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การทดสอบความปลอดภัยและภาวะภูมิคุ้มกันของวัคซีน HIV-1 Immunogen ในผู้ติดเชื้อ HIV : ศึกษาเฉพาะกรณีโรงพยาบาลศรีนครินทร์

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Safety and Immunogenicity of HIV-1 Immunogen in HIV Seropositive Subjects at Srinagarind Hospital : the first cohort study in Thailand.

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วัตถุประสงค์: เพื่อเพื่อศึกษาถึงความปลอดภัยและการเปลี่ยนแปลงของภาวะภูมิคุ้มกันของร่างกายภายหลังได้รับวัคซีน HIV-1 Immunogen (Remune TM)

รูปแบบการศึกษา: Randomized , double blind, adjuvant-controlled clinical trial

สถานที่ศึกษา: โรงบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

กระบวนการวิจัย: เป็นการวิจัย cohort แรกของการทดสอบในระยะที่ 2 ในประเทศไทย โดยมีอาสาสมัครเป็นผู้ติดเชื้อ HIV ที่ยังไม่มีอาการและมี จำนวน CD4+ มากกว่า 300 cell/mm^3 จำนวน 33 คน ได้รับวัคซีนจริงและวัคซีนหลอกในอัตราส่วน 2:1 ในสัปดาห์ที่ 1, สัปดาห์ที่ 12, สัปดาห์ที่ 24 และสัปดาห์ที่ 36 ของการวิจัย

ผลการวิจัย: พบว่า ไม่พบอาการข้างเคียงและภาวะแทรกซ้อนใดๆ ทั้งจากกลุ่มที่ได้รับวัคซีนและกลุ่มที่ได้รับวัคซีนหลอก น้ำหนักโดยเฉลี่ยของทั้งสองกลุ่มเพิ่มขึ้นเล็กน้อย จำนวนของ CD4+ ในกลุ่มที่ได้รับวัคซีนเพิ่มขึ้นมากกว่ากลุ่มที่ได้รับวัคซีนหลอกอย่างมีนัยสำคัญทางสถิติ และมีผลต่อภาวะภูมิคุ้มกันเฉพาะที่ตรวจได้จาก HIV-1 DTH skin test และ Western blot ส่วนปริมาณของสำเนา HIV-RNA และสำเนา log RNA ลดลงทั้งสองกลุ่ม แต่ไม่แตกต่าง

Objectives: To assess the safety and immunogenicity of HIV-1 Immunogen in HIV seropositive subjects.

Study Design: Randomized, double blind, adjuvant-controlled clinical trial.

Setting: Srinagarind Hospital. Khonkaen University.

Methodology: The 40 weeks trial was conducted in 33 volunteers who were randomized to receive either HIV-1 Immunogen or IFA at a 2:1 ratio on Week 1, week 12, 24, and 36.

Results: The primary end point for the trial was changes in CD4+ cell counts with secondary parameters of changes in CD8+ cell counts, percentages of the CD4+ and CD8+, the ratio of CD4+ to CD8+, body weight, plasma HIV-1 RNA, HIV-1 DTH skin test and Western blot. As regards safety, there was no serious adverse event in both treatment groups. The result also showed that HIV-infected subjects who received HIV-1 Immunogen had significant higher increase in CD4+ cell counts. This increased in CD4+ cell was associated with increased HIV specific

กันอย่างมีนัยสำคัญ ซึ่งอาจจะต้องใช้ระยะเวลาติดตามนานมากกว่านี้

สรุป: ผลการศึกษานี้สามารถชี้แนะด้านความปลอดภัยและการเปลี่ยนแปลงภาวะภูมิคุ้มกันที่เป็นผลจากการได้รับวัคซีน HIV-1 Immunogen ที่เป็นไปในทางที่ดีขึ้นสำหรับผู้ติดเชื้อ HIV ที่ยังไม่มียาตัวใดตัวหนึ่งเพียงอย่างเดียว (monotherapy) ในปัจจุบันที่รักษาได้ผล จึงควรจะทำการศึกษาในจำนวนอาสาสมัครให้มากขึ้น และเวลาที่ติดตามนานขึ้น เพื่อให้ได้ประสิทธิผลที่ชัดเจน อันจะนำไปสู่ความสำเร็จของการใช้วัคซีนรักษา (therapeutic vaccine) ในอนาคตต่อไป

immunogenicity on Western blots and enhanced HIV-1 DTH skin test. Although there was no significant difference in the body weight, but increased in body weight was slightly higher for the HIV-1 Immunogen group compared to the IFA group. The plasma HIV-1 RNA remained stable for both treatment groups over the course of the trial.

Conclusions: The results of this trial suggest that HIV-1 Immunogen is safe and significant increased in CD4+cell counts and HIV specific immunity compared to the adjuvant control group. This preliminary study also suggests that this therapy may be important treatment alternative in countries where access to antiviral drugs is limited.

Key words: HIV-1 Immunogen, IFA, immunogenicity, body weight.

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Introduction

Thailand has one of the highest prevalence of HIV infection in South-East Asia. Based on surveillance surveys, 1 million people have been infected and 100,000 have developed AIDS.[1] The HIV virus first spread among intravenous drug users but the epidemic now appears to be driven by patterns of heterosexual behavior.[2] HIV transmission is from men to families, hence the high incidence of HIV infection among pregnant women and their newborns. It has been estimated that each year a large number of new AIDS cases and HIV-infected infants will die.[3] This will have a wide impact on the medical, psychological and economic situation and will lead to a great social burden.

Many already have friends or relatives whom they suspect have died from an HIV-related illness.[4] In the absence of an effective cure for AIDS, counselling and testing may help reduce the further spread of HIV. However, studies in developed countries have shown that HIV counselling is stressful.[5-6] Cousellors face the added difficulty that HIV affects their personal as well as their professional life. Moreover, their personal experiences and feelings may affect the effectiveness of their counselling. Since HIV was first identified as the cause of AIDS, enormous research efforts have concentrated on identifying and developing compounds to suppress its replication.[7] In 1987, Zidovudine (ZDV) was approved by the US Food and Drug Administration, in the years that followed, four other drugs of the same family were introduced. Large multicenter clinical trials then showed that double therapy in terms of disease progression and patient surviral with two of these drugs was superior to monotherapy. Greater and more sustained decreases in plasma levels of HIV-1-RNA were achieved with double combinations. Monotherapy for the treatment of HIV infection is now regarded as obsolete because of serious problems of resistance. Significantly larger reductions in the viral load have been acheived by adding a new class of agents, the protease inhibitors, which became available in early 1996. Since then, new antiretroviral (ARV) treatments, particularly the triple therapies using a combinations of drugs from different classes, have shown impressive short-term results.

Nevertheless, clinicians express concern about the long-term benefit of the ARVs. Only clinical experience over several years will provide evidence that a reliable, long-term treatment has been found. Critical issues still require clarifications : when to start and change treatment, and with which drug combinations, and what drug sequence strategy to adopt. Despite these challenges, ARVs are present in most poor countries of the world, but accessible to a wealthy minority. Efforts to obtain the drugs,

often in an irregular and haphazard fashion, may absorb the entire resources of a poor family. In these situations, problems of incorrect and unsafe use, unreliable supply, and a black market in both good quality and counterfeit drugs are likely to appear. These problems have serious public health implications because of the almost certain development and spread of ARV-resistant strains of HIV. The long latency period observed between initial HIV-1 infection and the development of AIDS suggests that early HIV-1 replication is controlled by an effective immune response directed against HIV.

Agents that cause the immunologic system to increase the immunologic activity against HIV may represent a strategy of importance. Recently, there has been increased interest in the relationship between a strong HIV-1 specific immune function and improved clinical outcomes and the potential to utilize immune-based therapies to stimulate similar immune responses.[8-11] The HIV-1 Immunogen (Remune™) is chemically and physically inactivated, gp 120-depleted HIV-1, which is processed and highly purified prior to formulation with Incomplete Freundís Adjuvant (IFA). Previous studies utilizing HIV-1 Immunogen as a monotherapy had shown activity on proviral HIV-DNA copies, CD4 cells, body weight, and HIV-1 specific immune function in asymptomatic subjects prior to the advent of the potent antiretroviral drug therapy.[12-13] Moreover, phase I trials of the HIV-1 Immunogen as a monotherapy in thirty asymptomatic Thai subjects not taking ARVs confirmed the safety of this approach.[14-15] In Thailand, despite aggressive public health measures and a possible slowing of the epidemic, an estimated 1 million deaths will occur from AIDS by the year 2014[16-17]. Thus, cost effective strategies including preventive and therapeutic approaches to decelerate progression of disease are urgently needed. Therefore, there is a strong need to provide this HIV-1 specific immune-based approach used as a monotherapy for HIV-seropositive subjects who have little access to antiretroviral drug therapy.

Study objective

The objective of this study was to assess the safety and immunogenicity of the HIV-1 Immunogen in HIV-seropositive-Thai subjects at Srinagarind Hospital.

Study design

Randomized, double-blind, adjuvant-controlled clinical trial.

Methodology

It was a first cohort study of a phase II multi-site, double-blind, randomized, adjuvant-controlled study. The project site was Srinagarind Hospital, Khon Kaen University Thailand. The duration of the study was 40 weeks, a total of 33 HIV-1-infected subjects with CD4 cells $\geq$ 300 cells/mm^3 were randomized to receive either HIV-1 Immunogen or Incomplete Freundís Adjuvant (IFA) at a 2:1 ratio, yeilding 22 volunteers on the HIV-1 Immunogen arm and 11 in the IFA arm. Subjects were given 1.0 ml. intranuscular injection into the triceps or deltoid muscle of the blinded study treatment on day 1 and at week 12, 24 and 36. According to protocol, the body weights, the CD4+ and CD8+ cell counts, the percentages of CD4+ and CD8+ and the ratio of CD4+ to CD8+ were evaluated prior to each inoculation and at week 40. Plasma-HIV-RNA, humoral response by Western Blot analysis and HIV-1 Delayed Type Hypersensitivity (DTH) skin test were examined at day 1 and week 40. Complete medical history including all medications and adverse events were recorded, physical examination and blood chemistries were performed. A completed analysis of data was done.

The primary immunogenicity endpoint of this study was to compare HIV-1 Immunogen to IFA with respect to changes in the CD4+ cell counts over 40 weeks. The secondary endpoint was to compare the two treatment groups by measuring changes in CD4+ and the body weight, the CD8+ cell counts, the percentage of CD4+ and CD8+, the ratio of CD4+ to CD8+, plasma-HIV-RNA, HIV-1 DTH skin test and Western blot. Moreover, safety andtolerability of HIV-1 Immunogen were characterized.

Study data were recorded on case report forms and entered into a database which was verified at the Biostatistics Department, Faculty of Public Health, Mahidol University prior to unblinding. Two of the 33 randomized subjects discontinued their assigned treatment and terminated study prior to the 40th week. One subject in the HIV-1 Immunogen group died in a car accident prior to completing the protocol. One on the IFA subject discontinued on the advice of the site investigators because the subject had contracted tuberculosis.

Results

The baseline demographics, HIV-subtype, risk factors and duration of infection of the HIV-1 Immunogen (n=22)

and the IFA (n=11) groups are compared in Table 1-2. The median age was 28 years and the study population was 66% female. The predominant HIV-subtype of the subjects in this cohort was "E". The most common adverse event was a transient local injection site reaction which subsided without medication, this occurrence was similar between the HIV-1 Immunogen and IFA groups. There was no significant difference in physical examinations, blood chemistries and adverse events between the two groups.

Table 1. Baseline demographics for the two groups.

Demographics		HIV-1 Immunogen		IFA	
Sex	Male	7		4	
	Female	15		7	
Age	range	20-41		20-40	
	mean	29		27	
Education		**No**	**%**	**No**	**%**
Primary		12	54.55	6	54.55
High-school		5	22.72	3	27.27
Junior college		3	13.64	2	18.18
University		2	9.09	-	-
MSc		-	-	-	-
Occupation		**No**	**%**	**No**	**%**
Civil service		1	4.55	1	9.09
Business		3	13.64	1	9.09
Labourers		9	40.91	5	45.45
Agriculturists		6	27.27	3	27.27
Housewives		3	13.63	1	9.09
Others		-	-	-	-
Domicile		**No**	**%**	**No**	**%**
Khon Kaen		11	50	6	54.55
Others		11	50	5	45.45
Number of previous live births		**No**	**%**	**No**	**%**
0		4	18.18	3	27.27
1		14	63.64	5	45.45
2		4	18.18	3	27.27
Contraception		**No**	**%**	**No**	**%**
No		4	18.18	1	9.09
Pill		3	13.64	1	9.09
TR		10	45.45	5	45.45
Condom		5	22.73	4	36.36
DMPA		-	-	-	-

Table 2. HIV- subtype, risk factors and duration of infection.

Demographics		HIV-1 Immunogen		IFA	
Subtype	**E**	22		11	
	B	0		0	
Risk Factors		No	%	No	%
Heterosexual		22	100	11	100
IVDUs		-	-	-	-
Blood transfusion		-	-	-	-
Duration of infection (yrs.)		No	%	No	%
< 1		4	18.18	1	9.09
1 - 3		15	68.18	8	72.72
4 - 6		3	13.64	1	9.09
7 - 10		-	-	1	9.09

A comparison of the changes in the mean body weight between the two groups is presented in Table 3. Both the HIV-1Immunogen and IFAgroups gained weight with higher outcome in the first group but there were no significant difference in body weights from the baseline (p = 0.41).

Table 3. Changes in mean body weight (kg.)

	HIV-1 Immunogen	IFA	P. value
Day 1	54.90	53.11	0.41
Week 40	55.68	54.38	0.64
Gained	0.85	1.27	0.25

Comparison of CD4+ cell counts, lymphocyte subsets, plasma RNA copy and Log RNA copy between the two treatment groups are presented in Table 4/1-2. The mean CD4+ cell counts at the baseline were 354 in the HIV-1 Immunogen group and 359 in the IFA group. The two treatment groups were well-balanced with respect to all lymphocyte subsets. After four treatments, subjects in the HIV-1 Immunogen group increased from baseline by 280 cells on average, and the IFA group increased by 206 Cells. There was a statistically significant increase in the HIV-1 Immunogen group compared to the IFA group (p = 0.025). Similarly, trends apparently favoring the HIV-1 Immunogen group for the other lymphocyte parameters are also shown in these table.

The HIV-1 DTH skin test showed induration at week 40 (Table 5) was higher for the HIV-1 Immonugen group than for the IFA group (p = 0.042).

The results of HIV-1 RNA quantification are shown in Table 6. At baseline, the mean viral load was 19,503 copies/mL (3.81 logs) and 28,110 copies/ml (4.04 logs) in each of the two groups. At week 40, plasma RNA was reduced to 18,975 copies/ml (3.71 logs) in the HIV-1 Immunogen group and 13,895 copies/ml (3.86 logs) in IFA group. According to log RNA copy, both groups remained stable, and there was no significant difference between the two treatment arm. Moreover, there was increased of the HIV-1 specific antibody immunoreactivity on the Western blots; in terms of the increased generation of new bands in the HIV-1 Immunogen group compared to fewer attenuation bands in the IFA group. Patients in the HIV-1 Immunogen group did experience significantly better change in Western blot (p = .001).

Discussion and conclusion

The objective of this trial was to assess the safety and immunogenicity of HIV-1 Immunogen (Remune™) in HIV-seropositive subjects who has CD4+ cell counts greater than 300 cells/mm^3. This was achieved by conducting a double blind, randomized trial in which 22 volunteers were assigned to HIV-1 Immunogen and 11 were assigned to an IFA at a 2 : 1 ratio. The primary immunogenicity endpoint of the study was the change in CD4+ cell counts between the baseline and week 40.

Table 4/1. Immunological & virological data: HIV -Immunogen

Immunological & Virological	Baseline (Day 1)	Week 40
Mean CD4 cells count	353.86 cells/mm^3	633.71 cells/mm^3
Mean CD4 %	18.93 %	23.52 %
Mean CD8 cells count	1,002.09 cells/mm^3	1,521.24 cells/mm^3
Mean CD8 %	48.95 %	53.85 %
Ratio CD4 +/CD8+	0.42	0.46
Plasma RNA Copy	19,503 (n=21)	18,974.76 (n=21)
Log RNA copy	3.81 (n=21)	3.71 (n=21)

Table 4/2. Immunological & virological data: IFA

Immunological & Virological	Baseline (Day 1)	Week 40
Mean CD4 cells count	358.82 cells/mm^3	565.10 cells/mm^3
Mean CD4 %	19.65 %	21.33 %
Mean CD8 cells count	835.27 cells/mm^3	1,759.40 cells/mm^3
Mean CD8 %	45.02 %	60.47 %
Ratio CD4 +/CD8+	0.46	0.37
Plasma RNA Copy	28,110 (n=10)	13,895 (n=10)
Log RNA copy	4.04 (n=10)	3.86 (n=10)

Table 5. Delayed type hypersensitivity skin test to HIV-1 antigens.

Skin test reaction at week 40	HIV-1 Immunogen (n = 19)	IFA (n = 10)
Positive (diameter > 20 mm.)	7	-
Positive (diameter 15 -19 mm.)	5	2
Positive (diameter 10 - 15 mm.)	3	4
Negative	4	4

Note: HIV-DTH skin test on Day 1 revealed all negative results.

Secondary endpoints included changes in body weight, the percentages of CD4+ and CD8+, the ratio of CD4+ to CD8+, HIV-1 RNA, HIV-1 DTH skin test and Western blot. As regards safety, both treatment groups appear to be well-tolerated and no serious adverse event were reported. There was significant difference between the HIV-1 Immunogen and IFA control groups with respect to the primary endpoint. The increase of 280 in the CD4+ cell counts over 40 weeks for an HIV-seropositive subject may indicate the potential for a longer healthier life. Moreover, subjects in the HIV-1 Immunogen group experienced better changes in CD8+ cell counts, the percentages of CD4+ and CD8+, the ratio of CD4+ to CD8+. Interestingly, the increase in absolute CD4+

Table 6. Viral Load data - HIV-1 Immunogen and IFA group.

HIV-1 Immunogen					IFA				
I.D	Day 1		Week 40		I.D	Day1		Week 40	
	Copies	Logs	Copies	Logs		Copies	Logs	Copies	Logs
104	18,000	4.26	1,500	3.18	113	87,000	4.94	22,000	4.34
101	300	2.48	400	2.60	125	78,000	4.89	14,000	4.15
102	76,000	4.88	54,000	4.73	126	8,700	3.94	350	2.54
103	90,000	4.95	49,000	4.69	106	26,000	4.41	33,000	4.52
109	15,000	4.18	7,600	3.88	110	54,000	4.73	34,000	4.53
114	20,000	4.30	8,400	3.92	112	1,500	3.18	2,500	3.40
115	1,700	3.23	3,700	3.57	117	18,000	3.26	6,100	3.79
116	31,000	4.49	46,000	4.66	132	1,200	3.08	1,500	3.18
119	1,100	3.04	1,700	3.23	105	1,800	3.26	8,500	3.93
121	11,000	4.04	13,000	4.11	124	4,900	3.69	17,000	4.23
123	750	2.88	870	2.94	**Total**	**281,100**	**40.38**	**138,950**	**38.61**
128	31,000	4.49	55,000	4.74	**Mean**	**28,110**	**4.04**	**13,895**	**3.86**
129	5,100	3.71	2,900	3.46					
130	5,200	3.72	11,000	4.04					
131	1,200	3.08	1,500	3.18					
133	78,000	4.89	3,500	3.54					
107	9,000	3.95	52,000	4.72					
108	429	2.63	13,000	4.11					
118	10,000	4.00	50,000	4.70					
120	2,900	3.46	17,000	4.23					
127	1,900	3.28	6,400	3.81					
Total	**409,579**	**79.94**	**398,470**	**82.04**					
Mean	**19,503**	**3.81**	**18,975**	**3.71**					

cells in the HIV-1 Immunogen group was also associated with an enhanced HIV-specific-immunogenicity as determined by the HIV-1 DTH skin test and the Western blots. Thus, the study demonstrates immunogenic activity of HIV-1 Immunogen on most of the markers and suggests that this treatment increased both humoral and cell-mediated immune responses to core proteins of the virus. Nevertheless, both absolute CD4+ cells and HIV-1 specific immune function were also enhanced from the baseline in the IFA treatment group in this study. This finding could be explained by the improved care that subjects received whole participating in the clinical trial and by the direct immunostimulatory activity of the IFA, but more superiority of HIV-1 Immunogen in IFA compared to IFA alone. Over the course of the study, however, there was no significant difference in body weight and plasma HIV-1- RNA, it was probably the effect of HIV-1 Immunogen on the viral specific immune function differs from the antiviral drug therapy, which potently suppresses viral replication. Even if, no significant effect on viral load was demonstrated during the 40 weeks of this trial, all volunteers are being followed-up with HIV-1 Immunogen every 3 months for 2 years. Periodic monitoring of this cohort should show the impact of HIV-1 Immunogen on this important marker.

Further study of HIV-1 Immunogen is, therefore, proposed in another eight cohort studies to further investigate the effect of HIV-1 Immunogen in a larger population. The proposal has already been submitted for 297 volunteers, five test sites, doing the study of 9 cohorts with 33 volunteers per cohort. Study data obtained will give valuable information on the efficacy of this therapeutic vaccine as Immune-based monotherapy. Although, the study will only be conducted in Thailand but if successful, will be beneficial to all HIV-infected persons around the world.

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