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Research Article

Efficacy and safety of dose comparison (60mg/30mg) response of intravenous (IV) pulse pamidronate therapy in non-steroidal anti-inflammatory drugs (NSAIDS) refractory ankylosing spondylitis.

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ABSTRACT:

OBJECTIVE: To assess the efficacy and safety of differentdoses (60mg/30mg) of intravenous (IV) Pamidronatetherapy in non steroidalanti inflammatory drugs (NSAIDS) refractory Ankylosing Spondylitis (AS).

Methodology:A single blind randomized controlled trial conducted at department of RheumatologyPakistan institute of medical sciences (PIMS) hospital Islamabad, from 15 January 2018 to 14Th July 2018 ,Duration of study was 6 months ,including 30 patient divided 15 in each group. All those cases of AS included in this study who fulfill Modified New York diagnostic criteria for AS.

Results: Baseline characteristics of studied samples were divided into two treatment groups, 15patients in each group , Group A of 60 mg drug, 86.7% participants were male and in group B of 30 mg drug there were 80% male participants. In group A, 73.3% patients reported for peripheral joint involved, 33.3% had family history, 46.7% reported for HLA B27 and 40% reported for UVEITIS. However, all parameters were found statistically independent except UVEITIS gives significant association with treatment group (p-value =0.03).Inter group analysis and mean of baseline, 3rd month and 6th month were compared within group with each other, results showed that, all mean differences were significantly positive, and BASDAI, BASFI, VAS and ESR scores at 3rd and 6th month found significantly low as compared to baseline, in all treatment groups.

Conclusion: Pamidronate is effective in improving the disease activity and functional ability (Irrespective of dose) in NSAID refractory AS patients, so pamidronate represent new direction in the treatment of financially constrained AS populations .

Keywords: Ankylosing Spondylitis, pamidronate,BASDAI, BASFI, VAS, ESR, Arthritis

INTRODUCTION:

Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis characterized by sacroiliitis, enthesitis, and a marked propensity for sacroiliac joint and spinal fusion. AS is a condition in the spondyloarthritis (SpA) family of diseases, which share several clinical, genetic, and immunologic features. AS is distinguished in this family by universal involvement with sacroiliac joint

inflammation or fusion, and more prevalent spinal ankylosis; these more advanced sacroiliac changes form the core of the modified New York criteria for the classification of AS. Radiographic features may take years to develop, which limits these classification criteria by potentially excluding patients early in the disease course. Ankylosing spondylitis (AS) is a chronic systemic inflammatory rheumatic disease of unknown etiology affecting the sacroiliac joints and the spine, predominantly. Its prevalence is around 0.5–1% worldwide with male predominance[1,2]disease, M:F ratio vary from2:1 to 9:1[3]. (NSAIDs) and physiotherapy has been the mainstay of -therapy and effective during painful periods of AS[4]. NSAIDs provide very quick & dramatic relief of inflammatory backpain.But overtime the disease often becomes refractory to theses agents, also in some cases ,resistant to these intervention [4,5]furthermore , there is no more evidence that NSAIDS alter or arrest the structural damage . Gastro intestinal tolerability and increased cardiovascular risks limit chronic use[5,6].In patients refractory or intolerant to NSAIDs, disease modifying anti-rheumatic drugs (DMARDs) like methotrexate and sulfasalazine has been tried with minimal effect[6].Few published reports are found the use of corticosteroids treatment provide rapid and considerable relief,but long term use associated with serious adverse events.In AS refractory to NSAIDS,corticosteroid intravenous (IV)pulse therapy can provide rapid temporary symptomatic improvement[7].

Tumor necrosis factor(TNF) antagonists suppress the disease activity & improves functional ability in patients with AS who are refractory to convential treatment. These targeted therapies not only shows rapid & consistent effectiveness in reducing patients symptoms of AS ,but also slowing disease progression .but are much more expensive than conventialtherapies .TNF blockers are contraindicated in patients with tuberculosis,demylinatingdiseases,and potential risk of malignancy[7,8] ,For resource poor countries its high cost,and in tuberculosis endemic areas its use is the major issue thus alternatives are needed.Osteoporosis is commonly observed in AS ,An important role in progression of skeletal lesions in AS is played by local overactivity of osteoclastic bone resorption followed by excess bone formation (Syndesmophytes)[9] .

Bisphosphonates , in addition to their anti osteoclastic effects, associated with anti inflammatoryactivity by suppressing proinflammatory cytokines such as IL-1,TNF-alpha,and IL-6[10,11].Pamidronate infusions lead to significant improvement in parameters like Bath AnkylosingSpondylitis disease activity index(BASDAI),erythrocyte sedimentation rate (ESR) visual analogue scale (VAS).There was reviews of two studies which have shown that pamidronate have significant beneficial effects in patients of NSAID refractory AS[,10,11]. A double blind controlled trial also conducted to examine the therapeutic effect for six months. When initial dose of pamidronateis given, myalgia and arthralgia was reported[12,13].This is first single center trial on the assessment of efficacy of different doses of pulsepamidronate therapy among NSAIDS refractory AS patients in Pakistan.

OBJECTIVES:

To assess the efficacy and safety of dose comparison response (60mg/30mg) of IVP amidronatetherapy in NSAID Srefractory Ankylosing Spondylitis (AS).

MATERIALS AND METHODS:

It was a single blinded randomized controlled trial conducted at department of Rheumatology, Pakistan Institute of Medical Sciences (PIMS) Islamabad,after approval of study design from the ethical review board (IRB) of Shaheed Zulfiqar Ali Bhutto University of Medical and Health Sciences. Duration of study was 6 months including 30 patients, 15 in each group. All those cases of AS who fulfill Modified New York diagnostic criteria for AS, all chronic cases who received NSAIDS (max: dose of 2 NSAIDS at

least for 3 months or more) & conventional DMARDS and especially those who are non-affording for anti TNF-ALPHA were included. Patients with renal impairment, end-stage AS, skeletal deformity other than AS, and women of childbearing age or planning to conceive were excluded.After taking written informed consent from patients who fulfill the inclusion criteria was enrolled in the study. Demographic data of each patient is recorded. They were immediately divided into two treatment groups. One group of patients was given 30 mg of pamidronate and another was given 60 mg of pamidronate infusion in 100ml normal saline. The medication administered after obtaining informed consent from the patients. Sulfasalazine and methotrexate were continued for peripheral arthritis. NSAIDS were also allowed. An initial assessment was conducted before pamidronateadministration, and then after 3,6 months intervals. The total observation period was six months. The assessments conducted by using visual analogue scale, Bath AS Functional Index (BASFI) for the measurement of functional improvement, BASDAI for measurement of disease activity & (ESR) measured 3 and 6 monthly. All data recorded on especially designed proforma separately for each case and duly verified by consultant**.**Data entered and analyzed with SPSS version 23. Mean and standard deviation calculated for quantitative variables like age, BASDAI & BASFAI, ESR etc. Frequency and percentage presented forquantitativevariables. Efficacy compared by chi-squared test between both groups after 06 months. P-value less than 0.05 were considered significant.

STATISTICAL ANALYSIS:

Data was stored and analyzed using IBM SPSS version 23.0, count and percentages were reported for baseline characteristics, mean and standard deviation were reported for age, duration of disease, BASDAI, BASFI, VAS and ESR scores. Chi squared test was used to see the association of baseline characteristics between two drug groups, for intra group analysis independent sample t-test was done that compared the means scores between groups at baseline, third and sixth month, inter group analysis was done using repeated measure ANOVA, that gave the results of multiple comparison of mean scores from baseline to sixth month within each treatment group.

RESULTS:

There were selected 30 patients, 15 in each group to conduct the RCT. Table 1 described the baseline characteristics of studied samples in two treatment groups, each treatment group contains fifteen patients, in group A of 60 mg drug, 86.7% participants were male and in group B of 30 mg drug there were 80% male participants. In group A, 73.3% patients reported for peripheral joint involved, 33.3% had family history, 46.7% reported for HLA B27 and 40% reported for UVEITIS. However, all parameters were found statistically independent except UVEITIS gives significant association with treatment group (p-value =0.03).

Table 1: Baseline Characteristics of Studied Samples (n=30)

Characteristics		Treatment Group				p-value
		Group A (60 mg) n=15		Group B (30 mg) n=15		
		Frequency	Percentage	Frequency	Percentage	
Gender	**Male**	13	86.7	12	80.0	0.63
	Female	2	13.3	3	20.0	
Peripheral joint involved	**Yes**	11	73.3	13	86.7	0.36
	No	4	26.7	2	13.3	
Family history	**Yes**	5	33.3	5	33.3	1
	No	10	66.7	10	66.7	
HLA B27	**Yes**	7	46.7	4	26.7	0.25

	No	8	53.3	11	73.3	
UVEITIS	**Yes**	6	40.0	1	6.7	0.03
	No	9	60.0	14	93.3	

Table 2: Mean Comparison of Studied Parameters at Baseline between two Groups

Baseline Parameters	**Group A (60 mg)**		**Group B (30 mg)**		**p-value**
	Mean	**S.D**	**Mean**	**S.D**	
Age (years)	34.33	7.6	29.73	7.94	0.11
Duration of disease (years)	9.53	5.88	6.8	4.79	0.17
BASDAI Baseline	6.58	1.55	6.06	0.98	0.27
BASFI Baseline	6.57	1.52	6.4	0.83	0.71
VAS Baseline	8.14	1.36	8.87	0.64	0.06
ESR Baseline	30	16.91	41.39	23.03	0.14
*p<0.05 was considered significant using Independent sample t-test					

Table 3 reports the mean comparison of BASDAI, BASFI, VAS and ESR scores at third month between two treatment groups. Results showed only BASDAI of group B gives significant decrease in scores; all other differences were found statistically insignificant.

Table 3: Mean Comparison of Studied Parameters at 3rdmonth and 6th monthbetween two Groups

3rd Month Parameters	**Group A (60 mg)**		**Group B (30 mg)**		**p-value**
	Mean	**S.D**	**Mean**	**S.D**	
BASDAI 3rd Month	4.63	0.98	3.51	1.31	0.013*
BASFI 3rd Month	2.68	1.09	1.96	1.08	0.07
VAS 3rd Month	4.66	1.54	3.72	1.26	0.055
ESR 3rd Month	2.85	1.13	2.29	0.98	0.25
6th Month Parameters					
BASDAI 6th Month	2.68	1.09	1.96	1.08	0.07
BASFI 6th Month	4.66	1.54	3.72	1.26	0.15
VAS 6th Month	2.85	1.13	2.29	0.98	0.8
ESR 6th Month	5.54	1.46	6.4	0.83	0.4
*p<0.05 was considered significant using Independent sample t-test					

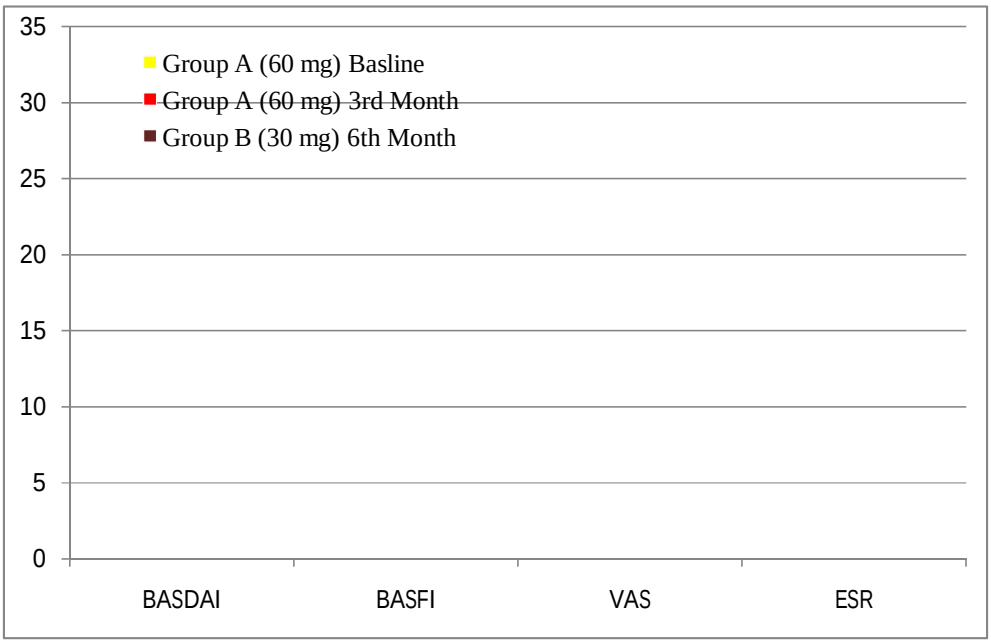

Fig. 1: Mean Score of Parameters in Group A (60mg) versusGroup B (30mg).

DISCUSSION

This study was conducted to compare the two different doses (30mg and 60mg) of pamidronate to see the effect on the NSAID refractory AS patients. Patients in group A who received 60mg pamidronatefor 6 months with monthly dose have significant improvement on clinical outcome as compared to group B who received 30mg of pamidronatebut this group also showing marked clinical improvement.It is proved that either doses of pamidronateimprove the overall quality of life especially in those patients who are having shorter disease course <6yrs as compared to longer duration.There were observed adverse effects on first dose of intravenous infusion but overall treatment was well tolerated. Both groups were compared regarding toxic effects but not observed.In our study, inter group analysis and mean of baseline, 3rd month and 6th month were compared within group with each other, results showed that, all mean differences were significantly positive, and BASDAI, BASFI, VAS and ESR scores at 3rd and 6th moth found significantly low as compared to baseline, in all treatment groups. A study conducted by Walter et al in 2000 at Canada to compare the effects of pamidronate 60mg IV and 10mg IV for the treatment of AS. Studies conducted by Maksymowych et al and concluded that pamidronate has good control for NSAID refractory AS[14-16]. It was conducted in Italy and results showed that there is significant reduction in mean BASDAI score after 6 months whether it was a use of infliximab or neridronate[17]. There was observed dose dependent reduction in the mean score of BASDAI at six months of pamidronate administration. There was also significant reduction in the mean score of BASDAI, BASMI, BASFI and ESR[18].

In our results there was significant reduction in the level ESR in the patients who were given 60mg pamidronate as compared to 30mgpamidronate. These results were also proved by the previous studies. There was significant reduction in the level of ESR[19-21]. These results also endorsed by a study conducted in Canada with comparison of 10mg and 60mg of pamidronate.

CONCLUSION:

This study has shown that pamidronate has excellent therapeutic effect in NSAIDS refractory AS patients .There was significant improvement in disease activity and functional ability as assessed by BASDAI and BASFI scores.No difference was found in clinical efficacy of two doses,30 mg and 60mg of pamidronate.

Therefore in early and active disease there is reason to offer IV pulse pamidronate in the absence of any other useful alternative in financially restricted population of Pakistan who are unable to afford anti TNF therapy.

This study is to be endorsed with further trials and give a better choice for the management of AS patients.

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Conflict of Interest: None declare

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