The pediatric patient: immunology and response to HIV

Group Discussion

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Unique Immunologic Characteristics of HIV-Infected Neonates that Favor Cure

- Distribution of CD4+ target cells of HIV infection
  - High proportions of naïve cells that are relatively resistant to infection compared to effector memory cells
  - Low expression of CCR5 in circulating CD4+ T cells (albeit not in the gut)
- T cell repertoire
  - While adults may have been exposed to antigens similar to HIV, the neonatal repertoire is less biased and less likely to respond to HIV infection with low affinity CTL due to “antigenic sin”
- Innate immune responses comparable to adults

Immunologic Characteristics of the HIV-Infected Neonate that Do Not Favor Cure

- High proportions of regulatory T cells (Treg), which are susceptible to HIV infection
- High proportions of T follicular helper cells (Tfh), which are also susceptible to HIV infection and seem to be protected from CTL by virtue of being located in the germinal center
- High proportion of Treg may attenuate immune responses to microbial antigens
  - The duration of the Treg-mediated attenuation of adaptive immune responses in the infant has not been defined, but live-attenuated vaccines are effective after 6 to 9 months of life, suggesting that this may be the age threshold for overcoming immune regulation

Virologic Characteristics that Favor Cure in the HIV-Infected Neonate

- The transmitted founder virus (T/F) crosses the placenta at a cost of fitness
- The reservoir is likely to be homogeneous because it has not been selected by CTL or other immunologic pressure
- The reservoir in neonates infected with HIV in utero seems to be quite low when the mothers receive ARV during pregnancy
- The viral decay on treatment does not have the 2 distinct phases described in adults and is overall faster than in adults
- Studies in non-human primates (NHP) suggest that the CNS reservoir in neonates may be minimal

How Long after Birth Are These Considerations Valid

- 3 months, but maybe up to 6 months and possibly later

Public Health Considerations that Favor Cure in Early Life

- Birth is a global point of healthcare contact in LMIC and HIC
- The EPI schedule is global pediatric vaccine schedule recommended by the WHO and supported by many local authorities in LMIC

NEONATES ARE CLEARLY A UNIQUE POPULATION FOR CURE STUDIES

IF NEONATES CAN BE CURED THEY WILL BE PREVENTED FROM A LIFETIME OF ARV

Approach to in Utero-Infected Infants from the Cure Perspective

- Rapid diagnosis
  - 2 positive nucleic acid tests are necessary, but sometimes may be difficult to obtain due to the low RNA and DNA in infants born to treated mothers
- Early intervention
  - ARV
  - bnAb cocktais (studies already in progress)

  AND/OR
  - Vaccine when available

  AND/OR
  - AAV vectors containing HIV gene inserts when a shut-off mechanism is optimized

  AND/OR
  - CAR-T cells when/if shown to be safe

Regulatory Perspective for HIV Cure-Directed Interventions in Neonates

- Safety data from pre-clinical animal studies and from studies in HIV-infected adults
- Proof of concept data showing that the desirable outcome could be attained

INTERVENTION IS SAFE AND HAS A POTENTIAL BENEFIT FOR THE INFANT

Note: HIV infection in children cannot be considered a rare disease because of the high number of infected adults

Breastmilk-Infected Infants

- These infants are different from the in utero-infected infants
  - The T/F viruses were selected by maternal antibody pressure, including antibodies in the breastmilk, and may be more resistant to bnAbs than transplacentally-transmitted viruses
  - Infection occurs through the gastro-intestinal tract, which may not exert the same type of fitness-selective pressure as the placenta
  - Early diagnosis may not be always possible
- These children may be best protected by vaccination in early infancy (when available)

Protection of Infants through Vaccination

- Neonatal vaccination is effective, albeit not against all antigens
- TLR 7/8 agonists, which decrease Treg activity in infants, may be used as adjuvants to increase the immunogenicity of infant HIV vaccines
- STING agonists (with alum) are promising adjuvants that activate IFN type I pathway
- Maternal vaccination may be protective, but may also decrease immune responses of the infant to the same vaccine when administered after birth (shown for influenza, pertussis and CRM-adjuvanted *H. influenzae* vaccines)

Children with Established Infection Differ from Adults with Chronic Infection

- Children >2 to 4 years of age and adolescents mount more robust immune responses to vaccines than adults; immunologic interventions are more likely to be successful in children and adolescents compared with adults
- Pediatric long term non-progressors (LTNP), who represent approx. 5% of the perinatally-infected children, seem to be tolerant to HIV infection (similar to sooty mangabeys), whereas adult LTNP have vigorous anti-HIV CTL

Cure Approach in Children and Adolescents with Established/Chronic Infection

- Similar to adult interventions
  - CCR5 32-deletion (studies in progress)
  - Latency reactivation agents (LRA) + immunologic boost (bnAb AND/OR T cell vaccines prior to LRA therap yAND/OR immunologic checkpoint inhibitors
- Since results of studies in adults may not be extrapolated to children and adolescents, clinical trials in the pediatric population may be conducted in parallel with clinical trials in adults

THE INTERVENTION IS SAFE AND HAS A POTENTIAL BENEFIT FOR THE CHILD/ADOLESCENT

Medical Necessity for Cure Interventions in Early Childhood or Adolescence in the Context of Universal Effective ARV

- Immune responses are stronger in children > 2 to 4 years of age than in adults; best chance to elicit anti-HIV immune responses as a cure strategy
- Immense (cannot be overemphasized) psychological advantage of intervening in early life
- Intervene before adolescence rebellion interferes in their care
  - Poor adherence
  - Intense sexual activity, which may be result in 2^{ary} infections

Conclusions

- In utero-infected neonates are an excellent target population for HIV cure interventions
- Immune-based cure interventions in the setting of chronic infection are more likely to succeed in older children and adolescents than in adults and, therefore, studies in older children and compliant adolescents should be conducted in parallel with studies in adults