Monoclonal Antibodies for Treatment and Prevention of HIV-1

CROI 2018

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Introduction: Human monoclonal antibodies

- **Monoclonal Antibodies:**
  - Are identical immunoglobulins made by clone cells that descent from a parent plasma B cell

- **Structure:**
  1. **Variable region (Fab):**
     - Antigen specificity
     - Pathogen neutralization
  2. **Constant region (Fc):**
     - Effector functions and immune response
     - Affect pharmacokinetics by binding to cell receptors

- **Human monoclonal antibodies:**
  - Transgenic mice can be engineered to generate **human** monoclonal antibodies
  - Target many different diseases (cancer, MS, Alzheimer's, Rheumatoid Arthritis, etc)
  - Usually administered as IV or SC
Broadly neutralizing antibodies (bNAbs)

- Human monoclonal antibodies target various epitopes on the HIV-1 envelope (neutralizing), envelope is variable within host and between hosts
- Broad range (active against multiple HIV-1 variants)
  - Initially isolated from infected individuals ("elite neutralizers")
  - Human monoclonal antibodies
  - Can be engineered for increased half-life and multi-specificity
- Also enhance immune effector function:
  - Complement-mediated lysis of infected cells
  - Increase HIV-specific immune response
  - Enhance antibody-dependent cell-mediated cytotoxicity and phagocytosis
Broad neutralization by monoclonal antibodies

- bNAbs show a continuum of potency and breadth
- Different bNAbs target different parts of HIV-1 envelope protein (gp120)

Slide adapted from Malcolm Martin presentation at CROI 2018

Slide adapted from Dan Kuritzkes presentation at CROI 2018
Potential clinical uses of bNAbss

Slide adapted from Dan Kuritzkes presentation at CROI 2018

Adapted from Klein F et al Science 2014

- **A** HIV-1 Treatment Intensification
  - ART
  - bNAb
  - Improvement of HIV-1 Therapy by concomitant treatment with classical ART and bNAb

- **B** Maintaining HIV-1 suppression
  - ART
  - bNAb
  - In viral-controlled HIV-1* individuals: Preventing viral rebound by bNAb administration

- **C** HIV-1 Immunotherapy
  - bNAb
  - Possible HIV-1 treatment alternative (e.g., in the case of multi-drug resistance, ART intolerance, etc.)

- **D** HIV-1 Prevention
  - bNAb
  - Pre- and Post-exposure prophylaxis, pMTCT (for late presenters)
bNAbs currently in development

• VRC01 (Phase 2)
• 3BNC117 (Phase 2)
• 10-1074 (Phase 1)
• PGT121 (Phase 1)
• VRC07-523LS (Phase 1)
• VRC01/PGDM1400-10E8V4 (tri-specific)
• And many more!

PreP potential: A single dose of bNAbs can protect against SHIV challenge
Immediate Treatment: combination VS mono-bNAb treatment in acute SHIV model

Combination of two bNAbs resulted in comparable reduction in plasma SIV-RNA iv as daily ART treatment.

Slide adapted from Dan Kuritzkes presentation at CROI 2018.
Martin et al. Abstract # 48.
Immediate treatment in SHIV model induction of long lasting immunity

- 6 of 13 animals controlled virus to background level for both I.V. and intra-rectal virus inoculations
- These animals became elite controllers
Martin et al. Abstract # 48. continued...immediate treatment in SHIV model affects the size of the viral reservoir

- Low level of infected CD4\(^+\) T cells in elite controllers (1 cell in 10\(^6\) cells)

Summary:
- Early treatment with combo-bNAb resulted in sustained control of viremia (elite controllers 6/13 animals)
- Infected CD4\(^+\) T cell levels were very low, suggesting a role in controlling the viral reservoir
- CD8\(^+\) T cell depletion led to virus rebound, suggesting a role for these cells in bNAb-mediated virus control (data not shown)
Mono-treatment in humans results in:
1. Initial reduction in VL
2. Followed by emergence of minority variants and development of resistance
3. Similar results observed for bNAb 3BNC117 (Caskey et al. Nature 2015)
Maintenance therapy after ARV cessation in humans: escape/resistant variants

- bNAb mono-therapy is not sufficient to maintain viral suppression after ARV discontinuation
- Emergence of resistant virus populations (pre-existing minority variants)
- Similar results observed with BCN117
How to overcome resistance/escape to bNAbs?

- bNAb combination protects against mixed SHIV challenge in macaques
- Combination of 3 bNAbs was more protective than 2 bNAbs (Wag et al. plos path 2016)
- Combination of 4 bNAbs was not more advantageous than 3 bNAbs (data not shown)
Synthetically engineered bNAb with three specificities:
- VRC01
- 10E8V4
- PGDM1400

Combination gave good coverage and protection was very thorough
Continued

TRISPECIFIC ANTIBODIES IN ANIMALS WITH ACUTE INFECTION

- Developed novel trispecific Ab that targets three different epitopes on HIV-1 envelope
- These trispecific Abs display close to 100% breadth and very high potency (IC80 < 0.1 μg/ml)
- Trispecific Abs have in vivo PK profile similar to parental bnAbs
- Trispecific Abs provide complete protection to animals from mixture of SHIVs compared to partial protection provided by single bnAbs

- Developed in collaboration with Sanofi
- Advancing to phase 1b for safety evaluation
Pharmacokinetics: bNAb-specific differences

- PK of VRC01 **is not** affected by infection status
- PK of V3BNC117 **is** affected by infection status:
  - More rapid decay in HIV infected may be due to infected cells/free virus serving as bNAb “sink”
  - Clinical implications not clear

Slide adapted from Dan Kuritzkes presentation at CROI 2018
A PHASE 1 TRIAL OF THE COMBINATION OF 3BNC117 AND 10-1074 IN HIV-UNINFECTED ADULTS SHOWS THAT THERE IS NO AbAb INTERACTION AND IS SAFE

• This trial was designed to evaluate the safety and pharmacokinetic profile of the combination of the broadly neutralizing antibodies 3BNC117 and 10-1074, which target different epitopes on the HIV-1 envelope

• intravenous infusion n=24

• Preliminary pharmacokinetic measurements performed by non-compartmental analysis demonstrate a half-life for 3BNC117 and 10-1074 of 18 and 24 days, respectively. These results are similar to previously published half-lives for each antibody administered alone

• well tolerated
Improving bNAb half-life: LS modification in Fc region

- Phase 1 open-label clinical trial in **healthy adults**
- LS modification in Fc fragment of VCR01 **prolongs half-life**

**Mechanism of Action:**

1. bNAbs normally bind to Neonatal Fc Receptor (FcRn), which is involved in antibody recycling
2. The LS mutations (M428L and N434S) in Fc increases bNAb binding affinity for FcRn.
3. This results in increased recycling and less lysosomal degradation of bNAbs, which in turn, extends serum half-life of bNAbs.

**Historical data**

Different doses of VCR01

- 5 mg/kg SC
- 5 mg/kg IV
- 20 mg/kg IV
- 40 mg/kg IV

**Different doses of VCR01**

Gaudinski MR et al PLoS Medicine 2018
Gaudinski MR et al CROI 2018 Abstr 1061
• VRC07-523LS is approximately 10 fold more potent than VRC01 and active against 96% of diverse HIV-1 strains, including clade C.

• The LS mutation in the antibody Fc region is designed to lengthen its half-life by increasing binding affinity to the neonatal Fc receptor.

• Phase 1 trial to determine its safety, tolerability, and pharmacokinetics (PK)P challenge model (n=25)

• Tested dosing and delivery route (I.V. VS S.C.)

• Serum concentrations 4 weeks post-infusion demonstrated greater persistence and were more than 4 times higher than levels from prior studies of wildtype VRC01.
Late breaker presentation: Barouch et al. Abstract 73LB
bnAb with TLR-7 agonist in acute infection in monkeys

- Study combined bNAb (PGT121) with TLR-7 agonist (GS-9620) to monitor effect on:
  - Viral rebound after ARV discontinuation
  - Viral reservoir
Late breaker presentation: Barouch et al. Abstract 73LB
bnAb with TLR-7 agonist in acute infection in monkeys

Conclusions

- PGT121+GS-9620 led to a 5-fold delay in the time to viral rebound and reduced viral loads following ART withdrawal in acutely treated, SHIV-SF162P3-infected rhesus monkeys

- 5 of 11 monkeys that received PGT121+GS-9620 showed no viral rebound for >6 months, with negative adoptive transfer studies

- Residual PGT121 cannot explain the delay in rebound; levels <1 μg/ml (rebound threshold) for >2 months prior to ART withdrawal

- Mechanism may involve activation of infected CD4+ T cells by GS-9620 followed by enhanced binding and clearance by PGT121; no evidence of a bNAb induced “vaccinal effect”

- These data suggest that bNAbs combined with an innate immune stimulant may effectively target the viral reservoir
Exciting news!
“Theratechnologies Announces FDA Approval of Breakthrough Therapy, Trogarzo™ (ibalizumab-uiyk) Injection, the First HIV-1 Inhibitor and Long-Acting Monoclonal Antibody for Multidrug Resistant HIV”

-NATAP March 2018

Weinheimer et al. Abstract # 561: IBALIZUMAB SUSCEPTIBILITY IN PATIENT HIV ISOLATES RESISTANT TO ANTIRETROVIRALS

• “In combination with other ARTs, Trogarzo™ is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen”

• In Phase III:
  • Trogarzo™ significantly reduced viral load within seven days after the first dose
  • Patients experienced a clinically-significant mean increase in CD4+ T-cells

• Mechanism of Action:
  • Trogarzo™ is a humanized monoclonal antibody but it is not a bNAb per se
  • It binds to domain 2 of CD4 receptor on CD4+ T cells (and not viral envelope like other bNAbs)
  • it blocks HIV-1 from infecting CD4+ T cells by interfering with post-attachment steps required for the entry of HIV-1 virus particles
Summary

**Prophylactic use**

- Combination of IgG mAbs (or one bi/tri-specific antibody)
- Combination should target >98% of HIV strains
- Target populations:
  - High-risk of infection populations
  - MTCT (at birth + during breastfeeding)
- Delivery
  - Sub-cutaneous
  - Every 3-6 months (infants 1 time at birth)
- Minimal adverse events
- Cost: less than 50$ per person per year

**Therapeutic use**

- Easy, convenient dosing (long acting)
  - Ideal at least monthly (ideal 6 months)
  - Combo Abs should have similar PK profile
  - Self administration or at clinic
  - Single needle
- Potency and durability
  - Cover >98% of virus strains
  - Avoid susceptibility testing and development resistance
  - Maintain suppression at least for 1 year
Summary: Challenges for future development

- Clinical trial design:
  - Choosing the best combination is difficult
  - Dose finding

- Adverse effects
  - May lead to development of ADA (anti-drug antibodies)
  - Immune-based adverse events
    - Antibody dependent enhancement

- Emergence of bNAb resistance
  - Need for susceptibility testing?

- Delivery
  - Subcutaneous is preferred to IV
  - Acceptability of infusion/ injectability
  - Dosing frequency

- Impact on viral reservoir is unclear

- Costs

- Global access
Acknowledgements

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HIV Next Gen will be held prior to and as part of the 22nd International AIDS Conference in Amsterdam in July.