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Passive immunization with polyclonal anti-SHIV IgG: partial protection or increased acquisition of heterologous tier 2 SHIV – depending on IgG dose

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Background

While passively administered broadly neutralizing monoclonal antibodies (bnmAbs) prevented SHIV acquisition, polyclonal Abs with high neutralizing titers provided only moderate protection in primates.

Methods

We tested whether passive immunization with polyclonal IgG raised in rhesus monkeys (RMs) with chronic clade C SHIV infection, termed SHIVIG, could protect RMs against multiple low-dose intrarectal challenges with the R5 tier-2 SHIV-2873Nip carrying an HIV clade C envelope heterologous to the viruses/envelopes against which the IgG responses had been elicited. We compared in vitro SHIVIG characteristics with in vivo protection.

Results

In vitro, SHIVIG demonstrated binding to SIV Gag, HIV Tat and Env of different clades, contained b12 and 4E10-like Abs and neutralized tier-1 and 2 viruses, including SHIV-2873Nip. NK-cell depletion decreased neutralizing activity in PBMC assays 20-fold. SHIVIG completely inhibited viral replication by ADCVI assay, but showed only 35% target-cell killing by ADCC assay.

Four groups of RMs were given SHIVIG at different doses: Group 1 (400 mg/kg), Group 2 (675 mg/kg), Group 3 (25 mg/kg) and Group 4 (none; virus-only control) followed by weekly low-dose challenges with SHIV-2873Nip. All controls and all SHIVIG-treated animals became systemically infected. RMs given 400 mg/kg of SHIVIG showed significantly lower peak viral RNA loads compared to controls. Surprisingly, single-genome analysis revealed a significant increase in the number of transmitted variants in Group 3 compared to controls (P=0.032), suggesting increased acquisition. Complement-mediated Ab-dependent enhancement of infection (C'-ADE) at low SHIVIG concentrations was observed in vitro.

Conclusion

Lack of protection and possibly increased acquisition has been reported for a passive immunization study that tested the efficacy of HIV hyperimmune globulin in preventing infection in Ugandan infants born to HIV-positive women (Onyango-Makumbi, JAIDS 2011). Thus, our primate model data paralleled clinical phase III results and suggest that polyclonal anti-HIV-1 Abs play a dual role upon virus encounter.

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