

Immunological Assessment of the activity of a Therapeutic Vaccine during Analytical Treatment Interruption

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Objectives

We have previously shown [1] that long-term treatment with an HIV-1 Immunogen (Remune; REM) plus antiretrovirals (ARV) delays virological failure (Study STIR-2102).

In this study we have determined whether therapeutic immunization with REM during analytical treatment interruption (ATI) maintain the existing HIV-1 specific responses in HIV+ patients previously sensitized with REM. We have also analyzed whether those HIV-1 specific responses could influence the control of viral replication.

Patients and Methods

REMIT is a prospective, randomised, double blind ATI pilot study that included patients who had participated in STIR-2102 receiving ARV plus either REM or placebo (IFA) every 3 months (m) for 36m, followed by an open label extension receiving REM plus ARV for 24 additional months. 39 immunized patients who met the criteria of inclusion in REMIT, interrupted the ARV and were randomised to receive REM (n=21) or IFA (n=18) every 3 m for 48 weeks.

-3 years (12 doses)-	-2 years (8 doses)-	-1 year (4 doses)-
Double-blind Period STIR-2102 (REMUNE)	Open-label Period REMUNE	Double-Blind-Period REMUNE (REMUNE)
STIR-2102 (IFA)		REMIT (IFA)

Table 1

Patients in REMIT study varied with respect to the number doses of REM received prior to randomisation and during ATI. We have evaluated patients that have received higher number of doses (REM^{high}: >12 dosis; n=18) compared to patients who received lower number of doses (REM^{low}: <12 doses; n=21) along a period of 6 years (Table 1).

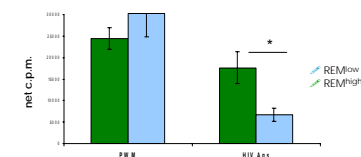
• Specific lymphoproliferative responses (LPR) were determined by both ³H-thymidine incorporation and CFSE (5,6-carboxyfluorescein diacetate succinimidyl ester) assays.

• T cell subsets were evaluated by 4 colour flow cytometry. ELISpot Assays were used to evaluated CD8+ HIV-1 specific responses to Gag and HIV-1 Ags.

• ANOVA Mixed Model was used for time curves.

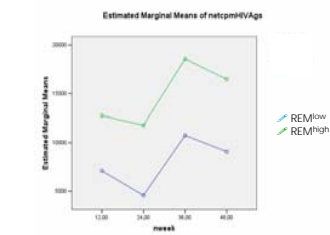
Results

Fig. 1: Lymphoproliferative responses (LPR) to HIV-1 Ags and to mitogens (PWM) by ³H-thymidine incorporation at week 48



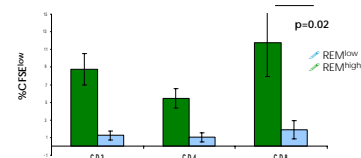
LPR to HIV-1 Ags were significantly higher at w48 in REM^{high} group compared to REM^{low} (p=0.03).

Fig. 2: Specific CD4+ T-cell LPR to HIV-1 Ags during ATI



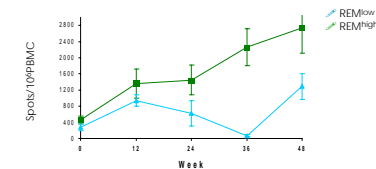
There is a significant difference between REM^{low} and REM^{high} patients at all time points (p=0.004).

Fig. 3: Specific T-cell lymphoproliferative responses to HIV-1 Ags assessed by CFSE at week 48



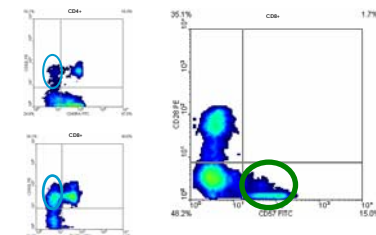
HIV-1 specific CD8+ T-cell LPR to HIV-1 Ags were significantly higher at w48 in REM^{high} group compared to REM^{low} (p=0.02).

Fig. 4: IFN- γ production against Gag/pol antigens evaluated by ELISPOT assays



REM^{high} patients showed a significant increase of CD8+ specific IFN- γ producing cells against Gag/pol antigens compared to REM^{low} patients (p=0.027).

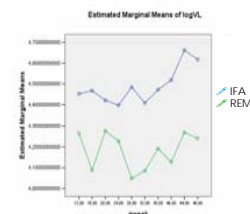
Fig. 5: Long term immunization expands central memory CD4+ and CD8+ T cells and generates terminally differentiated effector CD8+ T cells



Increased % of central memory T cells (CD45RA- CD62L+) from w0 to w48 (CD4+ : 34.2 vs. 42.2; p=0.021 and CD8+ : 10±1 vs. 14±1; p=0.048) in REM^{high} patients

Only REM^{high} patients showed a positive association between LPR, HIV-1 specific IFN- γ producing cells (p=0.017) and terminally differentiated effector CD8+ T cells (CD28 CD57+) (p=0.01).

Fig. 6: Time log VL curves according to randomised study arms (Mixed Model Analysis)



There is a significant difference in the HIV-1 RNA plasma viremia between immunized group vs. placebo (p<0.0001). The mean difference in logs is 0.3 log. At week 48 mean log 10 VL was 3.86 in the REM arm vs. 4.64 in the IFA arm (p<0.05). A difference of 0.78 log.

Conclusions

• Therapeutic vaccination with an HIV-1 Immunogen during ATI maintained existing lymphoproliferative HIV-1 specific CD4+ and CD8+ T-cell responses.

• Immunization during ATI generated IFN- γ producing HIV-1 specific CD8+ T cells in response to gag/pol Ags.

• Boosting HIV-1 specific immune responses with an HIV-1 Immunogen during ATI in patients previously sensitized to the Immunogen results in a better VL control.

Literature cited

Fernandez-Cruz E, Moreno S, et al. Therapeutic immunization with an inactivated HIV-1 immunogen plus antiretrovirals versus antiretroviral therapy alone in asymptomatic HIV-infected subjects. *Vaccine*. 2004 Aug 13; 22 (23-24): 2966-73.

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