III**
	10E8V2.0/iMab **(bi-specific)**	MPER/**host** CD4 binding site	Preclinical
	SAR441236 **(tri-specific)**	CD4 binding site/MPER/V1V2 site of gp120	Phase I

Antiviral mAbs: under development

- **publicly available data and not a complete list**
- **does not include products discontinued from development**

Indication	mAb	MOA	Development Status
Influenza	CT-P27	hemagglutinin (HA)	Phase II
	MHAA4549A		Phase II
	VIS140		Phase II
	TCN-032	matrix 2 protein M2e	Phase II
RSV	MEDI8897	RSV F protein inhibitor	Phase II
	ALX-0171 (nanobody, **inhalation**)		Phase II
Ebola	ZMapp (2G4/4G7/13C6)	Ebola virus glycoprotein	Phase II
	REGN-EB3 (3470/3471/3479)		Phase I
	mAb114		Phase I
	MBP134 (ADI-15878/23774)		Preclinical
Rabies	CL184 (CR57/CR4098)	Rabies virus glycoprotein	Phase II
	SYN023 (CTB011/CTB012)		Phase II
	RAB-1		approved in India

Clinical pharmacology related opportunities and challenges

Fc-based $t_{1/2}$ enhancing strategy: in vitro and in vivo

- **Fc-based $t_{1/2}$ enhancing strategy:**

  A (N434A), AAA (T307A/E380A/N434A), LS (M428L/N434S), QL (T250Q/M428L), YTE (M252Y/S254T/T256E)

- **MEDI8897:**
  - Indication: prevention of RSV for all infants (IM, Phase II)
  - $t_{1/2}$ enhancing strategy: YTE modification
  - In vivo:
    $t_{1/2}$: **85-117** days in adults; **63-73** days in preterm **infants**
    once-per-RSV-season dose
  - In vitro:
    enhanced neonatal Fc receptor (FcRn) binding at pH 6.0

*Ref: 1. Pediatr Infect Dis J. **2018**, 37, 886; 2. Antimicrob Agents Chemother. **2017**, 23, 61*

Clinical pharmacology related opportunities and challenges

Fc-based $t_{1/2}$ enhancing strategy: in vitro and in vivo

- **Some Fc variants with improved FcRn binding at pH 6.0 in vitro do not exhibit increased $t_{1/2}$ in vivo.**

- **The $t_{1/2}$ enhancing effect depends on both increased FcRn binding at pH 6.0 and minimal effect on FcRn binding at pH 7.4:**

  - underestimation of binding effect at pH 7.4

  - affinity threshold (KD: 860 nM) at pH 7.4 determining IgG recycling efficiency

  - increased FcRn binding at pH 7.4 beyond the threshold offsetting the benefits of increased binding at pH 6.0

Ref: J Biol Chem. ***2015****, 13, 290, 4282*

Clinical pharmacology related opportunities and challenges

mAb PK in patients with organ impairment

- **Renal impairment:**
  FDA guidance: the clearance of therapeutic proteins (TPs) with MW<69 kDa may be affected by renal impairment (mAb MW: ~ 150 kDa)

- **Hepatic impairment (HI):**

  - FDA or EMA guidance: no information for biologics

  - 2013 paper by FDA researchers – Are HI studies necessary for TPs?

    7 TPs (only 3 mAbs) with HI information
    Results inconclusive due to limited data
    *Ref: Clin Ther. **2013**, 35, 1444*

  - New research – Does HI affect PK of mAbs? (TPs with HI data after 2013)

    Almost no data for severe HI (n=0 or 1 for all)
    Limited data for moderate HI (4 mAbs/2 antibody-drug conjugates [ADCs] with n≥5)
    Sufficient data for mild HI (~ 20 mAbs with n=tens to hundreds)
    Research team: Qin Sun, Shirley Seo, Simbarashe Zvada, Chao Liu, Kellie Reynolds

Clinical pharmacology related opportunities and challenges

mAb PK in patients with organ impairment

- **Hepatic impairment (HI):**

  - Significant exposure decrease for several mAbs or ADCs (mAb part):

    Ado-trastuzumab emtansine ADC: ↓40%/70% in mild/moderate HI
    Evolocumab: ↓40%/50% in mild/moderate HI
    Brentuximab vedotin ADC: ↓35% in moderate HI (n=1 for mild/severe HI)

  - Trend for AUC decrease/lower albumin level associated with lower exposure for additional mAbs

  - Potential mechanisms:

    factors affecting FcRn binding (endogenous IgG level), target-mediated drug disposition (TMDD), FcγR binding, etc.

  - HI may impact the disposition of mAbs (or ADCs [mAb part])

  - Additional data are needed, particularly for moderate/severe HI

Conclusions

- **Antiviral mAbs:**

  generally safe, long half-life (up to 3 to 4 months), less frequent dosing, good neutralization potency/breadth, increased resistance barrier (bi-, tri-, or multi-domain mAbs), minimal DDI concern

- **Multiple clinical pharmacology related challenges:**

  - **Fc-based $t_{1/2}$ enhancing:**
    balance FcRn binding at both pH 6.0 and 7.4
    no compromised efficacy and no increased immunogenicity

  - **mAb dose selection:**
    Specific population: patients with hepatic impairment; pediatric patients; patients with different levels of viral load/target expression or immune deficiency

    Dose level/ratio for combination therapy (e.g., anti-HIV mAbs)

    Inhaled mAbs (e.g., anti-flu or anti-RSV) with minimal systemic exposure (PK/PD correlation challenging/infeasible)

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