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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00637819
		Study Code:	HWA486_6014
Generic drug name:	Leflunomide	**Date:**	27/Mar/2008

Title of the study:	Double blind, randomized, placebo controlled pilot study of leflunomide in systemic lupus erythematosus (SLE)
Investigator(s):	L-S Tam, E. K. Li, C-K Wong, C. W. K. Lam, C-C Szeto Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong
Study center(s):	Single Center, Hong Kong

Publications (reference):	1.Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, Gomor B, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology 2000;39:655-65. 2.Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med 1999;159:2542-50. 3.Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 1999;353:259-66. 4.Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis 2000;59:841-9. 5.Popovic S, Bartlett RR. The use of the murine chronic graft vs host (CGVH) disease, a model for systemic lupus erythematosus (SLE), for drug discovery. Agents Actions 1987;21:284-6. 6.Bartlett RR, Popovic S, Raiss RX. Development of autoimmunity in MRL/lpr mice and the effects of drugs on this murine disease. Scand J Rheumatol Suppl 1988;75:290-9. 7.Remer CF, Weisman MH, Wallace DJ. Benefits of leflunomide in systemic lupus erythematosus: a pilot observational study. Lupus 2001;10:480-3. 8.Petera P, Manger B, Rosenburg R, Smolen JS, JR K. A pilot study of leflunomide in systemic lupus erythematosus (SLE). Arthritis Rheum 2000;43:S241. 9.Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725. 10.Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630-40. 11.Gladman DD, Urowitz MB, Goldsmith CH, Fortin P, Ginzler E, Gordon C, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:809-13.		
Study period: Date first patient/subject enrolled: 01-Feb-2003 Date last patient/subject completed: 31-Jul-2004		**Phase of development:** II	
Objectives:	To evaluate the efficacy and safety of LEF to control mild to moderate disease activity in SLE **Primary objective:** the mean change of SLEDAI at 24 weeks. **Secondary objective:** changes in proteinuria complement levels, anti ds-DNA binding and prednisolone dosage.		
Methodology:	Randomized, placebo controlled		
Number of patients/subjects:	Planned: 40	Randomized: 12 6 on placebo, 6 on leflunomide	Treated: 12
Evaluated:		Safety: 12	

Diagnosis and criteria for inclusion:	All patients must 1) fulfill the revised ACR criteria for SLE, 2) with evidence of active disease according to SLE Disease Activity Index (SLEDAI) of =6, with the presence of at least one of the following features: arthralgia in more than 3 joints with tenderness or /and swelling for more than 1 week; active discoid or malar rash; pleuritis or pericarditis; cutaneous vasculitis; proteinuria <2 g/day with or without active urinary sediments, 3.) use of prednisolone < 0.5mg/kg/day, 4) use of safe contraceptive method. Hydroxychloroquine and non-steroidal anti-inflammatory drugs are allowed to continue in patients who have been taking these mediciations before entering the study. Excluded are patients who are currently on immunosuppressants such as cyclophosphamide, azathioprine or cyclosporin A, pregnant or nursing women, or those with life threatening disease requiring other immunosuppressants such as cyclophosphamide or azathioprine.	
Investigational product:	Leflunomide	
Dose:	100mg daily for 3 days followed by 20mg daily for the remainder of the study	
Administration:	Oral	
Duration of treatment: 6 months		**Duration of observation:** 6 months
Reference therapy:	Placebo	
Dose:	unknown	
Administration:	Oral	
Criteria for evaluation:		
Efficacy: Or Pharmacodynamics:	Primary outcome of this study include the number of patients who are able to achieve complete remission, defined as a SLEDAI of 0. Secondary outcomes included number of patients who are able to achieve partial remission, as defined by a SLEDAI of 1-3. Other secondary outcomes included reduction in proteinuria; change in complement levels and anti ds- DNA binding. Treatment failure is defined as premature termination of treatment due to exacerbation of SLE or adverse events as a result of treatment.	
Safety:	Adverse events reported by the patient/subject or noted by the investigator.	
Statistical methods:	ANCOVA will be used to evaluate variation in prednisolone dose, SLEDAI score and scores for SF-36. Mann-Whitney U test and chi-squared tests will be used for comparison between baseline demographic and clinical variables between the 2 groups where appropriate. All tests were two-tailed and a p-value of < 0.05 would be considered significant.	

Summary:	Leflunomide was more effective than placebo in treating SLE patients with mild to moderate disease activity, and was safe and well tolerated. The clinical benefit and safety profile warrants confirmation by larger scale, multi-centered, randomized controlled trial
Efficacy results: or Pharmacodynamic results:	The disease activity of both groups of patients decreased significantly after 6 months of treatment (14.7± 6.0 to 3.7± 2.3 in leflunomide group, p = 0.007 and 9.7± 3.4 to 5.2 ± 4.1 in placebo group, p = 0.005). However, the reduction in the SLEDAI from baseline to 24 weeks was significantly greater in the leflunomide group compared with the placebo group (11.0± 6.1 in the leflunomide group and 4.5± 2.4 in the placebo group respectively, p=0.036). The changes in proteinuria, complement 3 (C3) levels, anti ds- DNA binding and prednisolone dosage were similar between the 2 groups.
Safety results:	Minor adverse events were reported in the majority of patients. One patient received leflunomide had elevated ALT > 5 x baseline requiring premature termination of study. She was also taking traditional Chinese herbal medications of unknown nature. The ALT level returned to normal 2 months after stopping both leflunomide and TCM. One patient in each group had transient elevation in ALT > 2x baseline which resolved on repeat testing. Two patients in the leflunomide treated group developed hypertension requiring antihypertensive compared to 1 patient in the placebo group. Leucopenia (WCC < 3x 109/l) observed was transient and did not require adjustment of study drug dosage (1 in leflunomide group and 2 in placebo group). No patients reported diarrhea. There was no significant change in the body weight, blood pressure, serum creatinine, albumin, complete blood count and CRP in both groups.
Date of report:	19 Mar-2008