The efficacy of Rhinos® SR on nasal resistance and nasal symptoms in patients with perennial allergic rhinitis : a randomized, double-blind, placebo-controlled study

Arini Setiawati[1], Iwan Darmansjah[1], Mulyarjo[2], Dwi Reno Parwati[2], Faiz[2], Roestiniadi Djoko Soemantri[2]

Abstrak

Rhinos® SR adalah kapsul kombinasi tetap loratadin 5 mg dengan pseudoefedrin 60 mg lepas cepat dan pseudoefedrin 60 mg lepas lambat. Studi ini bertujuan untuk menilai efikasi Rhinos® SR pada nasal airway resistance (NAR) secara obyektif dengan rhinomanometer dan gejala-gejala nasal serta nonnasal pada pasien dengan rinitis alergik sepanjang tahun (RAST) di negara tropis. Ini adalah studi paralel berpembanding plasebo, acak, tersamar ganda, dilakukan pada 59 pasien RAST berobat jalan di klinik THT RS Umum Dr. Soetomo, Surabaya. Pasien laki-laki dan perempuan, menderita RAST sedang sampai berat minimal 2 tahun, berumur 12 tahun ke atas, dengan total skor gejala nasal (TSGN) ≥ 6 dan skor kongesti nasal (SKN) ≥ 2, mendapat Rhinos® SR atau plasebo 2 kali sehari selama 7 hari. Parameter efikasi yang utama adalah berkurangnya nilai-nilai NAR (yang diukur dengan rhinomanometer pada hari pertama) dari Rhinos® SR dibandingkan dengan plasebo. Nilai-nilai NAR dihitung sebagai luas area di bawah kurva (area under the curve = AUC) dari NAR terhadap waktu. Parameter efikasi sekunder adalah berkurangnya gejala-gejala klinik (nasal dan nonnasal) yang dinilai oleh pasien maupun oleh dokter peneliti setelah 1 minggu penggunaan Rhinos® SR atau plasebo. Dari 59 pasien yang memenuhi syarat, semuanya menyelesaikan studi 1 minggu ini. Untuk nilai-nilai NAR, setelah baseline disamakan menjadi 100%, $AUC_{0\text{-}10\ jam}$ tidak berbeda bermakna antara Rhinos® SR dan plasebo. Akan tetapi waktu pseudoefedrin mencapai kadar puncak, yakni 2 jam untuk yang lepas cepat dan 6 jam untuk yang lepas lambat, maka $AUC_{0\text{-}2\ jam}$ dan $AUC_{0\text{-}6\ jam}$ Rhinos® SR lebih rendah secara bermakna dibandingkan dengan plasebo. TSGN berdasarkan penilaian penderita (jumlah skor 3 pagi terakhir) untuk Rhinos® SR menurun 33.0% dari skor awal (p < 0.001), untuk plasebo juga menurun 21.9% dari skor awal (p = 0.002), tetapi penurunan oleh Rhinos tidak berbeda bermakna dengan penurunan oleh plasebo. Penurunan TSGN berdasarkan penilaian dokter peneliti, serta penurunan skor kongesti nasal (SKN) dan total skor gejala (nasal dan nonnasal), dan bahkan skor masing-masing gejala, berdasarkan penilaian pasien maupun dokter peneliti, menunjukkan pola yang sama, yakni Rhinos® SR dan plasebo menurunkan gejala secara bermakna dari nilai awal, dan penurunan oleh Rhinos® SR lebih besar dibandingkan penurunan oleh plasebo tetapi tidak berbeda bermakna. Dalam studi ini tidak ditemukan efek samping. Dari penelitian ini disimpulkan bahwa pada pasien RAST sedang sampai berat di negara tropis, Rhinos® SR efektif dalam mengurangi kongesti nasal dengan pengukuran obyektf NAR. Rhinos® SR 2 x sehari selama 7 hari juga efektif dalam mengurangi gejala-gejala klinik RAST meskipun tidak mencapai kemaknaan statistik dibandingkan dengan plasebo, serta dapat ditoleransi dengan baik. ***(Med J Indones 2008; 17: 114-26)***

Abstract

Rhinos® SR is a fixed combination of 5 mg loratadine and 60 mg pseudoephedrine immediate release and 60 mg pseudoephedrine sustained release. The present study was aimed to assess the efficacy of Rhinos® SR on nasal airway resistance (NAR) objectively using rhinomanometer and on nasal symptoms in patients with perennial allergic rhinitis (PAR) in a tropical country. This was a randomized, double-blind, parallel group study in 59 PAR patients who visited the ENT clinic at Dr. Soetomo General Hospital, Surabaya. Outpatients of both gender, having moderate to severe PAR for a minimal of 2 years, aged 12 years or older, with a total nasal symptom score (TNSS) ≥ 6 and a nasal congestion score ≥ 2, received Rhinos® SR or placebo twice daily for 7 days. The primary efficacy parameter was the decrease in the NAR values (measured by rhinomanometer on Day 1) of Rhinos® SR from those of placebo. The NAR values were calculated as the area under the curve (AUC) of NAR versus time. The secondary efficacy parameters were the percentage reduction of the clinical symptoms (nasal and nonnasal) evaluated by both the patient and the physician after 1 week use of Rhinos® SR or placebo. From 59 eligible patients, all completed this 1-week trial. For NAR values, after the baseline were considered as 100%, the $AUC_{0\text{-}10\ h}$ were not significantly different between Rhinos® SR and placebo. However, as the pseudoephedrine reached its peak concentration, i.e. 2 hrs for the immediate release and 6 hrs for the sustained release, then $AUC_{0\text{-}2\ h}$ and $AUC_{0\text{-}6\ h}$ of Rhinos® SR were significantly lower compared to those of placebo. Total nasal symptom score (TNSS) evaluated by the patient (sum of the last 3 mornings) for Rhinos® SR decreased 33.0% from baseline (p < 0.001), for placebo decreased 21.9% from baseline (p = 0.002), but the decrease by Rhinos® SR was not significantly different from the decrease by placebo. TNSS evaluated by the physician, nasal congestion score (NCS) and total symptom score (TSS, total nasal and nonnasal), and even the individual symptom scores, evaluated by the patient and the physician, showed similar pattern, i.e. both Rhinos® SR and placebo decreased the symptoms significantly from baseline, and the decreases by Rhinos® SR were larger than the decreases by placebo, but the decreases by Rhinos® SR and placebo were not statistically different. No adverse event was found in this study. From the present study it was concluded that in patients with moderate to severe PAR in a tropical country, Rhinos® SR was effective in relieving nasal congestion by objective measurements of NAR. Rhinos® SR twice a day for 7 days was also effective in reducing the clinical symptoms of PAR although the reductions did not reach statistical significance compared to those by placebo, and was well tolerated. ***(Med J Indones 2008; 17: 114-26)***

Keywords: *loratadine, pseudoephedrine, rhinomanometry, perennial allergic rhinitis*

[1] *Clinical Trial Center, Medical Faculty, University of Indonesia, Jakarta, Indonesia*
[2] *ENT Department, Medical Faculty, University of Airlangga/ Dr. Soetomo General Hospital, Surabaya, Indonesia*

Rhinos® SR is a fixed combination of 5 mg loratadine and 60 mg pseudoephedrine in immediate-release formulation, and another 60 mg pseudoephedrine in sustained-release formulation. Loratadine is one of the generation of H_1 antihistamines which are less lipophilic and therefore have reduced ability to cross the blood brain barrier, and thus their sedating and anticholinergic side effects are minimized. Loratadine is metabolized to desloratadine, the major active metabolite. The mean half-life of loratadine is 8.4 hours, while that of desloratadine is 28 hours. The antihistaminic effect begins within 1 to 3 hours, reaches a maximum at 8 to 12 hours and lasts in excess of 24 hours.[1] Pseudoephedrine is an orally active α- and β-adrenergic agonist which exerts a decongestant action on the nasal mucosa. It is an effective agent for the relief of nasal congestion due to allergic rhinitis.[1] The plasma half-life of pseudoephedrine ranges from 4.3 to 8 hours. The time to peak concentration ranges from 1.4 to 2 hours after a single 60 mg immediate-release tablet (IR), and from 3.8 to 6.1 hours following a 120 mg controlled-release capsule (CR) oral dose.[2]

Perennial allergic rhinitis (PAR) is an antibody-mediated hypersensitivity response to allergens characterized by continuous inflammation of the nasal mucous membranes, with resultant nasal mucosal congestion and increased watery and viscous nasal airway secretions. These nasal symptoms (congestion, discharge, itching and sneezing) constitute the primary symptoms of PAR, while some nonnasal symptoms (involving the eyes and ears) may also present. These symptoms, especially nasal congestion, may be very troublesome for many patients and may cause significant impairment of their quality of life.[3] There are several treatment options that may be used to control these symptoms, but traditionally H_1 antihistamines have been used as initial pharmacological therapy because of their rapid and effective relief of most symptoms.[4] H_1 antihistamines are effective for nasal itching, sneezing and watery rhinorrhea, and for ocular symptoms, but they are not efficacious for the nasal congestion. α-adrenergic agents are generally used to relieve nasal congestion.[5]

Rhinos® SR is a copy drug of its innovator, Clarinase® from Schering-Plough. It differs from its innovator product in the sustained-release formulation of the pseudoephedrine.[6] Therefore, the clinical performance of this copy drug may be slightly different from its innovator. The clinical efficacy of Clarinase® in reducing nasal and eye symptoms, including nasal congestion, and its tolerability have been shown especially in patients with seasonal allergic rhinitis (SAR) with and without asthma.[1] However, the efficacy assessment of this fixed combination using rhinomanometer for objective measurements of nasal resistance has not been performed yet. The objective of the present study was to study the efficacy of Rhinos® SR on nasal airway resistance (NAR) and nasal symptoms in patients with perennial allergic rhinitis.

METHODS

Patients

Outpatients of either gender, aged 12 years or older, with moderate to severe perennial allergic rhinitis of at least 2 years were recruited into the study. They had a total nasal symptom score (nasal congestion, nasal discharge, sneezing and nasal itching) of at least 6 and nasal congestion score of at least 2. Patients had agreed to adhere to the dosing and visit schedules, and to record symptom severity scores, medication times, concomitant medications, and adverse event(s) on the diary cards provided, and to sign the written informed consent.

Excluded from the study were patients with sinusitis, rhinitis medicamentosa, nasal structural abnormalities including nasal polyps and marked septal deviation that significantly interfere with nasal airflow, and also patients with asthma requiring chronic use of inhaled or systemic corticosteroids, patients with upper respiratory tract or sinus infection requiring antibiotic therapy within 14 days prior to screening visit, or patients with a viral URTI within 7 days prior to screening visit. Also excluded were patients with significant hematopoietic, metabolic, cardiovascular, immunologic, neurologic, hematologic, gastrointestinal, hepatic, renal, psychiatric, cerebrovascular, respiratory, or any other significant medical illness or disorder. Other exclusions were a history of hypersensitivity to loratadine or pseudoephedrine or any of the excipients, pregnant women, nursing mothers, or women of childbearing potential without acceptible method of birth control, patients using any investigational product within 30 days, or any of the prohibited medications, or patients who were dependent upon nasal, oral or ocular decongestants, nasal topical antihistamines, or nasal steroids.

Study design and procedure

This was a randomized, double-blind, parallel group study, Rhinos® SR versus placebo, performed in outpatients with moderate to severe PAR who visited the ENT clinic at Dr. Soetomo General Hospital, Surabaya. The

study protocol was approved by the Ethics Committee of the Medical Faculty, University of Airlangga, Surabaya, and the study was conducted in compliance with Good Clinical Practice. Rhinos® SR and its identical placebo were provided by PT Dexa Medica, Jakarta. Treatment allocation was according to block-randomization using random permuted blocks of size 4.

Eligible patients received either Rhinos® SR or Placebo capsules to be taken two capsules daily every morning and evening for 7 days. Patients were instructed to swallow the whole capsule with a glass of water at approximately the same time each morning and evening.

Signs and symptoms of PAR were divided into nasal symptoms and non-nasal symptoms. Nasal symptoms consisted of 4 symptoms : nasal congestion, nasal discharge, sneezing and nasal itching, while non-nasal symptoms consisted of 2 symptoms : itching of ears, palate and/or throat, and itching, watery, red eyes. The severity of each symptom was scored 0 to 3 where 0 = none (no sign/symptom evident), 1 = mild (sign/symptom clearly present, but easily tolerated), 2 = moderate (definite awareness of sign/symptom, bothersome but tolerable), 3 = severe (sign/ symptom hard to tolerate, interfere with activities of daily living and/or sleeping). Signs and symptoms of PAR were scored by the investigator at each visit : baseline (day 1) and follow-up (day 8). These signs and symptoms of PAR were also scored by the patients themselves and recorded every morning and evening on the diary card provided.

Concomitant treatment with corticosteroids, cromolyn, other antihistamines, leukotriene inhibitors, sympathomimetic bronchodilators, decongestants, nasal saline, ipratropium or atropin intranasal, herbal medications for allergic rhinitis, eye washes/drops, ophthalmic NSAIDs, systemic antibiotics for upper and lower RTI, immunotherapy (desensitization), investigational medications, tricyclic/tetracyclic antidepressants and SSRIs were not allowed. The following medications were permitted before and during the trial : OTC pain medication not containing anti-rhinitis/anti-allergy, low-dose aspirin as antiplatelet, dermatological corticosteroids, antibiotics for non-respiratory infections; also stable dosage of a β_2-agonist or theophylline for asthma, hormone replacement therapy, or thyroid replacement therapy.

Patients could be withdrawn from the study for either safety or efficacy reason. Patients may withdraw from the study at any time and the reasons for this were recorded. Any adverse events reported were noted in the case report form.

Assessments

The primary efficacy variable in the present study was the nasal airway resistance (NAR) value on Day 1. To combine the hourly values of NAR (measured by anterior rhinomanometry), we calculated the area under the curve (AUC) of NAR versus time (from 0 until 10 hours) during both inspiration and expiration. The secondary efficacy variables were the total nasal symptom score (TNSS), the nasal congestion score (NCS), the total symptom score (TSS) and the individual symptom score (other than NCS), evaluated by both the physician and the patient (the last 3 mornings), and the last 3 evenings TNSS, NCS, and TSS, evaluated by the patient. TNSS was defined as the sum of severity scores of the 4 nasal symptoms (nasal congestion, nasal discharge, sneezing and nasal itching). The severity of each symptom was scored 0 to 3, making a maximum possible score of 12 for TNSS. Since physician evaluation was done during scheduled patient visit in the morning, the patient-evaluated TNSS selected for analysis was the sum of the last 3 mornings TNSS prior to the scheduled visit (a maximum possible score of 36) in order to obtain comparable conditions. TSS was the sum of severity scores of all symptoms (4 nasal symptoms and 2 non-nasal symptoms).

The primary efficacy parameter was the decrease in the AUC of NAR value (during both inspiration and expiration) of Rhinos® SR from that of placebo. The secondary efficacy parameters were the percentage reduction of TNSS, NCS, TSS, the individual symptom score, and the evening TNSS, NCS, and TSS from baseline, and the difference of the percentage reduction between groups (Rhinos® SR vs placebo).

The clinical efficacy was rated based on the TNSS and the NCS as complete relief (CR), marked relief (MaR), moderate relief (MoR), slight relief (SR), and treatment failure (TF). CR was defined as reaching 13% or less of the baseline value, MaR between 14 and 35%, MoR between 36 and 70%, SR between 71 and 90%, and TF more than 90% of the baseline value. CR and MaR combined was considered as the desired efficacy, whereas CR, MaR and MoR combined was considered as the success rate.

Data analyses

Descriptive statistics were used for demographic and baseline characteristics. Unpaired-t test or Mann-Whitney U test was used to compare the AUCs of NAR

versus time (during both inspiration and expiration) between groups (Rhinos® SR versus placebo), depending on the distribution of the data. Paired statistical tests were used to compare the scores before and after treatment : paired-t test for TNSS and TSS, and Wilcoxon matched-pairs test for NCS and other individual symptom scores. Unpaired statistical tests were used to compare the differences from baseline between groups (Rhinos® SR versus placebo) : unpaired-t test for TNSS and TSS, and Mann-Whitney U test for NCS and other individual symptom scores. The clinical efficacy rates based on TNSS and NCS were compared between Rhinos® SR and placebo, evaluated by patient and by physician, using X^2 test. Each statistical test was performed at 0.05 (2-tailed) level of significance.

Adverse events, whether considered related or unrelated to the study drug by the investigator, were listed with their respective incidences.

RESULTS

Patients

A total of 112 patients were screened and 59 patients were eligible to be included in the study. One patient received both Rhinos® SR and placebo. On the first day he entered the study, he received a package of the investigational drug for 7 days treatment, and he underwent the NAR test using rhinomanometer for 10 hours on that day 1. On the way home, he lost the whole package of the investigational drug. The next day he returned to the clinic reporting the lost, and received another package of investigational drug and again underwent the NAR test. When the drug code was opened, it turned out that the first drug was placebo and the second drug was Rhinos® SR. Because the package of placebo was lost, the clinical results were not available. This patient had rhinomanometer values for both placebo and Rhinos® SR, but had only clinical results for Rhinos® SR, the investigational product that he received for the second time.

The demographics and baseline characteristics of the 59 patients in the present study are presented in Table 1. There were almost as many male patients as females and about half were in the age group of 21 to 35 years with a mean of around 27 years. The mean body weight was around 51 kg. The mean duration of PAR was around 4 years. The mean TNSS at baseline (physician-rated) scored around 8, and the mean nasal congestion scored 2.3.

Table 1. Demographics and baseline characteristics of patients on Rhinos® SR and Placebo

		Rhinos®	Placebo
Number of patients		30	29
Gender : Male/Female		14/16	13/16
Age : 12 - 20 yrs		12	7
21 - 35 yrs		12	17
36 - 50 yrs		5	5
51 - 60 yr		1	-
Mean (SD)		26.3 (11,19)	27.9 (9,85)
Median		22	26
Range		12 - 54	14 - 49
Weight : Mean		51.2	51.0
(kg) Range		28 - 76	34 - 68
Duration of PAR :	Mean	3.8	4.2
(yrs)	Median	4	3
	Mode	2	3
	Range	2-7	2-10
TNSS at baseline :	Mean	7.7	8.3
(physician-rated)	Range	6 - 11	6 - 11
Nasal congestion :	Mean	2.3	2.3
(physician-rated)	Range	2 - 3	2 - 3

Efficacy

All eligible patients completed this 1-week trial. For rhinomanometry measurements, there were 30 values for Rhinos® SR and 30 values for placebo. For both inspiration and expiration, the measurements of NAR based on anterior rhinomanometry at 150 Pa pressure point produced different baseline (0 hour, before drug) values for Rhinos® SR and placebo (the baseline values of placebo were significantly higher than those of Rhinos® SR, $p < 0.05$), making direct comparison between groups impossible. Therefore, the baseline NAR values of both Rhinos® SR and placebo were considered as 100% and the NAR values at the subsequent hours were calculated as percentage of the baseline values (Figures 1 and 2). In order to assess the effect of Rhinos® SR on NAR, we compared the area under nasal airway resistance versus time curve (AUC) between Rhinos® SR and placebo. Since the distribution of the AUC data of Rhinos® SR were not normal during both inspiration and expiration, we used Mann-Whitney U test to compare the AUCs between Rhinos® SR and placebo. The AUCs of placebo were larger than the AUCs of Rhinos® SR during both inspiration and expiration, but the differences did not reach statistical significance ($p = 0.147$ and 0.074 during inspiration and expiration, respectively) (see Table 2).

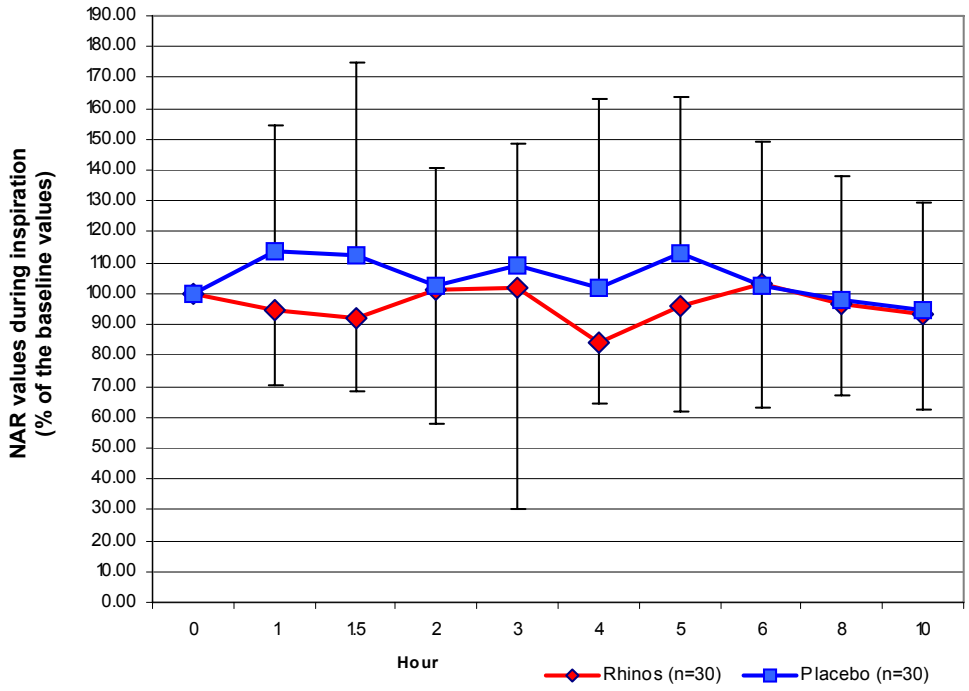


Figure 1. The mean (SD) values of the nasal airway resistance during inspiration of all subjects at different hours after Rhinos® SR and placebo administration (% of the baseline values)

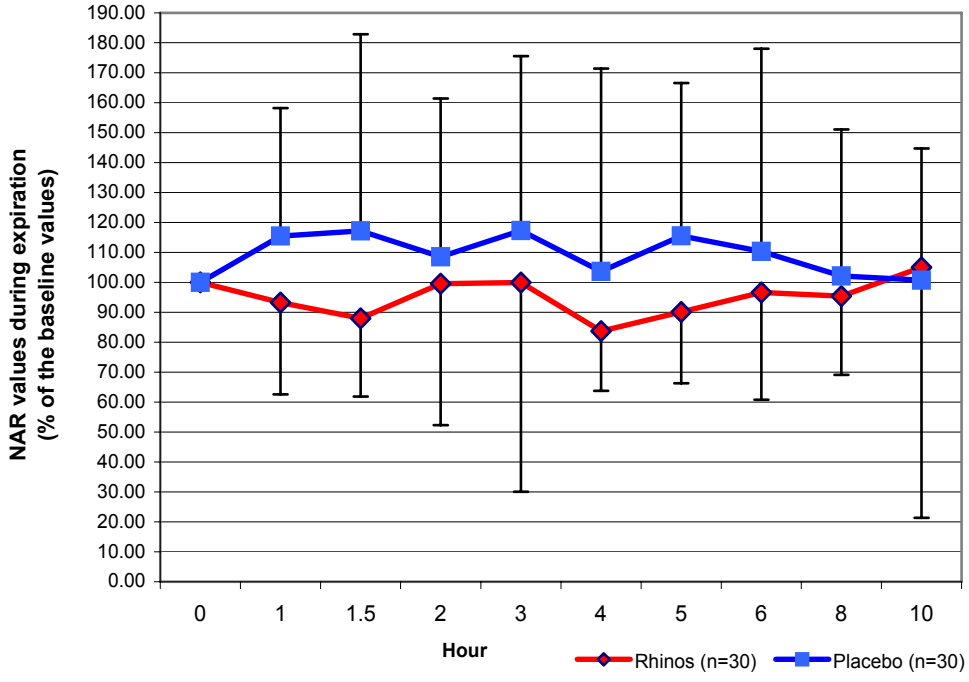


Figure 2. The mean (SD) values of the nasal airway resistance during expiration of all subjects at different hours after Rhinos® SR and placebo administration (% of the baseline values)

Table 2. $AUC_{0\text{-}10h}$ of NAR after Rhinos® SR and placebo treatment (baseline = 100%)

	During inspiration		During expiration	
	Rhinos	Placebo	Rhinos	Placebo
n	30	30	30	30
Mean	966.15	1036.60	953.20	1083.43
SD	232.92	256.17	258.79	378.01
Median	903.04	1081.13	905.64	1106.53
Range	723.19-1989.95	569.96-1596.15	598.94-1923.73	501.01-2535.19
Mann-Whitney U :				
Z	1.449		1.789	
p (2-tailed)	0.147 (NS)		0.074 (NS)	

The patient-evaluated TNSS (sum of the last 3 mornings) decreased significantly by Rhinos® SR from a mean of 21.0 at baseline to 12.9 after 1 week of treatment (a mean reduction of 33.0%; $p < 0.001$), and also by placebo from a mean of 23.6 at baseline to 17.1 after 1 week of treatment (a mean reduction of 21.9%; $p = 0.002$). The reduction by Rhinos® SR was larger, but not significantly different compared to the reduction by placebo ($p = 0.304$). The patient-evaluated TNSS evening and the physician-evaluated TNSS (during the morning visit) showed a similar trend. The decreases in TNSS evening were smaller than the decreases in TNSS morning, while the decreases evaluated by the physicians were larger than those evaluated by the patients, but still not significant between Rhinos® SR and placebo (Table 3).

Table 4 shows improvement of the nasal congestion. Patient-evaluated NCS morning improved significantly by Rhinos® SR but not significantly by placebo, and the difference in the improvement between Rhinos® SR and placebo was not significant. Patient-evaluated NCS evening showed smaller improvement, while physician-evaluated NCS demonstrated larger and significant improvement by both Rhinos® SR and placebo, and yet not significant between Rhinos® SR and placebo.

Table 5 shows improvement of the total symptoms, which have similar patterns as those of the total nasal symptoms.

Table 3. Total nasal symptom score (TNSS) before and after Rhinos® SR and placebo treatment

	Rhinos (n = 30)			Placebo (n = 29)			Rhinos		Placebo		Rhinos vs Placebo	
	Baseline	Follow-up	% reduction from baseline	Baseline	Follow-up	% reduction from baseline	paired t-test FU vs Baseline t	p (2-tailed)	paired t-test FU vs Baseline t	p (2-tailed)	t-test % reduction fr baseline t	p (2-tailed)
a. Patient evaluation (sum of the last 3 mornings)												
Mean	21.0	12.9	-33.0	23.6	17.1	-21.9	-5.57	< 0.001	-3.47	0.002	-1.04	0.304 (NS)
SD	6.58	6.34	39.42	5.85	7.97	42.31						
Median	19.5	12.0		24.0	17.0							
Mode	18	12		24	26							
Range	6 – 32	2 – 28	-91.7→100.0	12 – 35	0 – 28	-100.0→71.4						
b) Patient evaluation (sum of the last 3 evenings)												
Mean	18.2	11.9	-24.5	22.0	15.3	-19.1	-4.45	< 0.001	-3.43	0.002	-0.38	0.708 (NS)
SD	6.52	6.42	49.67	6.86	8.22	61.49						
Median	18.5	11.5		22.0	15.0							
Mode	18	12		27	9							
Range	6 – 30	0 – 28	-00.0→114.3	6 – 31	0 – 30	-100.0→177.8						
c) Physician evaluation (at the morning visit)												
Mean	7.7	3.6	-52.5	8.3	4.8	-41.2	-8.54	< 0.001	-7.10	< 0.001	-1.36	0.180 (NS)
SD	1.51	2.50	33.08	1.44	2.56	30.74						
Median	8.0	3.0		8.0	4.0							
Mode	6	2		8	3							
Range	6 – 11	0 – 9	-100.0→28.6	6 – 11	0 – 10	-100.0→28.6						

Table 4. Nasal congestion score (NCS) before and after Rhinos® SR and placebo treatment

	Rhinos (n = 30)			Placebo (n = 29)			Rhinos		Placebo		Rhinos vs Placebo	
	Baseline	Follow-up	% reduction from baseline	Baseline	Follow-up	% reduction from baseline	Wilcoxon FU vs baseline Z	p (2-tailed)	Wilcoxon FU vs baseline Z	p (2-tailed)	Mann-Whitney % reduction fr baseline Z	p (2-tailed)
a. Patient evaluation (sum of the last 3 mornings)												
Mean	6.20	4.17	-29.4	6.59	5.03	-20.4	-3.88	< 0,001	-1.70	0.090 (NS)	-0.973	0.330 (NS)
Median	6.0	4.0		6.0	6.0							
Mode	6	3		6	6							
Range	2 – 9	0 – 7	-100.0→100.0	4 – 9	0 – 9	-100.0→75.0						
b) Patient evaluation (sum of the last 3 evenings)												
Mean	5.60	3.97	-18.9	6.38	4.86	-12.2	-3.08	0.002	-2.53	0.011	-0.289	0.773 (NS)
Median	6.0	4.0		6.0	5.0							
Mode	6	3		6	6							
Range	2 – 9	0 – 8	-100.0→200.0	2 – 9	0 – 9	-100.0→250.0						
c) Physician evaluation (at the morning visit)												
Mean	2.27	1.27	-42.2	2.34	1.52	-34.5	-4.03	< 0.001	-3.62	< 0.001	-0.710	0.478 (NS)
Median	2.0	1.0		2.0	2.0							
Mode	2	2		2	2							
Range	2 – 3	0 – 2	-100.0→0.0	2 – 3	0 – 3	-100.0→50.0						

Table 5. Total symptom score (TSS) before and after Rhinos® SR and placebo treatment

	Rhinos (n = 30)			Placebo (n = 29)			Rhinos		Placebo		Rhinos vs Placebo	
	Baseline	Follow-up	% reduction from baseline	Baseline	Follow-up	% reduction from baseline	paired t-test FU vs baseline		paired t-test FU vs baseline		t-test % reduction fr. baseline	
							t	p (2-tailed)	t	p (2-tailed)	t	p (2-tailed)
a. Patient evaluation (sum of the last 3 mornings)												
Mean	25.1	15.9	-31.2	28.4	19.4	-26.4	-4.96	< 0.001	-3.98	< 0.001	0.44	0.660 (NS)
SD	9.35	8.87	42.21	8.81	9.89	40.45						
Median	21.5	15.0		29.0	19.0							
Mode	18	18		29	28							
Range	7 – 43	2 – 38	-93.3→114.3	12 – 47	0 – 40	-100.0→60.0						
b) Patient evaluation (sum of the last 3 evenings)												
Mean	21.3	14.7	-19.6	26.4	17.7	-22.2	-3.60	0.001	-3.67	0.001	-0.17	0,867 (NS)
SD	8.58	8.29	56.80	9.38	9.94	60.23						
Median	21.0	15.0		27.0	18.0							
Mode	18	15		18	9							
Range	7 – 42	2 – 33	-92.0→145.5	6 – 43	0 – 39	-100.0→181.8						
c) Physician evaluation (at the morning visit)												
Mean	8.9	4.2	-52.7	9.8	5.6	-42.0	-8.19	< 0.001	-6.62	< 0.001	1.23	0.224 (NS)
SD	2.53	3.23	34.21	2.28	3.18	32.41						
Median	8.5	3.5	-51.7	10.0	5.0							
Mode	6	3	-100.0	10	3							
Range	6 – 15	0 – 12	-100.0→25.0	6 – 15	0 – 12	-100.0→42.9						

Evaluation by patient on the clinical efficacy rates of Rhinos® SR and placebo showed that Rhinos® SR and placebo were equally effective in producing the desired efficacy based on both TNSS and NCS. Rhinos® SR was marginally more effective than placebo in producing the success rate and the difference was not statistically significant (Table 6).

Evaluation by physician on the clinical efficacy rates of Rhinos® SR and placebo showed that Rhinos® SR tended to be more effective than placebo in producing desired efficacy based on TNSS, but the difference was not statistically significant (Table 7). The success rates based on TNSS and NCS were similar for both Rhinos® SR and placebo (Table 7).

Table 6. Clinical efficacy rates based on patient evaluation

	TNSS				NCS			
	Rhinos	Placebo	X^2	p	Rhinos	Placebo	X^2	p
Complete Relief (CR)	1	2			2	2		
Marked Relief (MaR)	4	3			3	3		
Moderate Relief (MoR)	14	9			10	7		
Slight Relief	4	5			8	6		
Treatm. Failure	7	10			7	11		
CR + MaR (Desired Efficacy)	5	5	0.003	0.95 (NS)	5	5	0.003	0.95 (NS)
CR + MaR + MoR (Success Rate)	19	14	1.356	0.24 (NS)	15	12	0.442	0.51 (NS)

NS = Not Significant

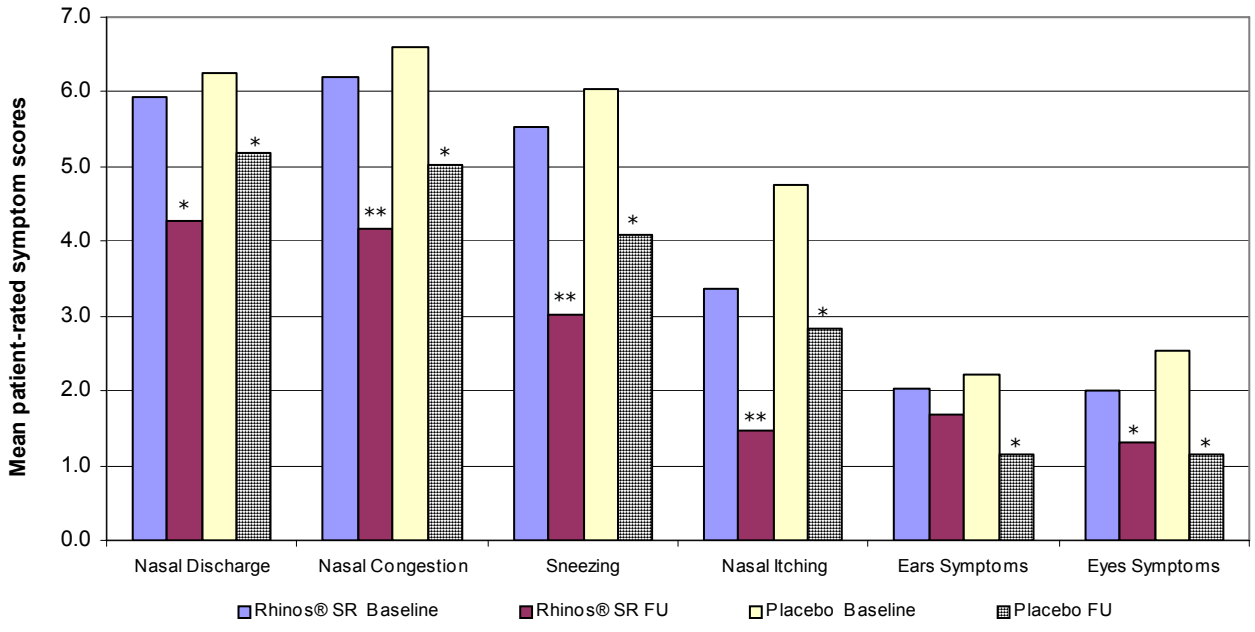
Table 7. Clinical efficacy rates based on physician evaluation

	TNSS				NCS			
	Rhinos	Placebo	X^2	p	Rhinos	Placebo	X^2	p
Complete Relief (CR)	5	2			5	4		
Marked Relief (MaR)	6	4			4	2		
Moderate Relief (MoR)	11	14			11	13		
Slight Relief	5	5			--	--		
Treatm. Failure	3	4			10	10		
CR + MaR (Desired Efficacy)	11	6	1.957	0.58 (NS)	9	6	0.750	0.69 (NS)
CR + MaR + MoR (Success Rate)	22	20	0.221	0.90 (NS)	20	19	0.009	0.93 (NS)

NS = Not Significant

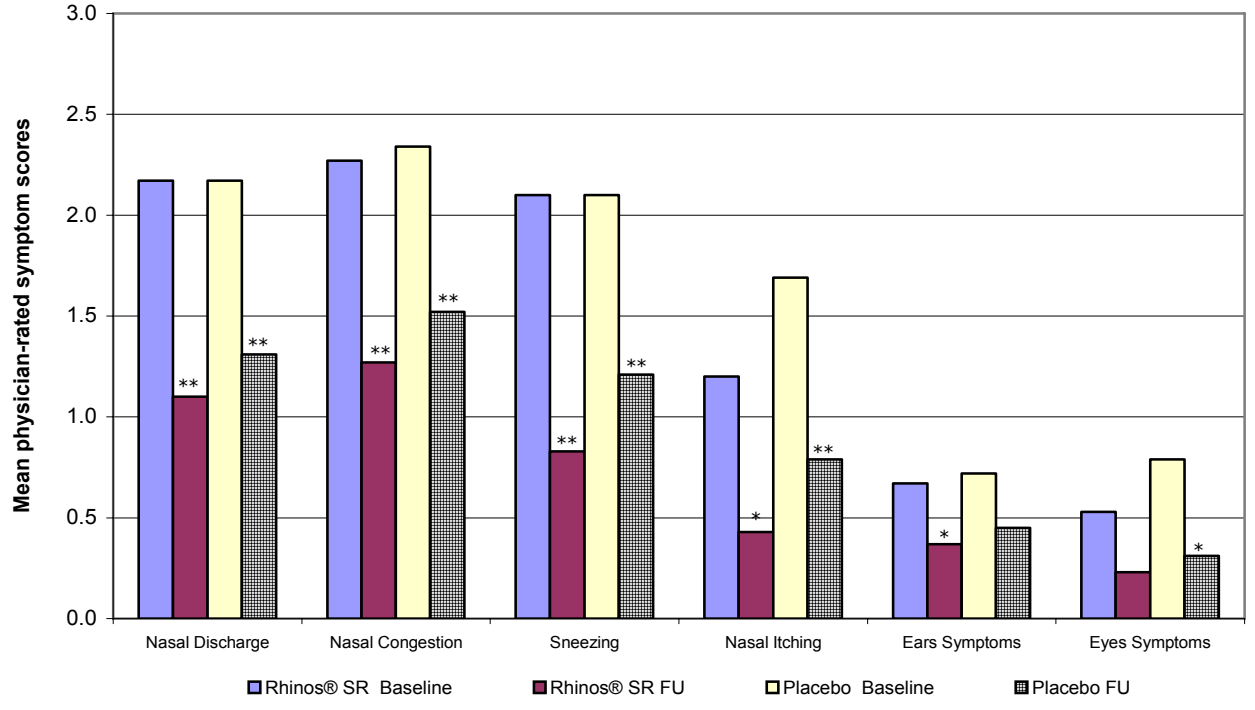
The improvement of the individual symptoms can be seen in Figures 3 and 4, as evaluated by the patient and by the physician, respectively.

Figure 5 shows the improvement of TNSS, NCS and TSS as evaluated by the patient in the morning and in the evening (sum of the last 3 days). The morning symptom scores were consistently higher than the evening scores.



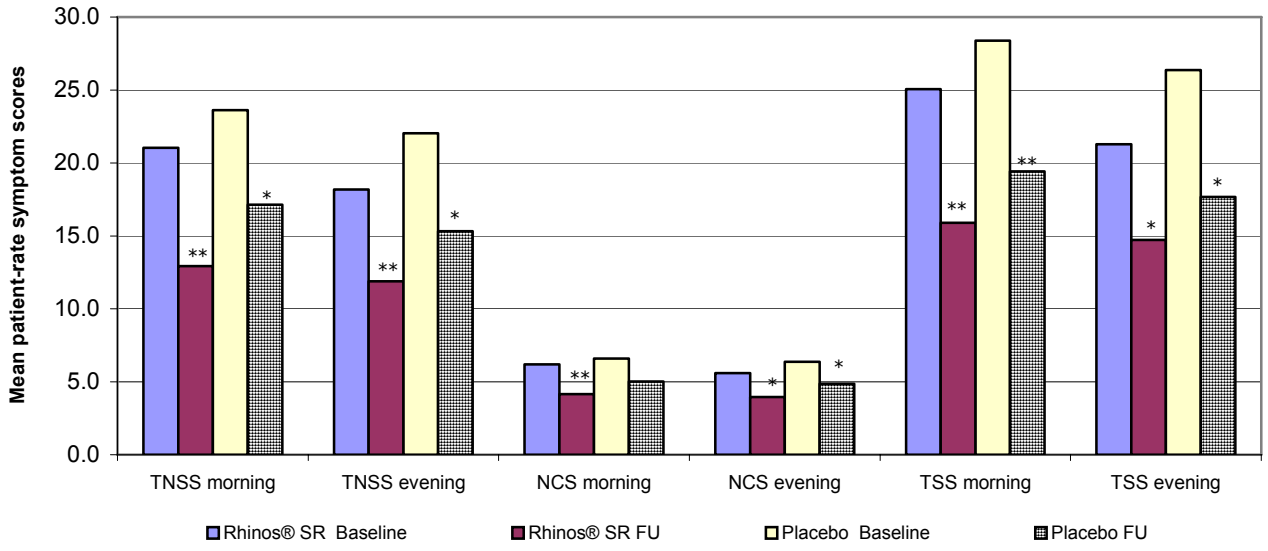
* $p < 0.05$ versus baseline ** $p < 0.001$ versus baseline

Figure 3. Patient-evaluated individual symptom scores for both Rhinos® SR and placebo at baseline and after 1-week treatment



* $p < 0.05$ versus baseline ** $p < 0.001$ versus baseline

Figure 4. Physician-evaluated individual symptom scores for both Rhinos® SR and placebo at baseline and after 1-week treatment



* $p < 0.05$ versus baseline ** $p < 0.001$ versus baseline

Figure 3. Morning and evening patient-evaluated symptoms for both Rhinos® SR and placebo at baseline and after 1-week treatment

Adverse events

No adverse event was encountered in the present study.

DISCUSSION

The results of the present study demonstrated the comparative efficacy of a twice-daily loratadine-pseudoephedrine fixed combination versus placebo on nasal airway resistance, nasal symptoms, and composite symptom scores (total nasal, total nasal and nonnasal) in patients with moderate to severe perennial allergic rhinitis in a tropical country.

This was the first study using rhinomanometer to measure the effects of loratadine-pseudo-ephedrine fixed combination on nasal airway resistance in comparison with placebo. In the present study, Rhinomanometer NR6 from GM Instruments was used. The total nasal airway resistance (NAR) was measured by active anterior rhinomanometry at 150 Pa pressure point. Validation in 23 Indonesian normal adult subjects resulted in mean (range) total NAR during inspiration of 0.287 (0.162-0.363) Pa/cm^3/sec and those during expiration of 0.303 (0.168-0.396) Pa/cm^3/sec. These values were somewhat higher than the values of normal adult Malays with a mean of 0.24 Pa/cm^3/sec (ranged from 0.12 to 0.52 Pa/cm^3/sec).[7]

Sixty PAR patients in the present study showed higher NAR values at baseline with mean (range) of 0.575 (0.333-1.789) during inspiration and of 0.585 (0.326-1.704) during expiration in 30 PAR patients in placebo group, and of 0.414 (0.314-0.699) during inspiration and of 0.443 (0.309-1.054) during expiration in 30 PAR patients in Rhinos® SR group. These data were in agreement with data from Malaysia that the total NAR values were significantly higher in patients with nasal disease than in normal subjects,[7] and also with data from London that the NAR values were higher during expiration than inspiration.[8]

Rhinomanometry is used to measure the nasal congestion which is relieved by pseudoephedrine, but not by loratadine. Therefore the effect of pseudo-ephedrine on NAR should be measured at its peak concentration, i.e. 1.4-2 hours for the immediate release, and 3.8-6.1 hours for the controlled release.[2] In other words, the effect of pseudoephedrine on NAR should be assessed by comparing the area under the NAR curve of Rhinos® SR from 0-2 hours and from 0-6 hours with those of placebo.

Comparing NAR $AUC_{0\text{-}10h}$ of Rhinos® SR versus placebo did not reach statistical significance (Table 2), while the NAR $AUC_{0\text{-}2h}$ of Rhinos® SR during inspiration and expiration were both significantly lower than

those of placebo (p = 0.039 and 0.012, respectively), and similarly the NAR AUC_{0-6h} values of Rhinos® SR were also significantly lower compared to the values of placebo (p = 0.046 and 0.020 during inspiration and expiration, respectively) (Tables 8 and 9). A previous study using rhinomanometry to measure the effect of pseudoephedrine immediate release on nasal congestion in patients with common cold showed that the NAR AUC_{0-3h} of pseudoephedrine was significantly lower compared to that of placebo.[10]

A similar study of pseudoephedrine with or without terfenadine using rhinometer to measure the effects on nasal airflow in acute rhinitis showed significant improvement of NAF compared to placebo at 1 and 2 hours after administration.[11]

Table 8. NAR AUC_{0-2h} after Rhinos® SR and placebo (baseline = 100%)

	During inspiration		During expiration	
	Rhinos® SR	Placebo	Rhinos® SR	Placebo
n	30	30	30	30
Mean	192.45	216.99	188.85	222.33
SD	29.20	55.84	35.51	60.54
Range	152.40-273.90	105.90-354.62	137.88-283.66	102.44-369.75
Unpaired t :				
t	2.133		2.613	
p (2-tailed)	0.039		0.012	

Table 9. NAR AUC_{0-6h} after Rhinos® SR and placebo (baseline = 100%)

	During inspiration		During expiration	
	Rhinos® SR	Placebo	Rhinos® SR	Placebo
n	30	30	30	30
Mean	576.32	644.00	560.78	668.16
SD	142.61	169.15	147.71	231.61
Range	419.98-1208.09	295.96-1066.98	393.16-1198.56	283.47-1553.44
Mann-Whitney U :				
Z	1.996		2.321	
p (2-tailed)	0.046		0.020	

The TNSS, NCS and TSS, and even the individual symptom scores, evaluated either by the patient or by the physician showed exactly the same pattern, i.e. both Rhinos® SR and placebo decreased the symptoms significantly, and the decreases by Rhinos® SR were larger than the decreases by placebo but the decreases by Rhinos® SR and placebo were not statistically different. Most probably these because of the sample size was too small, so that the study was not powered to detect the differences between the two treatment groups. Significant differences of those clinical parameters were shown in previous studies.[12-14]

CONCLUSIONS

The results of the present study showed that in patients with moderate to severe PAR, Rhinos® SR (a loratadine-pseudoephedrine fixed combination) was effective in relieving nasal congestion during the peak hours of pseudoephedrine, by objective measurements of the nasal airway resistance (NAR) using rhinomanometer. Rhinos® SR was also shown to be effective in reducing nasal symptoms, both the individual symptoms and the composite symptoms (total nasal, total nasal and nonnasal), although the reductions were not significantly different from placebo, but the trend was very clear. Rhinos® SR was also well tolerated.

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REFERENCES

1. Physicians' Desk Reference 2002. p. 3102-4.
2. Goodman & Gilman's the Pharmacological Basis of Therapeutics. 10th ed. New York : McGraw-Hill; 2001. p. 1999.
3. Naclerio RM. Allergic rhinitis. N Engl J Med 1991; 325 : 860-9.
4. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and management of rhinitis : complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy Immunol. 1998; 81: 478-518.
5. Harrison's Principles of Internal Medicine. 15th ed. New York : McGraw-Hill; 2001. p. 1921.
6. Data on file. Dexa Medica.
7. Suzina AH, Hamzah H, Samsudin AR. Active anterior rhinomanometry analysis in normal adult Malays. J Laryngol Otol. 2003; 117(8) : 605-8.
8. Suzina AH, Hamzah H, Samsudin AR. Objective assessment of nasal resistance in patients with nasal disease. J Laryngol Otol. 2003; 117(8) : 609-13.
9. Shelton DM, Eiser NM. Evaluation of active anterior and posterior rhinomanometry in normal subjects. Clin Otolaryngol Allied Sci. 1992; 17(2) : 178-82.
10. Eccles R, Jawad MSM, Jawad SSM, Angelo JT, Druce HM. Efficacy and safety of single and multiple doses of pseudoephedrine in the treatment of nasal congestion associated with common cold. Am J Rhinol 2005; 19(1) : 25-31.
11. Darmansjah I, Thamrin-Akib H, Indrawati A, Kurnia Y. Efektivitas sediaan kombinasi pseudoefedrin dan terfenadin untuk rinitis akut. Maj Farmakol Ter Indonesia. 1993; 10(1-4) : 14-8.
12. Bronsky E, Boggs P, Findlay S, Gawchik S, Georgitis J, Mansmann H, et al. Comparative efficacy and safety of a once-daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis. J Allergy Clin Immunol. 1994; 96(2) : 139-47.
13. Dockhorn RJ, Shellenberger MK, Hassanien R, Trachelman L. Efficacy of SCH 434 (loratadine plus pseudoephedrine) versus components and placebo in seasonal allergic rhinitis [Abstract]. J Allergy Clin Immunol. 1988; 81 : 178.
14. Storms WW, Bodman SF. Nathan RA, et al. SCH 434 : a new antihistamine/decongestant for seasonal allergic rhinitis. J Allergy Clin Immunol. 1989; 83: 1083-90.