The role of NSAIDs in psoriatic arthritis: Evidence from a controlled study with nimesulide

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ABSTRACT

Objective

To define the optimal dose of nimesulide (NIM) for treating psoriatic arthritis.

Methods

Eighty patients entered a 4-week, double-dummy, randomised, controlled study. Each patient was allocated to one of the following treatment groups: NIM 100 mg/day, NIM 200 mg/day, NIM 400 mg/day, or placebo. Primary end points for arthritis assessment were the scores for tender and swollen joints, and the physician's and patient's global assessment of efficacy.

Results. *76/80 patients completed the study. NIM decreased the score for tender and swollen joints from baseline to the end of therapy ($p < 0.05$). Pain severity on a visual analogue scale (VAS) was reduced by NIM 200 mg ($p = 0.03$) or NIM 400 mg ($p = 0.019$) compared to placebo, as was morning stiffness ($p = 0.038$ and $p = 0.008$, respectively), but the trends with 100 mg were not statistically significant. The investigators and patients assessed the global efficacy of the NIM 200 and 400 mg/day groups as better than placebo or NIM 100 mg. Side effects were observed in 12 patients (15%) during treatment. They were mostly mild, only one patient withdrew from the study as a result, and the trend for a higher incidence with NIM was not statistically significant. The Psoriasis Area Severity Index (PASI) and the ESR did not show any significant changes. Patients in the placebo group took more paracetamol per day compared with those in the NIM groups ($p = 0.007$).*

Conclusions

Nimesulide 200 and 400 mg/day are effective and safe in psoriatic arthritis.

Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease defined as an arthritis associated with psoriasis (1). Peripheral manifestations range from monoarthritis to severe destructive polyarthritis (2,3). The pathological aspects of PsA seem to be primarily related to enthesitis (inflammation at sites where ligament, tendon, joint capsule and fascia are inserted into bone), although synovitis is common in oligo-polyarticular types of PsA (4).

Treatment of PsA includes drugs, rehabilitation and surgical reconstruction, with concomitant skin management. In general, nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the management of PsA, although well-controlled studies are lacking in the literature (5). NSAIDs benefit most patients with the oligoarticular and/or monoarticular pattern of joint involvement (6). In contrast, PsA patients presenting with polyarticular, spondylitic and/or more severe forms of joint involvement require therapy that is more aggressive, mainly similar to that for rheumatoid arthritis (7, 8).

Various NSAIDs have been used, including indomethacin, piroxicam, diclofenac, naproxen and tiaprofenic acid (9, 10). In patients with PsA with spondylitic involvement, the response to NSAIDs is not well established. There is no conclusive evidence that NSAIDs either exacerbate or improve the underlying skin involvement (11). Side effects appear to be similar to those seen in the treatment of rheumatoid arthritis.

Nimesulide (NIM; 4-nitro-2-phenoxymethanesulfonanilide) is a weakly acidic NSAID that is effective in numerous inflammatory and pain states, and is generally better tolerated than other NSAIDs. The drug preferentially inhibits cyclooxygenase-2 (COX-2), and has various other actions relevant to inflammation (12). Our study was performed to assess the efficacy and safety of NIM 100, 200 and 400 mg daily in the treatment of patients with PsA compared to placebo.

Material and methods

Patient selection

80 patients with active oligo- or polyarticular PsA entered the study. PsA was defined as an inflammatory arthritis negative for rheumatoid factor in the setting of psoriasis (2-4). The inclusion criteria were: (a) age 18 to 70 years; (b) at least 3 swollen joints; (c) absence of rheumatoid factor; (d) a diagnosis of PsA of at least 6 months; (e) no treatment with slow-acting antirheumatic drugs during the 3 months preceeding the study, and (f) written informed consent.

Exclusion criteria included the following: a diagnosis of any concomitant rheumatic condition, active or suspected peptic ulceration or gastrointestinal bleeding, an important coagulation defect or any other disorder that might preclude NSAID use, malignant disease, renal or hepatic disorder, inflammatory bowel disease, hypersensitivity to analgesics/NSAIDs, any clinically abnormal pretreatment laboratory tests, and women who were pregnant, breast feeding, or not using adequate contraception.

The study was a 4-week, double-blind, randomised controlled investigation. After a 7-day wash-out period from NSAIDs, each patient was randomly and blindly allocated to one of the following groups: NIM 100 mg/day; NIM 200 mg/day; NIM 400 mg/day, or placebo. All study drugs were tablets of identical appearance. Paracetamol 500 mg tablets were allowed as rescue medication for pain (up to 2 g daily), but no other analgesics were allowed.

Screening

The patients were screened by medical history, physical examination and clinical laboratory tests 7 days before the first dose of study medication (D-7). Efficacy and tolerability were assessed from measurements at this baseline visit, at study entry, and after 2 and 4 weeks of treatment. The evaluated variables included: the number of tender and swollen joints, duration of morning stiffness, pain visual analogue scale, and the patient's and physician's global assessment of treatment efficacy and tolerability. The global assessment of efficacy was made after 14 and 28 days, using a 5-point scale (excellent, good, fair, poor, useless). A 3-point rating scale (good, fair or poor) was used to evaluate tolerability. Skin symptoms were scored using the Psoriasis Area Severity Index (PASI) (13). Paracetamol consumption was recorded at each visit.

An adverse event was defined as any reaction, side effect, intercurrent disease, or untoward event that occurred during the course of the clinical trial, whether or not the event was considered drug-related. All adverse events, however minor, were recorded. They were defined as mild, moderate, or severe, and their relationship to the trial drugs was classified by both the investigator and the medical monitor.

Laboratory assessment and monitoring of WBC, Hb, platelets, ESR, liver transaminase, alkaline phosphatase, serum creatinine, uric acid, total bilirubin, sodium, potassium, and urine analysis were performed at Day 7 and after 4 weeks of treatment.

Statistical analysis

We measured treatment efficacy by primary and secondary endpoints of arthritis assessments. All data at T_0 for PASI, VAS, and the score for tender and swollen joints, were analysed by the Kruskal-Wallis test, to assess any differences between the study groups during the run-in period.

Statistical analysis within groups was made by Friedman's non-parametric test. When a significant difference was observed, the Wilcoxon binomial test was performed between the different periods of study (T_0 - T_{14}; T_0 - T_{28}; and T_{14} - T_{28}). Variation between T_{28} vs T_0 was analysed for PASI and VAS using the Fligner Wolfe non-parametric test.

Morning stiffness was analysed by the Chi-square test, comparing the three classes of frequency (improved, not improved, worse) at T_{28} vs T_0. Efficacy (excellent, good, fair, poor, useless) and tolerability (good, fair, poor) were analysed similarly.

Results

Of the 80 patients randomised to treatment, 76 completed the trial. The four patient groups did not differ significantly with respect to demographic, clinical, or laboratory characteristics at Day 7 (Table I), or in baseline efficacy endpoint data at Day 0.

Arthritis assessments

The score for tender and swollen joints and VAS pain scale measurements were reduced in all three NIM groups from baseline to the end of therapy ($p < 0.05$; Table II), whereas the placebo group showed no significant change (Table II). The placebo group had a higher score for tender and swollen joints than the three NIM groups ($p < 0.05$; Table II). Overall pain (VAS) was reduced by NIM 200 ($p = 0.03$) or 400 mg/day ($p = 0.019$) compared to placebo, but the

Table I. Demographic, clinical and laboratory features of the patients admitted to the study.

	Placebo	NIM 100	NIM 200	NIM 400	p
No. of patients	20	20	20	20	NS
Sex M/F	15/5	12/8	10/10	14/6	NS
Mean age (± SD)	51.1 ± 11.4	50.2 ± 11.1	54.2 ± 9.4	53.3 ± 10.5	NS
Weight (mean ± SD)	75.6 ± 11.3	73.2 ± 11.0	67.0 ± 12.6	73.2 ± 12.9	NS
Height (mean ± SD)	169.1 ± 6.6	167.7 ± 9.6	165.2 ± 10.0	168.2 ± 7.8	NS
Tender joint score	12.45 ± 4.80	11.55 ± 4.05	13.40 ± 7.09	10.45 ± 6.28	NS
Swollen joint score	10.55 ± 3.71	9.70 ± 3.25	10.40 ± 5.62	10.00 ± 5.20	NS
VAS (Pain) 0-100 mm	42.10 ± 21.11	46.55 ± 24.21	47.65 ± 23.45	43.05 ± 24.07	NS
Morn. stiffness (<30' / >30 ')	11/9	16/4	12/8	10/10	NS
ESR (mmHg/1st hour)	25.80 ± 17.43	23.53 ± 11.16	30.70 ± 33.74	31.35 ± 39.11	NS
Uric acid (mg/dl)	5.42 ± 1.28	5.77 ± 1.99	4.81 ± 1.52	5.41 ± 1.58	NS

trend with NIM 100 mg/day was not statistically significant. Similarly, morning stiffness improved with NIM 200 or 400 mg ($p = 0.038$ and $p = 0.008$, respectively) compared to placebo (Table III), but not with NIM 100 mg. The ESR did not change significantly.

Patients given placebo took more paracetamol 500 mg tablets per day than those in the NIM groups ($p = 0.007$).

Both the investigators and patients assessed the global efficacy of NIM 200 and 400 mg/day as significantly better than placebo or NIM 100 mg/day (Figs. 1 and 2).

Safety

Side effects occurred in 12 patients (15%) during the treatment period. They were mostly mild, but one patient given NIM 200 mg/day withdrew because of gastric pain. Two patients in the placebo group withdrew for lack of efficacy, and one patient in the NIM 400 mg/day group was lost to follow-up on the last visit. Adverse events are reported in Table IV. The trend for a higher incidence of side effects with NIM was not statistically significant. There were no significant changes in the PASI or in laboratory haematological and biochemical measurements.

Table II. Mean measurements of disease activity (SD) in the patient groups at -7,0, 14 and 28 days of treatment.

	-7	0	14	28	p versus placebo
Tender joint score					
Placebo	11.20 ± 4.27	12.45 ± 4.80	11.05 ± 5.85	12.10 ± 5.51	
NIM 100	9.65 ± 3.54	11.55 ± 4.05	7.65 ± 3.95*	7.10 ± 3.04*	0.0006
NIM 200	12.60 ± 7.85	13.40 ± 7.09	10.35 ± 5.98*	9.30 ± 5.96*	0.0081
NIM 400	9.40 ± 5.32	10.40 ± 6.28	7.20 ± 3.81*	5.60 ± 2.84*	0.0002
Swollen joint score					
Placebo	10.10 ± 3.52	10.55 ± 3.71	9.85 ± 4.92	10.30 ± 4.96	
NIM 100	9.60 ± 3.33	9.70 ± 3.25	6.80 ± 2.88*	6.50 ± 3.36*	0.002
NIM 200	9.40 ± 5.92	10.40 ± 5.62	8.20 ± 4.57*	7.20 ± 5.06*	0.007
NIM 400	9.25 ± 4.18	10.00 ± 5.20	7.10 ± 4.68*	6.30 ± 4.26*	0.002
Global pain (VAS)					
Placebo	36.15 ± 18.85	42.10 ± 21.11	39.50 ± 27.14	40.50 ± 28.49	
NIM 100	46.45 ± 22.85	46.55 ± 4.21	34.90 ± 21.36*	32.45 ± 21.68*	n.s.
NIM 200	46.70 ± 23.76	47.65 ± 23.45	36.25 ± 20.98*	30.15 ± 22.12*	0.03
NIM 400	40.80 ± 24.01	43.05 ± 24.07	29.15 ± 21.48 *	23.00 ± 20.27*	0.019

Comparison within groups: *$p < 0.05$ (versus baseline values).

Table III. Morning stiffness (expressed as percentages).

	Improved	Unchanged	Worse	p
Placebo	25	55	20	
NIM 100	35	65	0	0.052
NIM 200	45	55	0	0.038
NIM 400	70	25	5	0.008

Comparison between the 4 groups: $p = 0.004$.

Table IV. Side effects of the patients admitted to the study.

	Placebo	NIM 100	NIM 200	NIM 400
Number of patients	20	20	20	20
System organ class				
GI system disordersA	1	2	2	3
Central and peripheral system disorders	0	1	0	3
Skin and appendages disorders	0	1	0	2
Hearing and vestibular disorders	0	1	0	0
Urinary system disorders	1	0	0	0
Number of side effects	2	5	2	8
Number of patients with side effects (%)	1 (5)	5 (25)	2 (10)	7 (35)
Number of withdrawals				
Lack of efficacy	2	0	0	0
Lost to follow up	0	0	0	1
Adverse reactions	0	0	1	0

Discussion

In many patients with PsA, NSAIDs control pain and stiffness. NIM 100 mg twice daily is recommended for the treatment of osteoarthritis and various other painful and inflammatory conditions (12). Our study demonstrates the clinical effectiveness of NIM in treating oligo-polyarticular PsA, with significant improvement in all clinical variables at the end of the 4-week treatment. Most side effects were gastrointestinal, which might relate to some inhibition of prostaglandin synthesis. The efficacy of NIM 400 mg/day was mainly similar to that of NIM 200 mg/day, whereas the 100 mg/day dose showed only a trend for clinical improvement.

The primary endpoints of efficacy in our study (score for swollen and tender joints, and physician's and patients' global assessment of efficacy) showed significant improvement in patients treated with NIM compared to placebo, and NIM also significantly improved other endpoints. Both the investigators and the patients rated the global efficacy of NIM 200 and 400 mg/day as significantly better than NIM 100 mg/day or placebo.

The failure of NIM to alter the ESR accords with the similar lack of effect

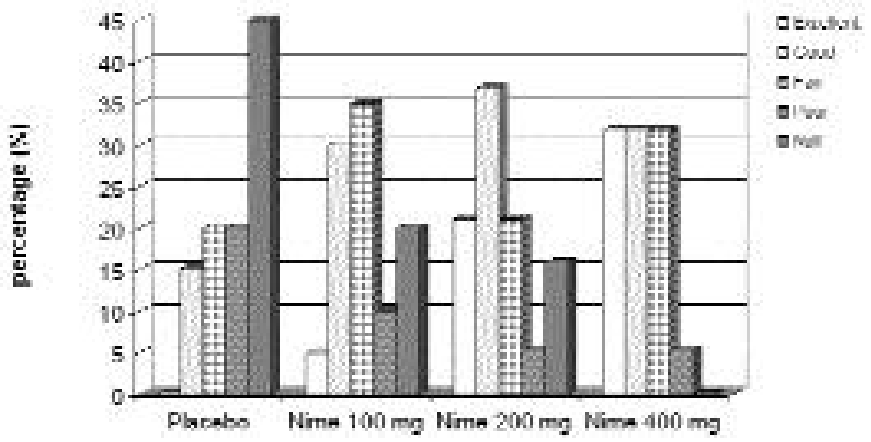

Fig. 1. Global evaluation of efficacy assessed by the investigator.

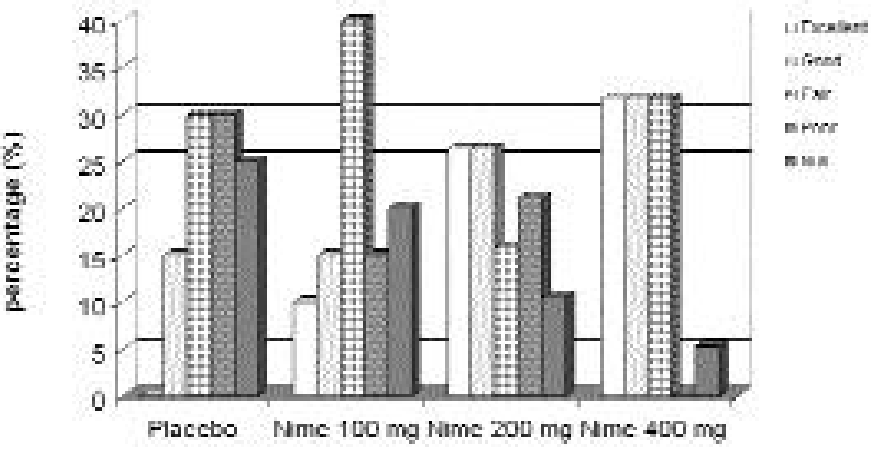

Fig. 2. Global evaluation of efficacy assessed by patients.

of other NSAIDs.

Global tolerance was not significantly different in the three treatment groups, in agreement with data from other studies showing good tolerability of NIM 100, 200 and 400 mg/day. The relatively low potential of NIM to cause gastrointestinal adverse events may be due to its preferential inhibitory effect on COX-2. There is substantial evidence that COX-2 inhibition is important therapeutically, whereas inhibition of constitutive COX-1 causes gastric and renal side effects (12).

Exacerbation of psoriatic lesions can occur with some NSAIDs or orally administered steroids (14, 15). With non-selective COX-1/COX-2 inhibitory NSAIDs, this might involve the increased formation of lipoxygenase products (16, 17). However, there were no observed changes in skin symptoms with NIM, possibly because of its preferential block of COX-2 and/or other of its actions, showing that the drug can be used safely in psoriasis.

In conclusion, NIM 200 and 400 mg/day were significantly more effective than placebo or NIM 100 mg/day in the treatment of patients with PsA. Although no significant differences were observed between the efficacy of 200 and 400 mg/day on primary efficacy variables, NIM 400 mg/day showed a higher global efficacy evaluation by patients and physicians, but with a trend for more adverse reactions. Overall, the trend for more gastrointestinal side effects in the three NIM groups was not statistically significant. NIM therefore appears to be an effective and relatively safe alternative to other NSAIDs for the treatment of PsA.

References

1. KAMMER GM,SOTER NA,GIBSON DJ, BRIGGS B: Psoriatic arthritis:A clinical, immunologic and HLA study of 100 patients. *Semin Arthritis Rheum* 1981; 9: 75-97.
2. MOLL JHM, WRIGHT V: Psoriatic arthritis. *Semin Arthritis Rheum* 1973; 3: 55-78.
3. SALVARANI C, OLIVIERI I, CANTINI F, MACCHIONI L, BOIARDI L: Psoriatic arthritis. *Curr Opin Rheumatol* 1998; 10: 299-305.
4. MCGONAGLE D, CONAGHAN PG, EMERY P: Psoriatic arthritis. A unified concept twenty years on. *Arthritis Rheum* 1999; 42: 1080-6.
5. CUELLAR ML, CITERA G, ESPINOZA LR: Treatment of psoriatic arthritis. *In* WRIGHT V and HALLIWELL P (Eds.): *Psoriatic Arthritis. Bailliere's Clin Rheumatol* 1994; 483-98.
6. GLADMAN DD, ESPINOZA LR: International symposium on psoriatic arthritis. *J Rheuma - tol* 1992; 19: 290-1.
7. ZBOJANOVA M, TRINAUSKY K, ULCEK F: Indocid in the treatment of psoriatic arthritis. *Cekoslovenka Dermatologie* 1974; 49: 129-32.
8. SCARPA R, PUCINO A, IOCCO M *et al.*: The management of 138 psoriatic arthritis patients. *Acta Dermatol-Ven (Stockolm)* 1989; 146: 199-200.
9. JONES G, CROTT M,BROOKS P: The Psoriatic Arthritis Meta-Analysis Study Group. Psoriatic arthritis:A quantitative overview of therapeutic options. *Br J Rheumatol* 1997; 36: 95-9.
10. ESPINOZA LR, KANE D: Clinical, immunopathogenetic, and therapeutic aspects of psoriatic arthritis. *Curr Opin Rheumatol* 1997; 9: 295-301.
11. GRIFFITHS CEM: Therapy for psoriatic arthritis: Sometimes a conflict for psoriasis. *Br J Rheumatol* 1997; 36: 409-12.
12. BENNETT A, VILLA G: Nimesulide: An NSAID that preferentially inhibits COX-2, and has various unique pharmacological activities. *Exp Opinion Pharmacother* 2000; 1: 277-86.
13. FREDERICKSSON T, PETTERSON U: Severe psoriasis: Oral therapy with a new retinoid. *Dermatologica* 1978; 157: 238-44.
14. RESHAD H,HARGREAVES GK,VICKERS CFH: Generalized pustular psoriasis precipitated by phenylbutazone and oxyphenbutazone. *Br J Dermatol* 1983; 108: 111-3.
15. POWLES AV, GRIFFITHS CEM, SIEFERT MH, FRY L: Exacerbation of psoriasis by indomethacin. *Br J Dermatol* 1987; 117:799-800.
16. SMITH DL, WERNICK R: Exacerbation of psoriasis by chrysotherapy. *Arch Dermatol* 1991; 127: 268-70.
17. BAKER H, RYANTJ: Generalized pustular psoriasis:A clinical and epidemiolo gical study of 104 cases. *Br J Dermatol* 1968; 80: 771-93.