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ORIGINAL ARTICLE

Effectiveness and safety of adalimumab in treating moderate to severe psoriasis patients with psoriatic arthritis in Taiwan

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ABSTRACT

Background/Objective: The incidence of psoriasis vulgaris in Asians is estimated at 0.05–0.30%. Studies in North America and Europe demonstrated that adalimumab, a fully human monoclonal IgG1 antibody, is an efficacious treatment for psoriatic arthritis and chronic plaque psoriasis. The aim of this study was to evaluate the efficacy and safety of adalimumab in treating psoriatic arthritis (PsA) in patients who have moderate to severe psoriasis.

Methods: This was a retrospective study comprising 12 patients with chronic plaque psoriasis and psoriatic arthritis who were treated with adalimumab between October 2008 and February 2013. All had failed treatment with conventional systemic agents. Patients were started on adalimumab 40 mg every other week.

Results: At week 12, 3 of 12 patients (25%) achieved a 75% improvement in their Psoriasis Area and Severity Index (PASI 75). With regard to PsA, at week 12, the improved Psoriatic Arthritis Response Criteria (PsARC) response was experienced by 75% (9 of 12) of the patients. Mean improvement in Dermatology Life Quality Index (DLQI) was 42%. Five of 12 patients (42%) experienced adverse events, which were generally mild.

Conclusion: Patients with refractory psoriatic arthritis appeared to be responsive to adalimumab. The achievement rate of PsARC in our study was comparable to the efficacy reported in previous literature. Detection of antinuclear antibodies was not associated with the responsiveness in this trial, nor did it influence the potential for adverse effects. Adalimumab as a monotherapy is generally effective and safe.

Introduction

Psoriasis is a common, chronic, immune-mediated disorder of the skin that affects 2–3% of the population worldwide.[1,2] In Asians, the incidence of psoriasis vulgaris is estimated at 0.05–0.3%.[3,4] Patients present with a broad range of clinical manifestations with symptoms that vary in severity. The most common form of psoriasis is plaque-type psoriasis, seen in up to 80% of patients and characterized by patches of raised, red lesions covered by silver-white scales. Patients with psoriasis report a reduction in physical and mental functioning, resulting in a severely impaired quality of life, comparable with that seen in patients with cancer, arthritis, hypertension, heart disease, diabetes, and depression.[1,2]

Long-term use of common disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), cyclosporine, and retinoids, is limited by potential adverse effects and cumulative organ toxicities.[5,6] Adalimumab has been investigated for the treatment of moderate to severe chronic plaque psoriasis based on recent findings implicating T lymphocytes and tumor necrosis factor (TNF) in the pathogenesis of plaque psoriasis.[7,8] Adalimumab is a recombinant, fully human, anti-TNF-α monoclonal immunoglobulin G1 antibody, which binds both soluble and cell-bound forms of TNF-α with high affinity and specificity. Adalimumab neutralizes TNF-α activity by directly blocking its interaction with p55 and p75 cell surface TNF-α receptors as well as by modulating biological responses that are induced or regulated by TNF-α.[5,9,10]

Previous studies of adalimumab in the treatment of psoriasis have been performed on patients, with moderate to severe psoriasis, who were selected under strict inclusion and exclusion

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criteria. In this study, we assessed the efficacy and safety of using adalimumab to treat psoriatic arthritis (PsA) in patients who have moderate to severe psoriasis.

Methods

This was a retrospective study of all patients with chronic plaque psoriasis and PsA who were treated with adalimumab between October 2008 and February 2013 in the Department of Dermatology, Chang Gung Memorial Hospital, Tao-Yuan, Taiwan. All of them underwent screening in order to exclude active or latent infections prior to adalimumab treatment. Information on demographics and psoriasis history, including age, sex, duration, and family history of psoriasis, presence of PsA, previous treatments, and Psoriasis Area and Severity Index (PASI), was recorded.

Patients were started on adalimumab when they failed to respond or stopped responding to at least one other systemic treatment for psoriasis. Because of the severity of the patients' disease, there was no washout time after treatment with previous systemic agents. According to the guidelines for the treatment of PsA with adalimumab, a dose of 40 mg was self-administered subcutaneously every other week, at Week 0, Week 2, Week 4, Week 6, Week 8, and Week 10.[10]

Efficacy was evaluated in all patients at baseline (Week 0) and at Week 2, Week 4, Week 8, and Week 12. Psoriasis disease activity was measured by calculating the PASI score. The PsA response achievement rate was defined, in accordance with the Psoriatic Arthritis Response Criteria (PsARC),[11] as the percentage of patients who showed improvement in two or more of the following ways: (1) $\geq$ 30% decrease in the number of swollen joints counted; (2) $\geq$ 30% decrease in tender joints counted; (3) improvement in patient's global assessment of disease activity; or (4) improvement in physician's global assessment of disease activity. To qualify as an improved response, the patient must not have shown analogously defined worsening in any of these ways and must have shown improvement on at least one joint count. In addition to the response achievement rate, the Dermatology Life Quality Index (DLQI), a self-administered questionnaire, was evaluated in all patients to assess the effect of the skin disease on their daily activities.[12]

In total, 12 patients were included in the study [6 men (50%), 6 women (50%), mean age 41.7 years, range 25–59 years]. All of them completed the 12-week treatment. The mean baseline PASI score was 24.6, [standard deviation (SD) 11.7], and the initial PASI score of each patient was > 10. Five patients (42%) had a family history of psoriasis. With regard to PsA, the overall population of treated patients had baseline scores of 11 (SD 14) for swollen joint count, 18 (SD 11) for tender joint count, and 16.5 (SD 7.43) for DLQI. All patients had more than three joints involved at the outset of adalimumab treatment (Table 1). These values are consistent with long-standing moderate to severe psoriasis and PsA.

Safety assessments were conducted throughout the study. Adverse events were assessed at Week 0, Week 2, Week 4, Week 8, and Week 12 during each visit. Laboratory evaluations, including measurement of erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) levels, and antinuclear antibody (ANA) levels were also recorded.

Results

Previous treatment

Of the 12 patients, four (33%) had been treated with MTX, five (42%) with cyclosporine, 7 (58%) with acitretin, one (8%) with penicillamine, six (50%) with nonsteroidal anti-inflammatory drugs, four (33%) with leflunomide, and one (8%) with prednisolone. One patient (8.3%) received subcutaneous etanercept prior to starting adalimumab treatment. The mean number of previous systemic treatments was 1.6 (range 0–4; Table 1).

Efficacy

At Week 12, 10 of 12 patients (83%) had achieved an improvement rate of at least 25% on the PASI score (PASI 25), seven patients (58%)

Table 1 Patient characteristics and baseline assessments.

	Age (y)	Sex	PASI score	DLQI	Family history	Psoriatic arthritis			ESR, mm/h	CRP, mg/L	Previous systemic medication	Psoriasis activity during the trial
						Swelling/76	Pain/78	Duration/y				
A	29	F	23.2	25	Yes	3	5	1	67	9	Cyclosporin (100–200 mg QD)	Initial aggravation
B	50	M	21.5	23	Yes	5	19	1	14	8	Acitretin (30 mg QOD)	Initial aggravation
C	56	M	42.9	20	Yes	8	11	18	64	49	Acitretin (25 mg QD) MTX (15 mg QW)	Gradual improvement
D	27	M	51.6	11	Yes	1	2	2	8	21	Acitretin (35 mg QD) Etanercept	Gradual improvement
E	47	M	18.3	15	No	10	18	3	124	189.89	Acitretin (25 mg QD) Cyclosporin (100 mg QD) Leflunomide (200 mg BID) Prednisolone (5 mg BID)	Progression
F	53	F	14.4	15	No	0	24	5	15	< 3.16	MTX (7.5 mg QD)	Gradual improvement
G	40	F	14.8	1	No	6	35	10	36	5.01	MTX (10 mg QW) Leflunomide (200 mg QD)	Gradual improvement
H	37	F	28	27	No	5	29	13	52	56	Penicillamine (300 mg BID) Cyclosporin (200 mg QD)	Initial aggravation
I	54	F	12.2	8	No	0	2	10	12	< 3.16	Acitretin (25 mg QD) MTX (7.5 mg QD)	Gradual improvement
J	37	M	21.8	21	No	20	22	20	1	< 3.16	Cyclosporine (100 mg BID) Acitretin (35 mg QD)	Initial aggravation
K	45	F	20.6	17	No	51	31	10	64	21	Acitretin (10 mg BID)	Gradual improvement
L	25	M	25.5	15	No	18	19	11	2	< 3.17	MTX (7.5 QW) Leflunomide (200 mg QD)	Gradual improvement
Mean ± SD	41.7 10.84		24.6 11.70	16.5 7.43		10.6 14.21	18.1 11.13	8.7 6.41	38.3 37.10	30.6 51.88		

BID = twice a day; CRP = C-reactive protein; DLQI = Dermatology Life Quality Index; ESR = erythrocyte sedimentation rate; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; QD = every day; QOD = every other day; QW = once a week; SD = standard deviation.

Table 2 Improvement of psoriasis activity as assessed by Psoriasis Area and Severity Index and Dermatology Life Quality Index.

	PASI score			DLQI		
	Week 0	Week 12	Improvement, %	Week 0	Week 12	Improvement, %
A	23.2	15.4	34	25	12	52
B	21.5	17.9	17	23	12	48
C	42.9	30.1	30	20	19	5
D	51.6	15.3	70	11	2	82
E	18.3	32.4	−77	15	13	13
F	14.4	2.8	80	15	3	80
G	14.8	3.8	74	1	1	0
H	28	19	32	27	16	41
I	12.2	1.6	87	8	4	50
J	21.8	8.1	63	21	10	50
K	20.6	7.6	63	17	8	53
L	25.5	1.6	94	15	10	33
Mean ± SD	24.6	13.0		16.5	9.2	
	11.70	10.62		7.43	5.72	

DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; SD = standard deviation.

achieved an improvement rate of at least 50% (PASI 50), and three patients (25%) achieved PASI 75. Among those whose PASI score had improved at Week 12, there were four patients (33%) patients with initial aggravation, seven patients (58%) with gradual improvement, and one patient (8%) with persistent progression of symptoms after beginning treatment with adalimumab (Table 1). The mean PASI score improved from 24.6 to 13.0, corresponding to a 47 % rate of improvement (Table 2). Moreover, three patients (25%) received additional systemic agents during the study: one received MTX, one received cyclosporine, and one received narrowband ultraviolet radiation b (UVB) phototherapy combined with MTX.

With regard to PsA, at Week 12, the improved PsARC response was experienced by 75% (9 of 12) of the patients. The mean reduction in count was 9 (from −49 to 18) for tender joints, and of 7 (from −7 to 48) for swollen joints, respectively (Table 3). Furthermore, therapy with adalimumab considerably improved patients' quality of life as assessed by DLQI, with average improvement from 16.5 to 9.2 at Week 12 (Table 2).

Safety

In our patients, adalimumab was generally well tolerated. No malignancy or infection serious enough to require hospitalization was reported. Seven patients did not have any side effects during the 12-week treatment course. Three patients reported blurred vision, two patients suffered from dizziness and malaise, and three patients experienced increased itchiness. One case each of upper respiratory tract infection, tinnitus, folliculitis, and urticaria was reported in four separate patients (Table 4). None of these nonspecific adverse events led to interruption of the adalimumab treatment.

All laboratory abnormalities were mild and none warranted discontinuation of therapy. Mean ESR was 38.3 (SD 37.10) initially and dropped to 21.5 (SD 29.22) at Week 12; mean CRP decreased from 30.6 (SD 51.88) to 11.4 (SD 29.67). At baseline, ANA was undetectable in 11 patients, and two of these patients were found to have weakly positive titer (1:40) at Week 12. Only one patient had elevated titer (1:640) initially; the ANA titer of this patient remained the same at Week 12.

Discussion

Adalimumab has been mainly investigated for the treatment of moderate to severe psoriasis. Our study demonstrated that patients who had chronic plaque psoriasis were responsive to adalimumab. Furthermore, the observed improvement in DLQI, as well as in the rate of PsARC responders, indicated that patients with PsA recalcitrant to previous systemic treatment were also responsive to adalimumab. No serious side effects leading to hospitalization or cessation of treatment occurred. The presence of ANA did not affect the resultant decrease in psoriasis disease activity.

Previous studies have shown that an initial loading dose of 80 mg followed by 40 mg every other week (eow) resulted in marked improvement of PASI scores.[13–15] In the ADalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), the double-blind, randomized, placebo-controlled study conducted by Mease et al,[16] also showed 49% achievement of PASI 75 at Week 12. In another open-label study

Table 3 Psoriatic arthritis response criteria measurements.

	Pain		Swelling		Improvement (%)		PGA (%)	PsARC
	Week 0	Week 12	Week 0	Week 12	Pain	Swelling		
A	5	3	3	0	40	100	30	+
B	19	3	5	1	84	80	70	+
C	11	4	8	1	64	88	30	+
D	2	1	1	0	50	100	90	+
E	18	11	10	3	40	70	50	
F	24	73	0	0	−204	No change	0	−
G	35	21	6	3	40	50	40	+
H	29	11	5	6	62	−20	80	−
I	2	0	0	7	100	−100	70	−
J	22	11	7	7	50	36	80	+
K	31	17	51	3	45	82	80	+
L	19	9	18	3	53	83	50	+

PGA = Patient Global Assessment; PsARC = Psoriatic Arthritis Response Criteria.

Table 4 Adverse effects during the study.

Event	$N = 12$, n (%)
Without adverse events	7 (58.3)
Total adverse events	0
Serious infections	0
Adverse events leading to discontinuation	0
Adverse events	
Blurred vision	3 (25.0)
URI symptom	1 (8.3)
Dizziness/malaise	2 (16,7)
Tinnitus	1 (8.3)
More pruritus	3 (25)
Urticaria	1 (8.3)
Folliculitis	1 (8.3)
Laboratory test	
ALT > 3 times the ULN	0

ALT = alanine aminotransferase; ULN = upper limit of normal; URI = upper respiratory tract infection.

Table 5 Efficacy result at Week 12 compared to previous studies.

	Study design	Treatment protocol	Baseline mean PASI	PASI 75 achievement, %	PsARC achievement, %
Our study	Retrospective	40 mg eow	41.7	25	75
ADEPT[16]	24-wk, randomized double-blind, placebo-controlled	40 mg eow	7.4	49	62
ACCLAIM[19]	12-wk, open-label, uncontrolled	40 mg eow	11.7	47.1	70.1
STEREO[18]	12-wk, open-label, uncontrolled	40 mg eow	None[a]	None[a]	78
Papoutsaki et al[17]	24-wk, open-label, uncontrolled	40 mg QW	19.2	87	None[a]
Gordon et al[23]	12-wk, randomized, double-blind, placebo-controlled	80 mg loading, then 40 mg eow	16.7	53	None[a]
		80 mg loading, then 40 mg QW	14.5	80	None[a]

eow = every other week; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; QW = once a week; ADEPT = adalimumab effectiveness in psoriatic arthritis trial; STEREO = safety and efficacy of adalimumab in patients with active psoriatic arthritis—an open-label, multinational study to evaluate the response to every-other-week adalimumab when added to insufficient standard therapy including patients who failed prior treatment with other TNF inhibitors; ACCLAIM = a Canadian open-label study to evaluate the safety and effectiveness of adalimumab when added to inadequate therapy for the treatment of psoriatic arthritis.

[a] Measurements were not assessed in the study.

with a regimen of 40 mg every week, PASI 75 at Week 16 was achieved in 87% of 30 patients.[17] An open-label retrospective study in Taiwan found that three of 13 patients (23%) had at least PASI 75 at Week 12 after receiving adalimumab 40 mg eow with a loading dose of 80 mg.[15] In our study, 25% of the patients with a higher baseline PASI score demonstrated PASI 75 achievement at Week 12. The adalimumab dosage regimen used in our study to treat PsA, 40 mg eow without an initial loading dose, was a lower dosage compared to previous studies (Table 5).[16–19,23] Asahina et al[14] compared the efficacy of different adalimumab dosage regimens in their randomized, placebo-controlled study. Among the three treatment groups, composed of patients who received 40 mg eow, 80 mg eow, or 40 mg eow following an 80-mg loading dose, the most rapid response rate was found in patients receiving 40 mg eow plus the loading dose. PASI 75 achievement was highest in the group receiving 80 mg eow (81.0%).[14] The reason the efficacy obtained in our study regarding plaque type psoriasis was lower than that obtained in clinical trials might be due to the lower dosage.

Despite this finding, our study demonstrated an efficacy in treating PsA comparable to that of previous studies mainly conducted in Europe and North America.[16–19] At Week 12, PsARC response achievement was 75%, which was very similar to that reported in an open-label, uncontrolled trial of adalimumab in patients with PsA with moderate to severe psoriasis[19] (Table 5). That significant alleviation of joint pain and swelling, as well as of functional disability, resulted from our adalimumab dosage regimen was also indicated by examination of the DLQI evaluations and the patient and physician global assessments.

Analysis of PASI score trajectory shows that when adalimumab treatment began, four patients (33%) exhibited initial aggravation, seven patients (58%) had gradual improvement, and one patient (8%) had persistent disease progression (Table 1). All of the patients who exhibited initial aggravation had received at least one systemic treatment before the trial, compared to 71% (5 in 7) of those who gradually improved. In contrast to the usual protocol of a minimum washout time of 2 weeks before adalimumab administration is begun, our protocol was to start adalimumab treatment immediately after discontinuation of the previous treatment. One patient was noted as having progression of PASI throughout the study, whereas his symptoms of psoriatic arthritis were found to gradually improve. This might imply that the response of psoriasis to adalimumab is not completely parallel with the response of psoriatic arthritis.

During the course of our study, systemic medication in addition to adalimumab was prescribed and administered to two patients, namely a regimen of MTX. Among others treated with adalimumab only, mean reduction rate of PASI was 54.6%, which was higher than that (35.9%) in the total population. Two previous randomized controlled studies in which concomitant use of DMARDs was excluded also showed a high rate of PASI 75 achievement.[14,16] In ACCLAIM trial (A Canadian open-label study to evaluate the safety and effectiveness of adaLimumab when Added to Inadequate therapy for the treatment of psoriatic arthritis), an open-label study, concomitant use of DMARDs was allowed at stable, prestudy dosages throughout the course. Response for patients with active PsA, as measured by percentages achieved in the Psoriatic Arthritis Joint Activity Index, showed no difference between groups treated with and without concomitant DMARDs.[19]

These studies suggest that adalimumab works effectively as a monotherapy for treating PsA.

ANA has been reported to be associated with loss of response to anti-TNF-α therapy. Pink et al[20] found that patients on anti-TNF therapy commonly developed ANA and anti-double–stranded DNA antibodies, which appears to be related to anti-TNF treatment failure. In our study, there were 11 patients with undetectable ANA titer and one with positive titer (1:640) at baseline. Two of the patients who had undetectable baseline ANA tested weakly positive (1:40) for ANA antibodies at Week 12. Their disease activity responsiveness to adalimumab was no different from the others. The single patient who had elevated baseline ANA continued to test at the same positive level during the 12 weeks of treatment and yet this patient exhibited fair improvement with respect to both psoriasis and PsA. None of our patients developed the lupus-like syndrome that has been reported in a few cases.[21,22] In our study, ANA was neither associated with responsiveness, nor did it influence the manifestation of adverse side effects.

Unlike previously published studies, we did not design inclusion and exclusion criteria in this retrospective study.[16,23,24] Not only did the small number of patients and short follow-up period make doing so unfeasible, but most of our patients would not have fulfilled the strict criteria in which patients selected for randomized controlled trials must fit. They had severe disease with mean PASI of 24.6 initially, and their response in terms of joint manifestations to previous systemic treatment had been poor. Randomized controlled trials also require a minimum washout period of 2 weeks for nonbiological systemic therapies, which would not have been possible in many of our patients due to the severity of their disease. The concomitant use of topical agents and additional DMARDs during the study are potential confounding factors that need to be analyzed further.

In conclusion, our study is the first to demonstrate that treatment with adalimumab improved symptoms of psoriatic arthritis and DLQI in Taiwanese patients with moderate to severe psoriasis. Patients with recalcitrant PsA and psoriasis who would have been ineligible for clinical trials showed a significant positive response to adalimumab in terms of both joint and skin manifestations, as well as in terms of quality-of-life measures. Adalimumab was generally

well tolerated and safety profiles were similar to what was observed in other trials. The considerable efficacy of adalimumab as monotherapy demonstrated in our study is also consistent with previous studies.

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