Thalidomide for Severe Refractory Ankylosing Spondylitis: A 6-Month Open-Label Trial

JAMES CHENG-CHUNG WEI, TSAI WEN CHAN, HUEY-SHYAN LIN, FENG HUANG, and CHAN-TE CHOU

ABSTRACT. ***Objective.*** To examine the efficacy of thalidomide in the treatment of active ankylosing spondylitis (AS) refractory to conventional therapies.

Methods. In a 6-month open-label trial, we studied 13 men with different subtypes of active AS: 3 juvenile AS, 9 adult AS, and one AS with psoriasis. All patients were resistant to conventional nonbiologic therapies including nonsteroidal antiinflammatory drugs, sulfasalazine, and methotrexate. After 3 months' observation on a preexisting regimen, oral thalidomide was added, starting at 100 mg/day for 1 week, then 200 mg/day for another 23 weeks. Outcome measures included the Bath AS Disease Activity Index (BASDAI), Functional Index (BASFI), Global Index (BAS-G), IgA, C-reactive protein (CRP), and eosinophil sedimentation rate (ESR). Response to treatment was defined following the Ankylosing Spondylitis Assessment criteria.

Results. Three patients withdrew due to rash. Two patients were lost to followup due to lack of efficacy. Eight patients completed the trial. Four patients attained > 50% improvement (2 juvenile AS, 1 peripheral AS, and 1 psoriatic arthritis). Four patients attained > 20% improvement (2 axial and 2 peripheral AS). Total response rate accordingly was 80% (8/10). Mean BASDAI improved significantly from baseline to Week 24 (4.97 vs 3.1; p = 0.0156). Mean BASFI improved from baseline to Week 24 (5.24 vs 3.06; p = 0.0078), and BAS-G from 6.02 to 3.21 (p = 0.0078). Significant laboratory improvements were found in ESR (from 69.5 to 34.2 mm/h; p = 0.0156), but not CRP (from 6.08 to 3.01 mg/dl; p = 0.078) or IgA (from 496 to 505 mg/dl; p = 0.375). Dry mouth, constipation, and dizziness were common, but no severe adverse events were found.

Conclusion. Thalidomide is a promising treatment for patients with active AS who are resistant to conventional therapies other than biologics. (J Rheumatol 2003;30:2627–31)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS THALIDOMIDE TUMOR NECROSIS FACTOR
DISEASE MODIFYING ANTIRHEUMATIC DRUG

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by sacroiliitis, spondylitis, enthesitis, and occasionally, peripheral arthritis. Until the advent of biologics, therapies for AS were somewhat unsatisfactory[1]. Nonsteroidal antiinflammatory drugs (NSAID), as well as the COX-2 inhibitors, are the major therapy for most patients with AS[2]. Sulfasalazine, a disease modifying antirheumatic drug (DMARD), may benefit AS patients with peripheral arthritis[3], uveitis[4], inflammatory bowel diseases, or psoriasis[5]. The effect of sulfasalazine on axial AS is still controversial. Methotrexate had shown effect on peripheral but not axial AS[6]. Intravenous pamidronate[7], a biphosphate, proved to improve both axial and peripheral AS but is quite expensive. Recently, anti-tumor necrosis factor-α (TNF-α) therapies, such as infliximab[8] and etanercept[9], have shown dramatic results for patients with refractory AS. But these biological modifying agents are expensive and not available in many countries so far.

Thalidomide is a drug that can inhibit TNF-α, presumably by enhancing degradation of messenger RNA[10], and interleukin (IL)-12 production[11]. Clinical efficacy of this drug has been reported in erythema nodosum leprosy[12], rheumatoid arthritis[13], Crohn's disease[14], toxic epidermal necrolysis[15], chronic graft-versus-host disease[16], Behçet's syndrome[17], aphthous stomatitis[18], severe orogenital ulceration[19], HIV-associated wasting syndrome[20], discoid lupus erythematosus[21], and some malignancies like multiple myeloma[22]. Recently, thalidomide was found to be beneficial for refractory AS[23,24]. No double blind study has yet been reported.

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We tested 13 patients with active treatment-refractory AS with thalidomide for 6 months.

MATERIALS AND METHODS

Patient selection. Thirteen men with different subtypes of active AS who fulfilled the modified New York criteria[25] were enrolled. All patients had active severe disease and were resistant to conventional therapies like NSAID, sulfasalazine, methotrexate, and steroid. Written informed consent and an agreement to use contraceptive measures during the period of study were obtained from each patient. The study was approved by the Human Protection Committee of the Institute.

Treatment protocol. After fixed-dose background NSAID and DMARD treatment for at least 3 months, thalidomide (TTY Biopharm, Taiwan) was added, starting from 100 mg/day orally for 1 week and then 100 mg, twice daily for another 23 weeks. In patients who felt severe daytime drowsiness during the twice-daily regimen, 200 mg thalidomide was taken once before bedtime. During the trial period, no changes of DMARD or steroid were allowed but NSAID were used as necessary.

Outcome measurement. Primary outcome measurements included clinical assessments by the Bath AS Disease Activity Index (BASDAI)[26], Functional Index (BASFI)[27], and patient global assessment. Secondary outcome measures included serum IgA, C-reactive protein (CRP), and eosinophil sedimentation rate (ESR). Both primary and secondary measures as well as safety profiles were recorded at baseline and Weeks 2, 4, 8, 12, 16, 20, and 24. Response to treatment was defined following the Ankylosing Spondylitis Assessment (ASAS) criteria[28] as > 20% improvement of more than 3 of 4 domains (patient global assessment, pain, morning stiffness, function) after treatment. Forty percent improvement of the ASAS criteria was calculated to determine the immunomodulatory effect. Safety profile questionnaires for possible side effects were obtained at every visit. Nerve conduction velocity studies were performed for patients with suspicious neuropathy. Complete blood count, serum creatinine, and liver function was checked every 4 weeks during study.

Statistical analysis. The degrees of statistical significance between values were analyzed by the paired Wilcoxon signed-rank test. Comparisons of number of individuals reaching a certain degree of improvement were calculated by chi-square test. P values were regarded as significant if they were < 0.05.

RESULTS

Patient demographics. All 13 patients were male and HLA-B27 positive: 3 juvenile AS with peripheral arthritis and Achilles enthesitis, 5 axial type with or without hip involvement, 4 AS with peripheral arthritis other than hips, and 1 AS with psoriasis. The mean age was 37 years (range 19–54) and mean disease duration 13.8 years (range 7–25) (Table 1).

Response to treatment. Three patients withdrew due to intolerable side effects. Two experienced severe drug eruptions of multiple itching erythema over trunk and extremities after 2 weeks of thalidomide therapy. The skin eruptions disappeared gradually after 2 weeks' oral antihistamine and discontinuation of thalidomide. One patient withdrew 1 week later due to severe dizziness and drowsiness. The discomfort disappeared after discontinuing thalidomide for 3 days. Two patients were lost to followup due to lack of efficacy after 8 weeks' treatment. The other 8 patients completed the 6 month trial. Of these 8, 4 (2 juvenile AS, 1 peripheral AS, and 1 psoriatic arthritis) experienced > 40% improvement of ASAS criteria. Another 4 (2 axial and 2 peripheral AS) patients got > 20% but < 40% improvement. Total response rate according to ASAS-20 was 80% (8/10) among enrolled patientss and ASAS-40 was 40% (4/10) (Table 2). The effect of thalidomide could be seen at Week 8 by BASDAI (5.39 ± 2.33 to 3.78 ± 1.67; p = 0.007) and ESR (70.03 ± 21.16 to 39.34 ± 11.42; p = 0.014) and was progressive until Week 24. The mean BASDAI improved significantly from baseline (4.97 ± 2.33) to Week 24 (3.1 ± 2.08; p = 0.0156). Mean BASFI improved from baseline (5.24 ± 2.6) to Week 24 (3.06 ± 2.14; p = 0.0078), and BAS-G from 6.02 ± 2.75 to 3.21 ± 2.01 (p = 0.0078) (Figure 1). ESR improved significantly (from 69.5 ± 21.2 to 34.2 ± 28 mm/h; p = 0.0156), but not CRP (from 6.08 ± 4.97 to 3.01 ± 3.55 mg/dl; p = 0.078) or IgA (from 496 ± 230 to 505 ± 323 mg/dl; p = 0.375) (Figure 2).

Adverse events. Minor side effects were common in the first 4 weeks but did not require stopping the drug. Dry mouth (7/8), constipation (7/8), and dizziness (6/8) were the most common side effects but all were tolerated after lifestyle modification and medication. Thalidomide improved sleep quality if taken before bedtime but sometimes patients complained of drowsiness (3/8) during the daytime. Two patients experienced severe drowsiness under the twice-daily regimen, then improved after changing to once before bedtime. In one patient who complained of mild numbness of the hands, nerve conduction velocity and electromyographic studies were normal, and the numbness subsided 2 weeks later. Neither neuropathy nor other severe adverse events were noted.

DISCUSSION

Thalidomide, with its immunomodulatory and anti-angiogenesis functions, is now being used for autoimmune diseases and malignancy[29]. Only 2 uncontrolled studies of

Table 1. Demographics of patients (n = 13).

Age, yrs, mean (range)	37 (19–54)
Disease duration, yrs, median (range)	13.8 (7–25)
Disease manifestations	
Juvenile onset (< 16 yrs) AS with peripheral arthritis	3
Axial type, including hip and shoulder involvement	5
Peripheral type (knees, ankles, and feet)	4
AS with psoriasis with knees, ankles, metatarsophalangeal arthritis	1

Table 2. Results.

Total n	13
Withdrew due to side effects	3
Dropout at 8 weeks due to no response	2
Completing 6 months' trial	8
ASAS 20% response criteria	8
Response rate among completers (%)	8/8 (100)
Response rate among enrollers (%)	8/10 (80)

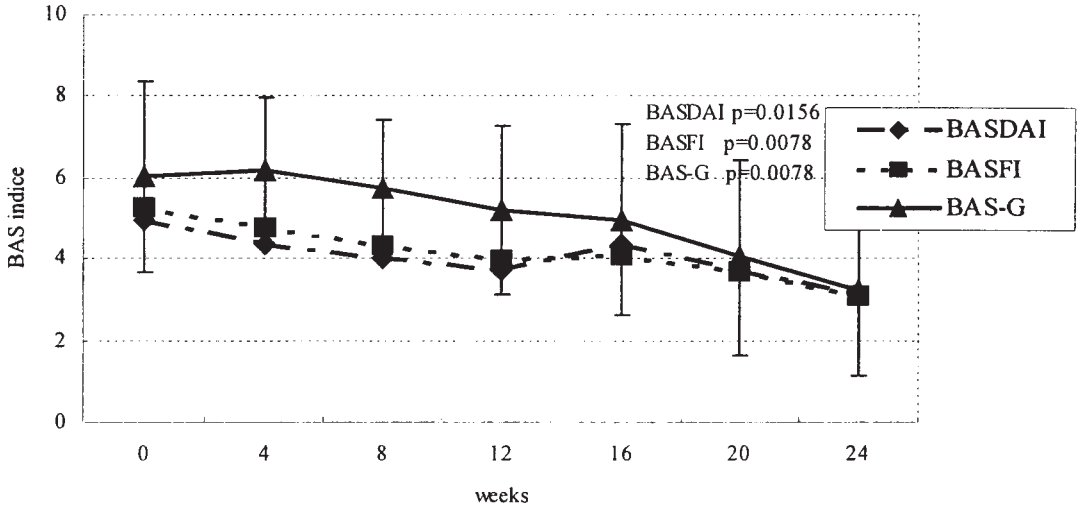

Figure 1. Mean primary outcome measures in the 8 patients completing the study. Mean BASDAI from baseline 4.97 ± 2.33 to 3.1 ± 2.08 (p = 0.0156), BASFI from 5.24 ± 2.6 to 3.06 ± 2.14 (p = 0.0078), and BAS-G from 6.02 ± 2.75 to 3.21 ± 2.01 (p = 0.0078) all decreased significantly after 24 weeks' thalidomide treatment.

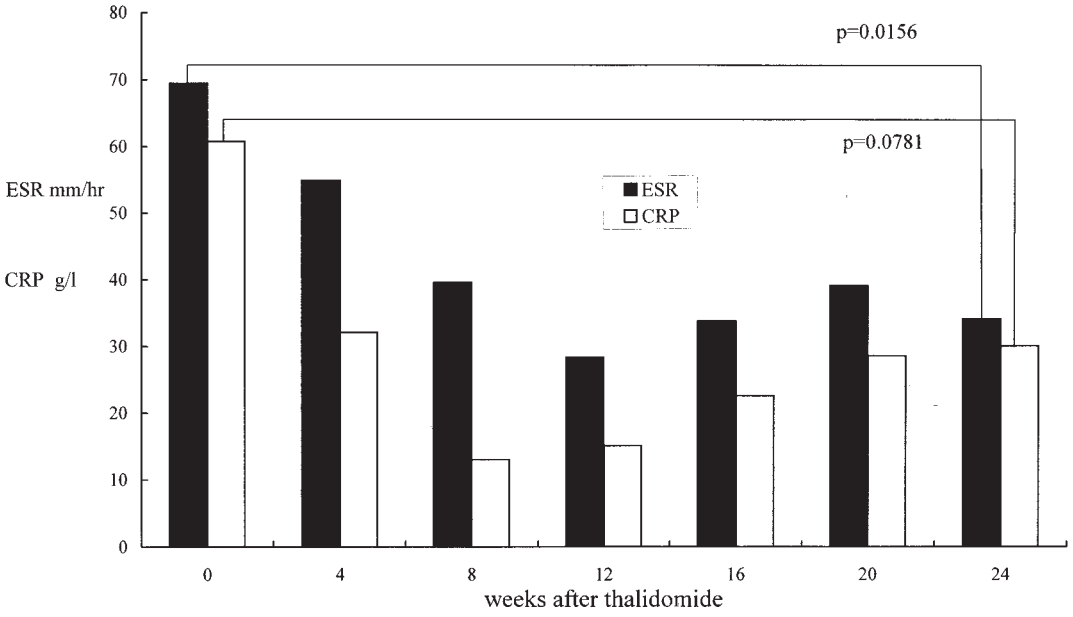

Figure 2. Mean secondary outcome measures in the 8 patients completing the study. ESR decreased from 69.5 ± 21.2 to 34.2 ± 28 mm/h (p = 0.0156).

thalidomide in spondyloarthropathies (SpA) have been reported. Breban, *et al*[23] first described 2 patients with treatment-resistant AS who eventually got dramatic improvement after thalidomide treatment. Since this initial description, a total of 12 patients with SpA have been treated in a 6 month open trial[24]. Evidence of clinical efficacy was found in 7 of 12 patients. Five stopped thalidomide before 6 months because of side effects. In a recent 1-year open trial, Huang, *et al*[25] found 70% of patients with refractory AS showed > 20% improvement in 4 of 7 primary indices after thalidomide at a dosage of 200 mg/day.

Unlike the direct effect of specific TNF-α antagonists, thalidomide seems to act slower and the extent of overall improvement is less. In our study, most patients showed improvement within 2 to 3 months, but for some, there may be a delay in the onset of improvement for up to 6 months

of treatment. The benefit may be dramatic. Most patients tolerated the thalidomide well after 2 months of treatment despite common minor side effects.

The mechanism of action of thalidomide is still unclear. Increased m-RNA degradation of TNF-α and other proinflammatory cytokines like IL-12 and interferon-γ are the major effects[31]. Thalidomide can also inhibit leukocyte chemotaxis into the site of inflammation, reduce phagocytosis by polymorphonuclear leukocytes, and enhance mononuclear cell production of IL-4 and IL-5[32]. Anti-angiogenesis might be another important function of thalidomide, explaining its effect on malignancy and proliferative inflammatory diseases[32]. In Huang's study, microarray with 588-gene and reverse transcriptase polymerase chain reaction showed significantly decreased expression after thalidomide treatment in 7 genes: TNFα, IL-1ß, M1P-1α, M1P-2α, c-jun, OX40 ligand, and the T lymphocyte maturation-associated protein MAL.

In comparison with Huang, our study has similar efficacy and safety profiles. The differences are that we enrolled only patients with very active AS who were resistant to all NSAID and DMARD therapies. Thalidomide was added into a stable background without change of DMARD. The responder rate according to ASAS criteria appears encouraging in these refractory patients. Specific TNF-α antagonists are not available or affordable in most Asian countries, although etanercept has been approved in Taiwan and Hong Kong. In these countries, thalidomide is a viable alternative. Most importantly, users should consider the teratogenetic potential of thalidomide and should follow the guidance of the manufacturer's controlled distribution system[33]. Adequate contraceptive measures must be taken during treatment.

In this 6-month open trial, we observed that thalidomide is very effective for both axial and peripheral types of active AS in patients resistant to conventional therapies.

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