



# A New Strategy of Drug Treatment in NSAID-Unresponsive Ankylosing Spondylitis: Combination of Pamidronate and Methylprednisolone Monthly Intravenous Infusions on The Background of A Combination of Disease Modifying Drugs Sulfasalazine and Methotrexate

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## Abstract

**Objectives:** To assess short term efficacy and tolerability of a therapeutic strategy in patients with ankylosing spondylitis (AS) unresponsive to nonsteroidal anti-inflammatory drugs (NSAIDs) or coxibs and unable to take anti-tumour necrosis factor- $\alpha$  (anti-TNF $\alpha$ ) biological treatment.

**Methods:** Established AS patients were given a background treatment consisting of subcutaneous injections of methotrexate weekly (MTX, dose stepped up to a maximum of 20 to 25 mg), weekly 12-16 mg of methylprednisolone orally 30 mts before methotrexate dose (for nausea prevention), sulfasalazine (SSZ, 1 gm orally twice per day) with folic acid supplementation (5 mg daily except on the day of MTX). Additionally, they were given monthly cycles of intravenous (IV) methylprednisolone 'pulse' (MPP) and pamidronate infusions (MPP 500 mg 3 consecutive days + pamidronate 60 mg in a slow IV infusion on day 2 of the MPP infusion). A minimum of six treatment cycles at monthly intervals were given. Adjunct treatment consisted of 1 gm elemental calcium supplementation, paracetamol 650 mg 'as-and-when-required' for symptomatic pain relief, amitriptyline 10 mg 2 hours before bed time daily.

**Results:** Of a total of 46 intent-to-treat patients, 39 patients achieved ASAS-20 and BASDAI-50 response (85%, 95% CI, range 71% to 94%); 7 (15%) patients failed to improve. The expense involved in 6 months of treatment was approximately 10-fold less than anti-TNF $\alpha$  treatment over the same period of time.

**Conclusion:** For AS patients unresponsive to standard NSAIDs/coxibs and unable to take anti-TNF biological agents a combination therapeutic strategy showed efficacy and good tolerability in a majority of patients evaluated over a short-term. ©

## INTRODUCTION

The mainstay of drug therapy in ankylosing spondylitis (AS) are nonsteroidal anti-inflammatory drugs (NSAIDs)/coxibs but, only about 50% of the patients get significant symptomatic relief in pain and stiffness over long-term.<sup>1</sup> The advent of biological response modifiers (BRMs) namely anti-tumour necrosis factor- $\alpha$  (anti-TNF $\alpha$ ) agents has improved

the response rate so dramatically that in the latest international recommendations for AS treatment BRMs are recommended as the drug of choice for unresponsive patients.<sup>2</sup> Unfortunately, for the patients in third world countries the exorbitant cost and serious threat of infectious complications, mainly reactivation tuberculosis, this promise has not been fulfilled.<sup>3,4</sup> Therefore, there is a major therapeutic need to find alternatives to anti-TNF $\alpha$  BRMs for treating AS that are affordable and less likely to cause reactivation tuberculosis.

Using treatment paradigms for RA where combination-DMARDs with glucocorticoids have been shown to be more effective than DMARD monotherapy,<sup>5</sup> Japanese workers have recently reported better efficacy of

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Received : 19.1.2006; Revised : 31.5.2006;

Re-revised : 1.12.2006; Accepted : 18.1.2007

combination of MTX+SSZ than SSZ alone.<sup>6</sup> In addition, there are recent reports of significant efficacy of pamidronate in AS.<sup>7,8</sup> The present study took advantage of combining these 2 treatment modalities developing a more innovative treatment approach for AS patients. The regimen consisted of a combination of SSZ (daily) + MTX (weekly) combined with monthly infusions of MPP (X3 monthly) + pamidronate (single monthly dose synchronised with MMP).

## MATERIAL AND METHODS

**Patients:** Patients were enrolled from the private clinic of one of the authors (ANM) or from among those attending the 'Joint Disease Clinic' at Indian spinal Injuries Centre Superspeciality Hospital (ISIC-SH), New Delhi. The diagnosis of AS was made according to modified New York criteria.<sup>9</sup> The criteria for recruiting patients included 1. Definite diagnosis of AS. 2. Absence of peripheral arthritis. 3. Failure to get symptomatic relief (pain, stiffness, constitutional symptoms) despite at least 3 months of adequate doses of NSAIDs or coxibs. 4. Unable to take anti-TNF $\alpha$  agents (for various reasons, two main ones being the expense and fear of developing active tuberculosis).

**Treatment:** After written consent and ethical clearance of the Hospital Ethics Committee selected patients were given the following treatment: (a) appropriate physiotherapy and occupational therapy advice; non-

steroidal anti-inflammatory drugs (NSAIDs) or coxibs (on as-and-when-required basis for temporary pain relief) with adjunct supportive medicines including calcium (1 gm daily), vitamin D2 (minimum of 250 IU daily) and amitriptyline (10 mg daily 2 hours before going to bed); (b) SSZ (stepped up to 1 gm twice daily dose in 10 days) + MTX (subcutaneous injection stepped up from 10 mg to 20-25 mg weekly dose in a period of 4 weeks) along with adjunct therapy including folic acid supplementation (5 mg daily except on the day of MTX dose) (c) pamidronate monthly infusions given in the following schedule: MPP (500 mg intravenous 'pulse' infusion on 3 consecutive days, monthly) + pamidronate 60 mg in a slow IV infusion (single monthly dose on day 2 of the MPP 'pulse'). A minimum of six treatment cycles at monthly intervals were given.

**Disease assessment and data analysis:** Disease was assessed using 'instruments' recommended by *Assessment in AS (ASAS)* working group namely: Bath ankylosing spondylitis disease activity score (BASDAI), Bath ankylosing spondylitis functional index (BASFI), Bath ankylosing spondylitis disease metrology index (BASMI), ASAS-recommended estimation of inflammation<sup>1</sup> and erythrocyte sedimentation rate (ESR)<sup>1</sup> (Appendix). Response was measured by comparing baseline values with values after completing 6<sup>th</sup> monthly cycle of treatment.

**Improvement criteria:** Improvement was defined

## Appendix

**CALCULATION OF BASDAI** (Garrett S, et al. *Bath Ankylosing Spondylitis Disease Activity Index*. *J Rheumatol* 1994; 21: 2286- 91).

(Scoring range 0-10) = (Mean score of the following 10 points)

Place a mark on each line below to indicate your answer to each question relating to the past 1 week.

(1) How would you describe the overall level of fatigue / tiredness you have experienced?

\_\_\_\_\_

(2) How would you describe the overall level of neck, back or hip pain you have had?

\_\_\_\_\_

(3) How would you describe the overall level of pain / swelling in joints other than neck, back or hips you have had?

\_\_\_\_\_

(4) How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

\_\_\_\_\_

(5) How would you describe the overall level of morning stiffness you have had from the time you wake up?

\_\_\_\_\_

(6) How long your morning stiffness lasts from the time you wake up?

15' 30' 45' 1 hr 1 hr 1½ hr 1 hr 2 hr  
or>  
 \_\_\_\_\_

**COMMENT:** 50% improvement in BASDAI value from the base-line is considered 'improvement'. This methodology has been popularly referred as 'BASDAI-50'

**CALCULATION OF BASFI** (Calin A, et al. *Bath Ankylosing Spondylitis Functional Index*. *J Rheumatol* 1994; 21: 2281-5):

(Scoring range 0-10) = (Mean score of the following 10 points)

**DRAW A MARK ON EACH LINE BELOW TO INDICATE YOUR LEVEL OF ABILITY WITH EACH OF THE FOLLOWING ACTIVITIES, DURING THE LAST 1 WEEK:**

(1) Putting your shoes / stockings without help:

\_\_\_\_\_

- (2) Bending forward from waist to pick up something from the floor without any aid:  
 EASY  IMPOSSIBLE
- (3) Reaching up to a high shelf without help:  
 EASY  IMPOSSIBLE
- (4) Getting out of an armless chair without using your hands or any other help:  
 EASY  IMPOSSIBLE
- (5) Getting up off the floor without help from lying in your back:  
 EASY  IMPOSSIBLE
- (6) Standing unsupported for 10 minutes without discomfort:  
 EASY  IMPOSSIBLE
- (7) Climbing 12-15 steps without using a hand-rail or walking aid – one foot on each step:  
 EASY  IMPOSSIBLE
- (8) Looking over your shoulder without turning your body:  
 EASY  IMPOSSIBLE
- (9) Doing physically demanding activities (e.g. physiotherapy exercises, household chores, sports)  
 EASY  IMPOSSIBLE
- (10) Doing a full day's activities at home or at work:  
 EASY  IMPOSSIBLE

### Assessments in ankylosing spondylitis (ASAS) working group criteria for *response*\* [5]

Improvement of  $\geq 20\%$  and absolute improvement of  $\geq 10$  units (on a scale of 0–100) in  $\geq 3$  of the following 4 domains:

- Patient global assessment
- Pain
- Function
- Inflammation

Absence of deterioration in the potential remaining domain, where deterioration is defined as a change for the worse of  $\geq 20\%$  and net worsening of  $\geq 10$  units (on a scale of 0–100)

\* Patient global assessment is represented by the VAS global assessment score (0–100 scale). Pain is represented by the VAS pain score (0–100 scale). Function is represented by the BASFI score (0–100 scale). Inflammation is represented either by (**first choice**) the mean of the two morning stiffness-related BASDAI VAS scores (Mean of two morning stiffness-related BASDAI VAS scores, one for duration of morning stiffness (0 = none, 100 =  $\geq 120$  minutes) and the other for intensity of morning stiffness (0 = none, 100 = very severe), or by (**second choice**) morning stiffness duration with a maximum of 120 minutes (0–100 scale).

**'Improvement' has been defined as:** Improvement of  $20\%$  and absolute improvement of  $\geq 10$  units (on a scale of 0-100) in  $\geq 3$  of the following 4 domain domains (with absence of deterioration in the potential remaining domain, where deterioration is defined as a change for the worse of  $\geq 20\%$  and net worsening of  $\geq 10$  units (on a scale of 0-100):

- **Patient's global Assessment.** (Same as BASDAI point no. 1); (Scoring range 0-10)
- **Pain VAS (0-100)** (Same as the mean of BASDAI point no. 2+3+4).
- **Function** (Same as BASFI); (Scoring range 0-10)
- **Inflammation (0-100):** Calculated (from BASDAI point no. 5 and 6. by measuring severity of AM Stiffness (scale 0-100) in % + duration of AM stiffness where 2 hr = 100%, then taking mean of these 2 parameters (i.e. divided by 2).

**CAUTION:** For scoring range 0-10 a centimetre scale is used; for scoring range 0-100 a millimetre scale is used. In effect it simply means that for all practical purposes a scale of 0-10 is used for final calculations.

according to ASAS criteria (called ASAS-20).<sup>1</sup> (Appendix). In addition, 50% improvement in BASDAI was taken as another parameter to describe 'BASDAI-50' improvement<sup>10</sup> (Appendix).

## RESULTS

**Demographic profile:** The study included 46 'intent-to-treat' patients. Details of patient characteristic are provided in Table 1. As can be seen, 63% of the patients had high disease activity with BASDAI  $\geq 4^{10}$  and ESR  $>$

30 mm in the 1<sup>st</sup> hour at the baseline.

**Analysis of results** (Table 2): 39 of the 46 patients achieved ASAS-20 and BASDAI-50 improvement (85%; 95% CI, range 71% to 94%). Seven (15.2%) patients did not achieve ASAS-20 or BASDAI-50 response.

**Comparative cost of the present treatment strategy versus anti-TNF $\alpha$  treatment:** The total cost of 6 cycles of the therapy (including drugs, hospitalisation and related expenses) was approximately Rs. 40,000/- over 6 months. In comparison the cost of 3 doses of infliximab

**Table 1 : Demographic characteristics of 46 'intent-to-treat' patients.**

Age	Median: 28 years	Range: 18-47
Gender	Males: 39	Females: 7
Disease duration	Median: 5 years	Range: 1-15 years
BASDAI at baseline	BASDAI > 4 (severe disease*)	29 (63%)
	BASDAI from 3.9 to 2 ( <i>moderately severe disease</i> )	12 (28.5%)
	BASDAI < 2 ( <i>low disease activity</i> )	5 (11%)
ESR at baseline (fasting Westergren)	ESR <i>very high</i> ( $\geq$ 100 mm 1 <sup>st</sup> hour)	6 (15%)
	ESR <i>high</i> (50 to 99 mm 1 <sup>st</sup> hour)	14 (34%)
	ESR <i>moderately high</i> (30 to 49 1 <sup>st</sup> hour)	13 (32%)
	ESR <i>normal</i> (< 30 mm 1 <sup>st</sup> hour)	8 (19%)

\*Ref. 10

**Table 2 : Forty-six 'intent-to-treat' patients with AS; 37 completed 6 months of treatment (9 drop-outs); results of 'response' as assessed by ASAS-20, B and ASDAI-50 improvement**

Parameter for measuring response	Number of patients who showed 'response'	Percentage of 'response'
ASAS-20	39	85 %
BASDAI-50	39	85 %

that would be required over a 6 month period (excluding the expense of hospitalisation) in a 70 kg man (needing 350 mg of the drug i.e. 4 vials @ of Rs. 36,000 per vial) would be Rs. 144,000/- X 3 = Rs. 432,000/- For 6 months of etanercept (50 mg weekly @ of Rs. 17,000/-) the cost would be Rs. 408,000/- It is obvious that the cost difference is ~ 10-fold.

**Tolerance and adverse effects:** In Four patients low grade fever (99-100 F) lasting less than 24 hrs. was noted after the first cycle of therapy. Five patients developed mild myalgias requiring paracetamol during first cycle of therapy. No abnormality in liver enzymes, renal parameters, haematological parameters were noted in any patient. One patient developed elevated blood glucose levels after the first cycle of therapy that returned to normal range after 2 days of the last dose of intravenous methylprednisolone. In subsequent infusions, the period was covered with appropriate insulin dosages. No other adverse effects were noted. (Since the manuscript was submitted originally, now the follow-up has gone up to 1 year in several patients and no late adverse effects have been noted in them till now).

## DISCUSSION

This study describes a novel strategy for treatment

of patients with AS that is effective and much more affordable for patients in developing countries. Considering that the over-all cost (including hospitalisations, drugs) was approximately 10-fold less than the internationally recommended anti-TNF $\alpha$  drug regimen, this treatment strategy could be a possible alternative for NSAID-unresponsive patients with AS in the third world countries.

The results showed that a majority of the patients unresponsive to NSAIDs achieved satisfactory response, with some of them showing dramatic improvement. The tolerability was excellent with only minor self-limiting adverse effects none of which required discontinuation of treatment.

It needs to be emphasised that this was not a comparative efficacy-assessing randomised controlled study with different intervention methods but only a strategy for treating NSAID-unresponsive patients. Also, despite efficacy of this combination-therapeutic strategy there are several shortcomings, problems and difficulties in its routine use. Firstly, it is cumbersome and expensive, as it requires monthly hospitalisation for IV infusions. Secondly, combining several drugs adds to the cost although it still remains much cheaper than anti-TNF $\alpha$  drugs. (Note: Pamidronate available in the Indian market is manufactured in India and its cost is several folds less than that in other countries).

Finally, long-term efficacy and safety of this therapeutic regimen remains unknown. Also, its comparison with 2-drug or 3-drug combinations or with TNF- $\alpha$  antibody, would require randomised control studies or in-practice cohort studies. Also, what happens to disease activity after six monthly IV infusion-cycles of methylprednisolone-pamidronate is discontinued, remains to be seen.

## Acknowledgement

Authors would like to thank Dr. H. S. Chhabra, Addl. Medical Director, ISIC Superspeciality Hospital for help, co-operation, support and encouragement for carrying out this work. The help and co-operation of the nursing staff, other supporting staff and the administrative staff of the hospital is gratefully acknowledged. We also thank Renuka Saha, Associate Professor, Department of Preventive and Social Medicine, Maulana Azad Medical College, New Delhi for help in statistical analysis of the data. Meticulous computer data entry and data updating by Mr. Prashant Deshmukh and Miss Kiran Negi made it possible to analyse the results without any problem.

## REFERENCES

- Anderson JJ, Baron G, van Der HD, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001;44:1876-86.
- Zochling J, van der Heijde, Dougados M, Braun J. Current evidence for the management of ankylosing spondylitis: a systemic literature review for the ASAS/EULAR management

- recommendations in ankylosing spondylitis. *Ann Rheum Dis* 2006;65:423-32.
3. Adebajo A, Furst DE. Biologic agents and their use in resource-poor countries. *J Rheumatol* 2005;32:1182-3.
  4. Hamilton CD. Infectious Complications of Treatment with Biologic. *Agents Curr Opin Rheumatol* 2004;16:393-8.
  5. Smolen JS, Aletaha D, Keystone E. Superior efficacy of combination therapy for rheumatoid arthritis: fact or fiction? *Arthritis Rheum* 2005; 52:2975-83.
  6. Calguneri M, Cobankara V, Ozturk MA, Ertenli I, Kiraz S, Apras S. Combination therapies in spondyloarthropathies. *Kobe J Med Sci* 2004;50:31-7.
  7. Cairns AP, Wright SA, Taggart AJ, Coward SM, Wright GD. An open study of pulse pamidronate treatment in severe ankylosing spondylitis, and its effect on biochemical markers of bone turnover. *Ann Rheum Dis* 2005;64:338-39.
  8. van Der LS, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
  9. Braun J, Davis J, Dougados M, Sieper J, van Der LS, van Der HD. First update of the International ASAS Consensus Statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2005;2005;[Epub ahead of print].
  10. Barkham N, Kong KO, Tennant A, Fraser A, Hensor E, Keenan AM, *et al.* The unmet need for anti-tumour necrosis factor (anti-TNF) therapy in ankylosing spondylitis. *Rheumatology* 2005;44:1277-81.

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