

Comparing the Efficacy of Pamidronate and Thalidomide for the Treatment of Refractory Axial Spondyloarthritis: An Open Label Randomized Clinical Trial

N SULTANA^a, AFMMALAM^b, IH BANDHAN^c, MM HASAAN^d, MG RABBANI^e, ME KABIR^f,
MA SHAHIN^g, MR CHOUDHURY^h, SA HAQⁱ, MM ZAMAN^j

Abstract:

Introduction: Spondyloarthritis (SpA) is a chronic systemic inflammatory rheumatic disease affecting sacroiliac joints, spine and peripheral joints. Pamidronate and thalidomide are proven to be effective in refractory axial SpA in some studies. This study aimed at comparing the efficacy and safety of pamidronate and thalidomide in refractory axial spondyloarthritis (SpA).

Methods: This open label randomized clinical trial was conducted on refractory SpA patients at the department of rheumatology of Bangabandhu Sheikh Mujib Medical University, Dhaka. Pamidronate 60mg intravenous monthly and thalidomide 200mg/day were given to pamidronate and thalidomide groups, respectively for 6 months. Both groups received non-steroidal anti-inflammatory drugs and therapeutic exercises. More than 20% improvements in Assessment of Spondyloarthritis International Society (ASAS-20) at 6 months were considered as primary outcome measure. Secondary outcome measures included Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis functional index (BASFI), Bath

ankylosing spondylitis meteorological index (BASMI), patient global assessment, physician global assessment, erythrocyte sedimentation rate (ESR), C-reactive protein, ASAS 40 etc.

Results: Significant improvement in ASAS 20 was observed in both pamidronate (76.9%) and thalidomide (85.2%) groups ($P=0.501$). Among the secondary outcome ASAS 40 response rates were 46.2% and 51.9% in the pamidronate and thalidomide groups respectively. All other secondary outcome indicators such as BASDAI, BASFI, BASMI etc. within-group showed significant improvements in both groups ($P<0.001$). Between-group differences were nonsignificant ($P>0.1$) except for ESR ($P=0.006$). There were no serious adverse events in any group.

Conclusions: Pamidronate and thalidomide were effective in refractory axial SpA and were well tolerated. However, there was no significant difference in the efficacy of the two drugs.

DOI: <https://doi.org/10.3329/jbcps.v41i4.68930>

(J Bangladesh Coll Phys Surg 2023; 41: 269-276)

- a. Dr. Nadia Sultanam, Medical Officer, Department of Medicine, Shaheed Suhrawardy Medical College Hospital, Sher-e-Bangla Nagar, Dhaka, Bangladesh, ORCID ID: <https://orcid.org/0000-0001-9789-5768>;
- b. Dr. AFM Mahbul Alam, Medical officer, Department of Medicine, Mugda medical College, Dhaka, Bangladesh, ORCID ID: <https://orcid.org/0000-0002-4721-6875>;
- c. Dr. Iftekhar Hussain Bandhan, Medical Officer (OSD), DG Health, Mohakhali, Dhaka, Bangladesh, ORCID ID: <https://orcid.org/0000-0002-3800-6155>;
- d. Dr. Md. Masudul Hasaan, Medical Officer, Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, ORCID ID: <https://orcid.org/0000-0002-9048-295X>;
- e. Dr. Md. Golam Rabbani, Associate Professor, Department of Statistics, University of Dhaka, Bangladesh.
- f. Dr. Md. Ekramul Kabir, Resident Physician, Kurmitola General Hospital, Dhaka Cantonment, Dhaka, Bangladesh.
- g. Prof. Md. Abu Shahin, Professor of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, ORCID ID: 0000-0001-6719-3896
- h. Prof. Minhaj Rahim Choudhury, Professor of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, ORCID ID: 0000-0002-8695-5240;
- i. Prof. Syed Atiqul Haq, Professor of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, ORCID ID: 0000-0003-4154-7283
- j. Mohammad Mostafa Zaman, Advisor (Research and Publication): World Health Organization: Dhaka, Bangladesh, ORCID ID: 0000-0002-1736-1342

Address of Correspondence: Dr. Iftekhar Hussain Bandhan, MD (Rheumatology), Medical Officer (OSD), DG Health, Mohakhali, Dhaka, Bangladesh, ORCID ID: <https://orcid.org/0000-0002-3800-6155>; Email: ibandhan@gmail.com; Mobile: 01922782470

Received: 16 Dec., 2022

Accept: 12 August, 2023

Introduction:

Spondyloarthritis (SPA) are a heterogeneous group of diseases consist of ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), and enteropathic arthritis¹. In ASAS consensus 2009, the patients are sub divided into axial SPA (inflammatory back pain (IBP) in the sacroiliac joints or spine or both) or peripheral SPA (such as peripheral arthritis, enthesitis, and dactylitis)². The SPA may have a deleterious effect on various domestic, occupational, and psychosocial aspects of daily living³.

Management of refractory axial SPA is often difficult because of the relative lack of efficacious treatment. ASAS recommends anti TNF therapy as a 1st line treatment for refractory axial SPA¹. As there is no evidence for the efficacy of disease modifying anti-rheumatic drugs (DMARDs), including sulphasalazine and methotrexate for the treatment of axial SpA. A large number of patients require biologics. In many developing countries including Bangladesh, high cost limits the use of biologics⁴. Recent recommendation from ASAS-EULAR 2022 suggest use of targeted synthetic DMARDs (tsDMARDs) in the treatment of refractory axial SPA⁵. Although the targeted synthetic DMARDs are available in a reasonable price, still a large number of patients cannot afford these. Comparing the price of both thalidomide and pamidronate to biologics, these two drugs are much cheaper and even cheaper than targeted synthetic DMARDs^{4,6}.

Despite potential side effects dominated by teratogenicity and peripheral neuropathy, thalidomide, a sedative drug has recently been used to treat Ankylosing Spondylitis. It affects proinflammatory cytokines, particularly IL-12 and TNF α . It has various anti-inflammatory, immunomodulatory, and anti-angiogenic activities. Thalidomide has proven efficacy and safety in active and refractory AS and refractory axial SPA in several studies⁶⁻⁹.

Pamidronate inhibits generation of proinflammatory cytokines, interleukin (IL)-1, TNF- α and IL-6. It reduced all three biochemical bone turnover markers in a study¹⁰. One possibility is that by reducing the rate of new bone formation, bisphosphonates may also reduce syndesmophyte formation. Several investigators have reported efficacy of pamidronate in refractory AS and other spondyloarthritis¹¹. Further evaluation of this agent in a controlled setting was recommended.

So far, the evidence of efficacy of thalidomide and pamidronate has remained anecdotal only due to small sample sizes and uncontrolled design of the trials.

Moreover, there is no report of head-to-head trial of thalidomide against pamidronate. The objectives of this study were to compare the efficacy and tolerability of pamidronate and thalidomide in patients with refractory axial SpA.

Methods:

Patients: Adult patients aged ≥ 18 years with low back pain > 3 months and age of onset of pain at < 45 yr, attending department of rheumatology, BSMMU, Dhaka, Bangladesh. were screened. Subjects fulfilling the ASAS classification criteria for axial SPA¹ and who underwent a trial of at least 2 course NSAIDs with optimum doses for at least 4 weeks without response were considered as refractory axial SPA and were included. All recruited subjects had active disease, defined by: Bath ankylosing spondylitis activity index (BASDAI) ≥ 4 ¹. Male of reproductive age not willing to maintain adequate contraception and female of reproductive age without completion of family were excluded. In addition patients with renal impairment (serum creatinine > 3.0 mg/dl or eGFR < 30 ml/min), heart failure and peripheral neuropathy were also excluded.

Study Design: This open label randomized clinical trial was carried out in the department of rheumatology, Bangabandhu Sheikh Mujib Medical University (BSMMU). The first patient was enrolled in January 2014, and the last patient completed the 6-month drug therapy in August 2015. The study was approved by the institutional review board of BSMMU, and written informed consent was obtained from all patients. After consideration of inclusion and exclusion criteria, eligible patients were randomized in either pamidronate or thalidomide group by block randomization (Figure 1). Pamidronate group received injection pamidronate 60mg intravenously monthly in the daycare/ inpatient department of rheumatology, BSMMU under the direct supervision of investigator. Thalidomide group received thalidomide 200 mg daily orally. Both groups received indomethacin 75mg twice daily for the period of initial 3 months and same mood of therapeutic physical exercises.

Sample size was calculated using the formula:

$$n = \left[\frac{P(1-P) + P(1-P)}{(P-P)^2} \right] \times (Z\alpha + Z\beta)^2$$

n = sample size for each group

$P_1 = 80\%$ (0.8), [derived from previous literature⁷]

$P_2 = 56\%$ (0.56), [derived from previous literature¹²]

$Z_{\hat{\alpha}} = 1.96$ at 5% level of significance

$Z_{\hat{\beta}} = 0.52$ at 70% power (when $\hat{\alpha} = 0.3$)

The calculated sample size was 44 in each group.

Study procedure and evaluations: Primary endpoint was ASAS 20 response at 6 months, defined as number and percentage of patients achieving a clinically meaningful improvement ($\geq 20\%$) in patient global, spinal pain, Bath ankylosing spondylitis functional index (BASFI), BASDAI questions 5 and 6 average from baseline.

Secondary endpoints included statistically significant difference between baseline and 6-month values of BASDAI, BASFI, Bath ankylosing spondylitis meteorological index (BASMI), Patient global, Physician global, spinal pain, stiffness of spine, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Other secondary endpoints included ASAS 40 response ($\geq 40\%$ improvement in ASAS domains without any deterioration) and incidence of adverse events during 6 months of observation period.

For laboratory tests, 5ml of blood and urine were collected by lab technician from each patient for the measurement of baseline CBC, ESR, CRP, serum creatinine, serum alanine amino transferase (ALT), urine routine examination. X-ray pelvis antero-posterior views were done in selected patients.

Statistical analysis: The differences between the pamidronate and thalidomide groups in ASAS 20 and ASAS 40 responses were tested with chi-squared test.

Between-group analysis was done by Student's 't' test and intra group analysis was done by paired sample 't' test. Wilcoxon signed ranks test and Mann-Whitney test were done for analysis of intra-group and between-group nonparametric data, respectively. P value < 0.05 was considered significant.

Results:

A total of 160 patients with low back pain for > 3 months were evaluated and out of them 105 patients were suffering from IBP. Among the IBP cases 86 fulfilled the ASAS criteria for axial SPA. 26 cases were excluded since they failed to fulfill the inclusion criteria. Finally, 60 subjects were enrolled and out of them 5 dropped out at the end of 3 months and 7 cases dropped out at the end of 6-month follow up. Finally, 53 subjects completed the 6-month trial. The mean age of 53 patients who completed the six months drug therapy was 32.53 (± 8.88) and 32.23 (± 8.85) years in Pamidronate and Thalidomide group respectively. Male and female ratio were 14:1 in Pamidronate group and 29:1 in Thalidomide group (Table-1).

The primary outcome measures were ASAS 20 response rates, which were 76.9% and 85.2% in pamidronate and thalidomide groups respectively. There was no significant difference between groups ($P=0.501$). The ASAS 20 response rates with their confidence intervals have been shown in Figure 2.

Table-I

Demographic characteristics of both study groups (n= 60)

Patients' characteristics	Pamidronate group (n=30)	Thalidomide group (n=30)
Age (mean \pm SD)	33.22 (± 9.08)	32.37 (± 8.96)
Male	28	29
Female	2	1
Educational status		
• Primary	12	07
• Secondary	13	09
• Higher secondary	02	11
• Graduate	03	02
• Post-graduate	00	01
Occupation		
• Service holder	08	13
• Business	18	12
• Housewife	02	01
• Student	01	05

\pm SD = Standard deviation

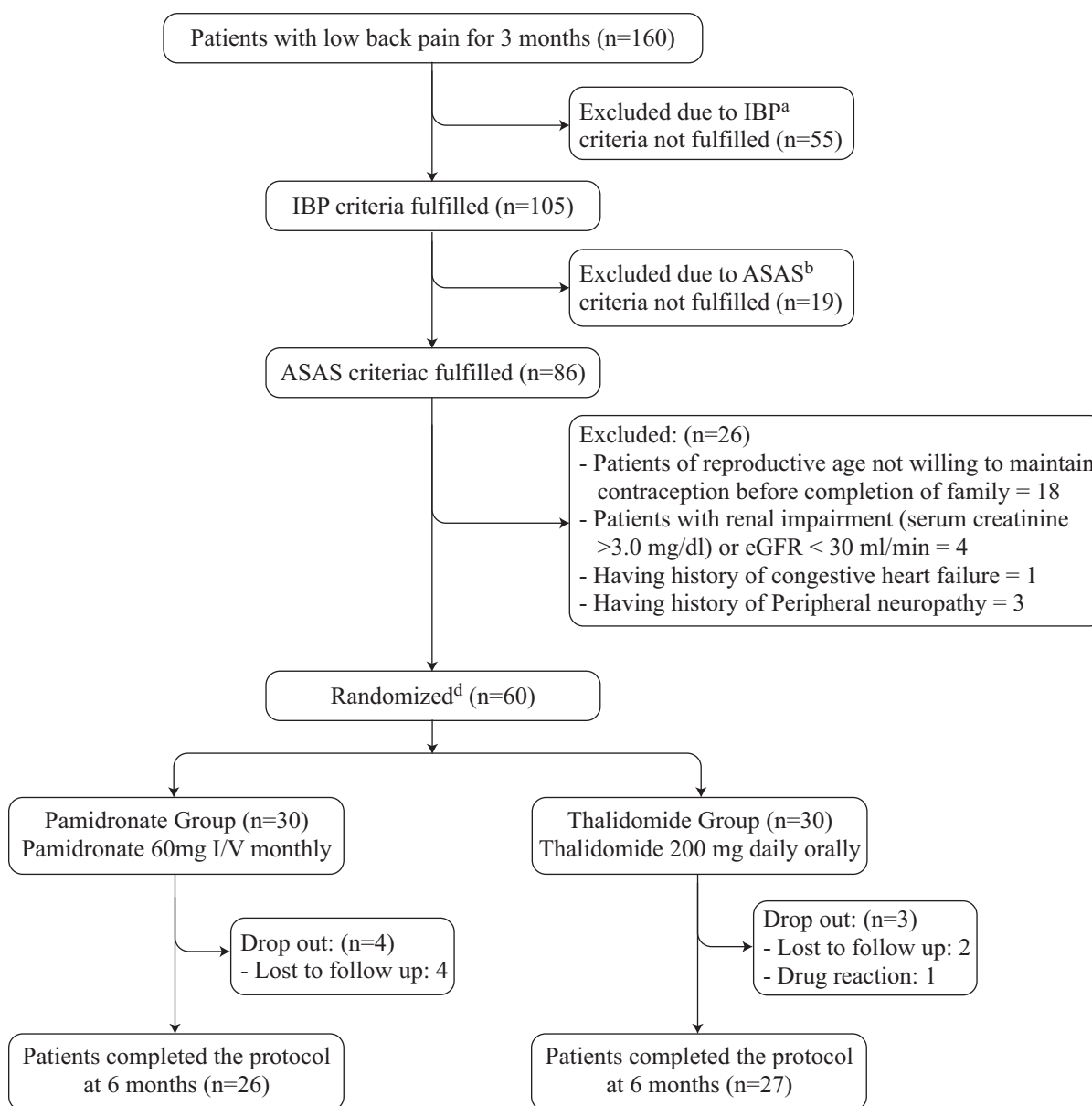


Fig.-1: Flowchart of recruitment of the patients of refractory axial spondylarthritis for examining the efficacy and tolerability of pamidronate and thalidomide

a. Inflammatory back pain criteria: According to ASAS in patients with chronic back pain (>3 months) the criteria are fulfilled if at least four out of five parameters are present: Age at onset <40 years, insidious onset, improvement with exercise, no improvement with rest, pain at night (with improvement upon getting up)

b. ASAS criteria for diagnosis of axial SPA: Back pain (age at onset <45 years, duration \geq 3 months) plus: Evidence of sacroiliitis on MRI or plain radiograph plus at least 1 of the following, or HLA-B27+ plus at least 2 of the following: inflammatory back pain, arthritis, heel enthesitis, dactylitis, uveitis, psoriasis, Crohn's disease or ulcerative colitis, good response to NSAIDs, family history of SpA, elevated CRP, HLA-B27+

c. Subjects fulfilling the ASAS classification criteria for axial SPA and who underwent a trial of at least 2 course NSAIDs with optimum dose for at least 1 month without response was counseled. All recruited subjects had to have active disease, defined by: BASDAI \geq 4.

d. All patients received NSAID along with therapeutic physical exercise

Among the secondary outcomes ASAS 40 response rates were 46.2% (95% CI : 26.6-66.6) and 51.9% (95% CI :31.9-71.3) in the pamidronate and thalidomide groups respectively. In both pamidronate and thalidomide groups, significant improvement took place in all the secondary outcome indicators such as BASDAI, BASFI, BASMI, spinal pain etc. compared to the baseline ($P < 0.001$). The difference between groups was not significant ($P = 0.678$), except ESR ($P = 0.006$) (Table II).

Regarding adverse effects, pamidronate was well tolerated. However, 13 patients noted mild arthralgia and myalgia, 9 patients developed low grade fever after transfusion; all these symptoms subsided within two to three days either spontaneously or with antipyretics.

Seven patients developed anorexia, nausea and also resolved spontaneously. No serious drug rash or adverse events were reported, and none of the patients dropped out due to adverse drug reactions (Table III). In the thalidomide group, 12 patients complained of somnolence during initial 2-4 weeks, and then were improved without medication. Six patients of the thalidomide group noticed dry mouth, which was improved after frequent fluid intake. Six patients noticed constipation in initial 4-8 weeks, improved after dietary modifications, however one patient required laxative for the improvement. One patient developed skin rash and discontinued the therapy and dropped out. None was found to have peripheral neuropathy, orthostatic hypotension or leg oedema.

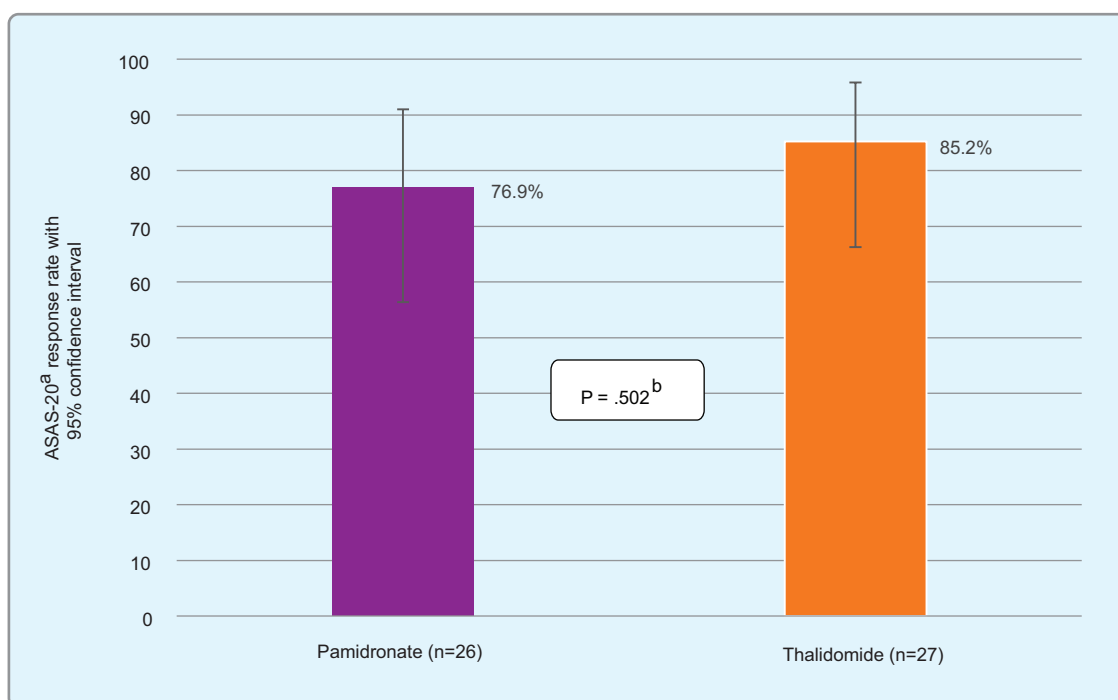


Fig.-2: The primary outcome measure (ASAS-20) at the end of 6 months (n=53)

a. ASAS: Assessment of Spondylo Arthritis International Society, ASAS-20: defined as number and percentage of patients achieving a clinically meaningful improvement ($e \geq 20\%$) in patient global, spinal pain, Bath ankylosing spondylitis functional index (BASFI), (Bath ankylosing spondylitis disease activity index) BASDAI questions 5 and 6 average from baseline.

b. Comparison between groups (Fishers exact test)

Table-II*Baseline and end of 6th month disease status of study groups (n=53)*

	Pamidronate (n=26)			Thalidomide (n=27)			P values for between-group differences at 6 months
	Baseline (Mean±SD)	6 months (Mean±SD)	P values within group at 6 months	Baseline (Mean±SD)	6 months (Mean±SD)	P values within group at 6 months	
BASDAI	6.18±1.08	2.62±1.07	0.001	6.35±1.13	2.83±1.02	0.001	0.44
BASFI	5.97±1.49	2.12±1.36	0.001	6.54±1.02	2.65±1.71	0.001	0.18
BASMI	3.00	2.00	0.001	3.00	1.50	0.001	0.99
Spinal pain	6.61±1.24	4.47±1.40	0.001	6.72±1.10	2.90±1.37	0.001	0.37
Patients global	7.38±1.02	5.09±1.22	0.001	7.0±1.0	3.27±1.42	0.001	0.84
Physician global	7.52±0.67	5.14±0.88	0.001	7.36±0.80	3.27±1.34	0.001	0.86
Stiffness spine	4.69±1.73	3.14±1.23	0.001	5.30±2.94	1.90±1.19	0.001	0.75
ESR	82.38±19.78	44.57±18.89	0.001	72.51±27.97	29.27±17.43	0.001	0.006
CRP	55.84±45.53	10.93±10.96	0.001	74.49±73.71	8.21±7.62	0.001	0.31

SD (Standard deviation), BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index), BASMI (Bath Ankylosing Spondylitis Metrology Index), ESR (Erythrocyte sedimentation rate), CRP (C-reactive protein)

Table-III*Adverse drugs reactions*

	Pamidronate group (n=30)n (%)	Thalidomide group (n=30)n (%)
Serious adverse events*Adverse events	0	0
Skin rash	0	1 (3.3%)
Anorexia and nausea	7 (23.3%)	0
Somnolence	0	12 (40%)
Myalgia	13 (43.3%)	0
Low grade fever	9 (30%)	0
Dry mouth	0	6 (20%)
Constipation	0	6 (20%)

* Serious adverse events defined as death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect¹⁷.

Discussion

In this study we have compared the efficacy and tolerability of pamidronate and thalidomide using 70% power of the test. We observed both the drugs being effective and well tolerated. In the literature, there is no such study that compared the efficacy of pamidronate with thalidomide, however, several studies were done to see the individual drug's efficacy and tolerability^{4,6}.

Maksymowych et al. reported significant efficacy of pamidronate at 6 months in both open label and randomized trials¹¹. Santra et al noted significant for mean BASDAI, BASFI, BASMI, BAS-G, ESR and CRP after six months and 85% achieved ASAS-20 and 77% achieved BASDAI-50 responses, which is in accordance with our report¹³. Haibel et al, in an open observational study with pulse IV pamidronate in AS patients, found significant reductions in the mean BASDAI scores at

the end of six months and a 20% improvement in ASAS in four out of nine patients¹⁴. In a study of 15 AS patients by Cairns et al, significant improvement was noted in BASDAI score (but not in BASMI, CRP or ESR) after six months of pulse IV pamidronate (60 mg) therapy¹⁰. In a study by Malaviya et al, significant improvement was noted with combined pamidronate and methylprednisolone therapy in 46 AS patients. Out of the 46 patients, 39 achieved ASAS-20 and BASDAI-50 responses (85%, 95% confidence interval 71%–94%), and seven (15%) patients failed to improve⁴.

Choudhury et al. in Bangladesh studied the efficacy and safety of thalidomide among 37 refractory AS patients and reported that the drug was effective in 63.4% and was safe⁶. In another study Huang et al. in China observed the efficacy of thalidomide for one-year in 26 patients, they reported that thalidomide was effective in AS. About 80% of the subjects showed 20% improvement in 4/7 indices⁷. In Taiwan, Wei et al. conducted a 3 months open-labeled study of thalidomide in 10 male patients affected with severely active AS, refractory to NSAID. According to AS assessment study criteria, which were used to evaluate efficacy of treatment, 7 of the 9 completers (78%) were responders. Statistically significant improvement was achieved for BASDAI, patient's global assessment, ESR and CRP¹⁵. Lee et al. reported clinical improvement with thalidomide in a patient with severe seronegative spondylarthritis¹⁶.

Limitations and strengths

The major limitations of the study were the open-label design and small size. They might lead to type I and II errors. Quality of life domain was not observed in this study. To our knowledge this is the first report of a study comparing the efficacy and tolerability of pamidronate and thalidomide in refractory axial SpA. To the best of our knowledge, this is the only study in which both ASAS20 and ASAS40 have been used as outcome measures.

Conclusion

Both pamidronate and thalidomide were effective and safe for the treatment of refractory axial SpA. Almost all patients of both groups tolerated the drugs reasonably. No significant difference was found between the efficacy of the two drugs. These drugs could have a special place in the treatment of refractory axial SpA

especially where cost of the treatment is a limitation. However, studies examining benefits of these drugs beyond six months would be more useful. Randomized blinded control trial will have an added value.

References

1. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis*. 2009 May 11;68(Suppl 2):ii1–44. DOI: <http://dx.doi.org/10.1136/ard.2008.104018>
2. Braun J, Inman R. Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis. *Ann Rheum Dis*. 2010 Jun 21;69(7):1264–8. DOI: <http://dx.doi.org/10.1136/ard.2010.130559>
3. Boonen A. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Ann Rheum Dis*. 2002 May 1;61(5):429–37. DOI: <http://dx.doi.org/10.1136/ard.61.5.429>
4. Malaviya AN, Kapoor S, Garg S, Ahmad I, Raja RR. 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. *J Assoc Physicians India*. 2007 Mar;55:193–7. PMID: 17598330
5. Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis*. 2022 Oct 21;82:19–34. DOI: <http://dx.doi.org/10.1136/ard-2022-223296>
6. Choudhury MR, Hassan MM, Kabir ME, Rabbani MG, Haq SA, Rahman MdK. An open label clinical trial of thalidomide in NSAIDs refractory ankylosing spondylitis. *Mod Rheumatol*. 2018 Feb 2;28(4):730–2. DOI: <http://dx.doi.org/10.1080/14397595.2018.1427430>
7. Huang F, Gu J, Zhao W, Zhu J, Zhang J, Yu DTY. One-year open-label trial of thalidomide in ankylosing spondylitis. *Arthritis Rheum*. 2002 Jun 5;47(3):249–54. DOI: <http://dx.doi.org/10.1002/art.10396>
8. Lee L, Lawford R, McNeil HP. The efficacy of thalidomide in severe refractory seronegative spondylarthropathy: Comment on the letter by Breban et al. *Arthritis Rheum*. 2001;44(10):2456–7. DOI: [http://dx.doi.org/10.1002/1529-0131\(200110\)44:10<2456::AID-ART418>3.0.CO;2-V](http://dx.doi.org/10.1002/1529-0131(200110)44:10<2456::AID-ART418>3.0.CO;2-V)
9. El Hassani S, Dougados M, Gombert B, Amor B, Breban M. Treatment of severe refractory spondylarthropathy (SPA) with thalidomide: Results of an open study. *Arthritis Rheum*. 1999; 42: S373

10. Cairns AP. An open study of pulse pamidronate treatment in severe ankylosing spondylitis, and its effect on biochemical markers of bone turnover. *Ann Rheum Dis*. 2005 Feb 1;64(2):338–9. DOI: <http://dx.doi.org/10.1136/ard.2004.022871>
11. Maksymowych WP, Jhangri GS, Fitzgerald AA, LeClercq S, Chiu P, Yan A et al. A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum*. 2002 Mar;46(3):766–73. DOI: <http://dx.doi.org/10.1002/art.10139>
12. Mok CC, Li OC, Chan KL, Ho LY, Hui PK. Effect of golimumab and pamidronate on clinical efficacy and MRI inflammation in axial spondyloarthritis: a 48-week open randomized trial. *Scand J Rheumatol*. 2015 Aug 14;44(6):480–6. doi: 10.3109/03009742.2015.1038300
13. Santra G, Sarkar RN, Phaujdar S, Banerjee S, Siddhanta S. Assessment of the efficacy of pamidronate in ankylosing spondylitis: an open prospective trial. *Singapore Med J*. 2010 Nov;51(11):883–7. PMID: 21140116
14. Haibel H, Fendler C, Listing J, Callhoff J, Braun J, Sieper J. Efficacy of oral prednisolone in active ankylosing spondylitis: results of a double-blind, randomised, placebo-controlled short-term trial. *Ann Rheum Dis*. 2013 Apr 26;73(1):243–6. DOI: <http://dx.doi.org/10.1136/annrheumdis-2012-203055>
15. Wei JC, Chan TW, Lin HS, Huang F, Chou CT. Thalidomide for severe refractory ankylosing spondylitis: a 6-month open-label trial. *J Rheumatol*. 2003 Dec;30(12):2627–31. PMID: 14719205
16. Lee L, Lawford R, McNeil HP. The efficacy of thalidomide in severe refractory seronegative spondylarthropathy: Comment on the letter by Breban et al. *Arthritis Rheum*. 2001;44(10):2456–7. DOI: [http://dx.doi.org/10.1002/1529-0131\(200110\)44:10<2456::aid-art418>3.0.co;2-v](http://dx.doi.org/10.1002/1529-0131(200110)44:10<2456::aid-art418>3.0.co;2-v)
17. What is a Serious Adverse Event? [Internet]. USA: US FDA; updated 2023 May 18; cited 2023 Aug 10. Available from: <https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event>