

H-115

Cytolytic and Non Cytolytic Antiviral Mechanisms Elicited by HIV-1 Whole Inactivated Vaccine in HAART-Naïve, Asymptomatic HIV-Infected Individuals

Daria Trabattoni¹, Andrea Gori², Renato Maserati³, Giuliano Rizzardini⁴, Claudio Fenizia¹, Antonella Marino¹, Francesco Mazzotta⁵, Georgia Theofan⁶, Dorothy H Bray⁷, Mario Clerici¹

¹Univ Milano, Milano, Italy; ²H. L. Sacco, Milano, Italy; ³H S Matteo, Pavia, Italy; ⁴H di Circolo, Busto Arsizio, Italy; ⁵H SS Annunziata, Firenze, Italy; ⁶The Immune Response Corp, Carlsbad, CA, United States; ⁷MRC, London, UK

Milano University Medical School, DISP LITA Vialba, Via GB Grassi, 74, 20157 Italy; E-mail: daria.trabattoni@unimi.it

INTRODUCTION

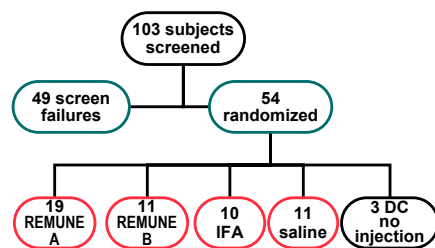
Background: Use of agents that increase immune response to HIV is being considered to delay initiation of antiretroviral therapy in subjects who are therapy naïve. We evaluated the ability of REMUNE®, a whole inactivated HIV-1 vaccine of gp120-depleted HIV antigen emulsified in Incomplete Freund's Adjuvant (IFA), to elicit cytolytic and non cytolytic antiviral mechanisms in antiretroviral-naïve, asymptomatic HIV-1 infected subjects.

Methods: Antiretroviral naïve subjects with HIV-1 RNA 10,000-40,000 copies/mL and CD4 400-800 cells/μL were randomized to receive either 3 injections of REMUNE® at baseline, wk 12 and wk 24 (n=19), (Group A); one single injection of REMUNE® at baseline (n=11)(Group B); IFA (n=10); or saline (n=11).

The following immunologic parameters were measured:

- Mitogen-stimulated alpha-defensin production (ELISA)
- HIV-specific IL-2 and IL-10 production in CD8+ T cells (ICC)
- Plasma RANTES and IL-7 (ELISA)
- Post-thymic CD4+ and CD8+ T cell maturation pathways (Naïve, CM, EM)
- Plasmatic p24-specific IgG1 (TH2) and IgG3 (TH1) concentrations

Study Disposition



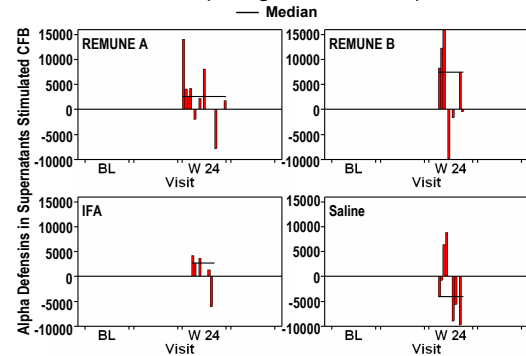
1 subject REMUNE® A d/c after wk 12
1 subject IFA d/c after wk 12

Baseline Demographics

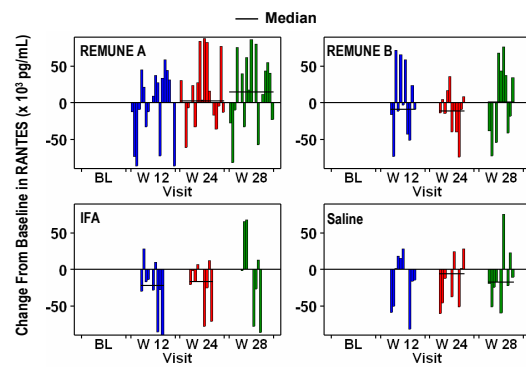
	REMUNE A (n=19)	REMUNE B (n=11)	IFA (n=10)	Saline (n=11)	Total (n=51)
Age (Mean)	36.6	35.6	34.6	38.6	36.5
Sex					
Male	14	4	8	10	36
Female	5	7	2	1	15
CD4 Count*	534 300, 730	470 336, 810	549 399, 778	497 309, 733	519 300, 810
HIV RNA Log*	4.1 3, 5	3.8 2, 5	4.1 4, 5	4.0 3, 5	4.0 2, 5

*Median, Min/Max

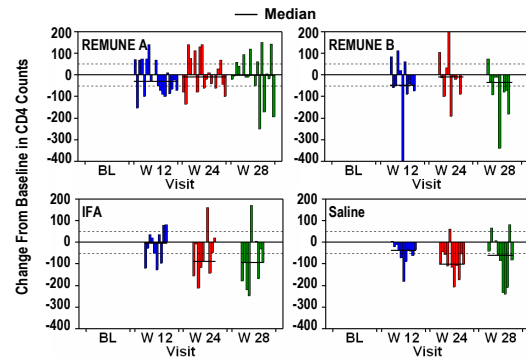
Alpha Defensin Production in Supernatants From PBMCs Stimulated with aCD3, aCD28, Irradiated Allogeneic Cells and IL-2 (Change From Baseline)



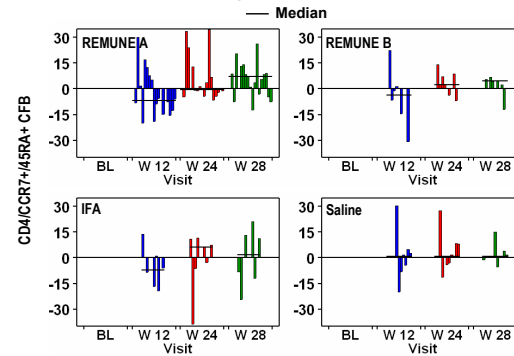
Plasma RANTES (Change From Baseline)



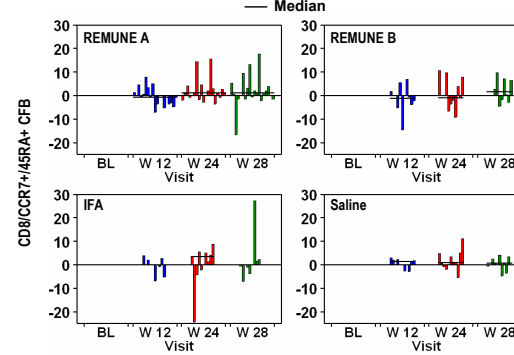
CD4 Counts (Change From Baseline)



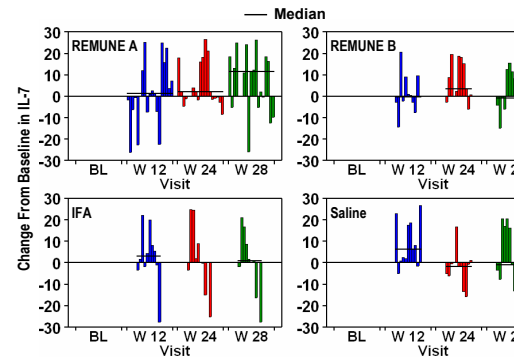
CD4+/CCR7+/CD45RA+ (Naïve Cells) (Change From Baseline)



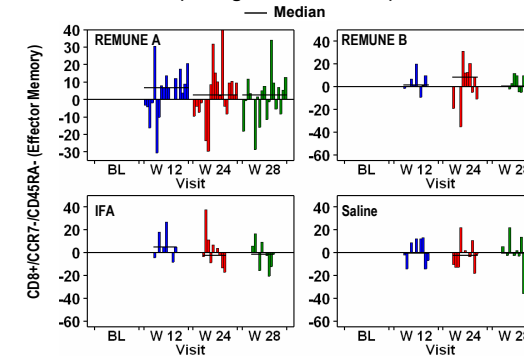
CD8+/CCR7+/CD45RA+ (Naïve Cells) (Change From Baseline)



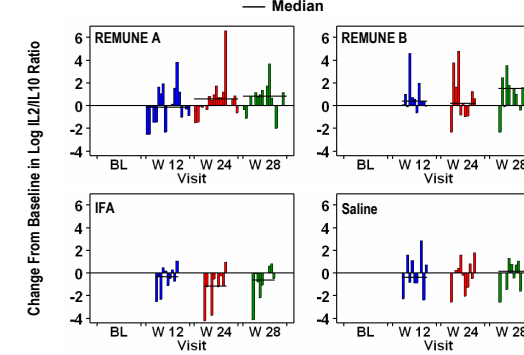
Plasma IL-7 (Change From Baseline)



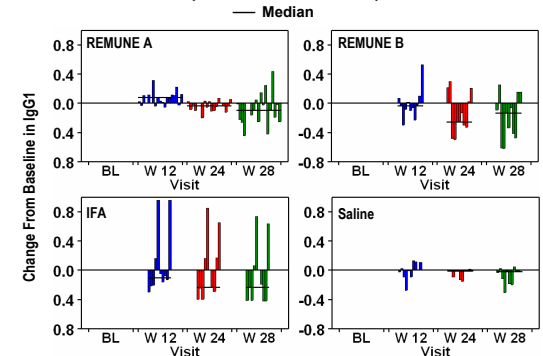
CD8+/CCR7-/CD45RA- (Effector Memory) (Change From Baseline)



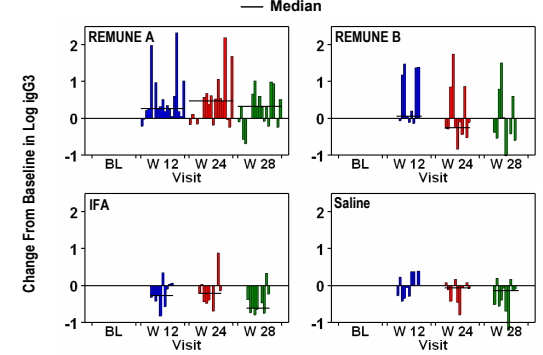
Log CD8 IL2/IL10 Ratio (Env) (Change From Baseline)



Plasma p24-Specific IgG1 (Change From Baseline) (O.D. at 1:10 Dilution)



Plasma p24-Specific IgG3 (Change From Baseline) (O.D. at 1:1 Dilution)



CONCLUSIONS

Three injections of REMUNE® in HIV-infected, HAART-naïve patients resulted in:

- Increased non-cytolytic antiviral activity (alpha-defensins, RANTES)
- Increased CD8-mediated cytolytic antiviral activity (EM CD8+ T lymphocytes)
- Increased thymic output as shown by the augmentation of naïve CD4+ and CD8+ T cells (CCR7+ CD45 RA+) and plasma IL-7 concentration
- Modulation of the TH1/TH2 equilibrium as shown by the increases in HIV-specific IL2/IL10 CD8+ ratio and in plasma concentration p24-specific IgG3, (TH1) and by the reduction of plasma p24-specific IgG1 (TH2)

FUTURE DIRECTIONS

- Well powered international clinical study with long-term treatment is being designed to correlate immunological activities of the whole inactivated vaccine to clinical benefit in therapy naïve patients
- Amplification of HIV-specific immunity elicited by the whole inactivated vaccine with a novel toll-like receptor agonist adjuvant, Amplivax™, is being tested in two clinical trials: IR103-111 and IR103-112. Preliminary data presented at the 3rd IAS Conference, Rio de Janeiro, Brazil, July 2005 (abstract #TuPeLB13.2B01)

The investigators gratefully acknowledge the contribution of all the patients who participated in this study