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Delayed diagnosis is linked to worse outcomes and unfavorable treatment responses in patients with ankylosing spondylitis

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ABSTRACT

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disease that affect the axial skeleton (spine and sacroiliac joints) , peripheral joints, enthesitis and specific organ involvement such as anterior uveitis, aortic valve disease. The hall mark of AS is inflammatory back pain associated with radiographic sacroiliitis and often spondylitis.

Objective: This study was conducted to evaluate the period from symptom onset to diagnosis of AS in Iraqi patients and the effect of delayed diagnosis on response to treatment.

Methods: A retrospective cohort study was conducted with a total of 108 consecutive patients with AS according to the modified New York criteria. Diagnostic delay was defined as the gap between the first spondylo-arthropathic symptom and diagnosis of AS, The patients, then, were classified into early and late diagnosis groups based on the median interval of the diagnostic delay, and a comparison was done between both groups for multiple parameters before and after 3 months of etanercept or infliximab therapy.

Results: Average of disease duration was 12.8 (range1-29). The average of age at disease onset was 25 years (range12-46) and average of age at time of diagnosis was 32.9 years (range15-54). The average of diagnostic delay was 6.9 years (range1-25) and the median was 7 years, on that basis our patients classified into early diagnosed group (<7years) and delay diagnosed group (≥7years). Mechanical back pain was the most common diagnosis prior to AS and patients without articular involvement experienced a significantly longer delay in diagnosis compared to patients with articular involvement (29.1%vs 54.7%,p=0.001).

At the time of diagnosis all parameters included in study were worse in late diagnosis group as compared with early diagnosis group, although none was statistically significant. After 3 months of treatment, BASDAI and BASFI score were significantly worse in delay diagnosis group (p=0.001).

Conclusion: Patients with delayed diagnoses showed worse outcomes in activity and function scores and less favorable treatment response.

Keywords: ankylosing spondylitis, BASFI, BASDAI

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting the axial skeleton, the entheses, and occasionally the peripheral joints. The hallmark of AS is inflammatory back pain associated with radiographic sacroiliitis and often spondylitis. In addition to the axial, entheseal, and appendicular skeletal involvement, AS can also be associated with extraarticular manifestations, especially uveitis and, less commonly, cardiac, pulmonary, and renal disease (1).

The AS is a disease of young adults (< 40 years of age) which is more frequently reported among Caucasian populations, its estimated prevalence is less than 0.5% in most population with a male to female ratio of approximately 3:1 (2). However in recent cohort studies this ratio has been found to be equally distributed between genders (3). AS occurs in all parts of the world, but there are race-related differences in prevalence. This might reflect differences in the distribution of HLA-B27 among races. Approximately 90% of white patients with AS possess HLA-B27, whereas AS and HLA-B27 are nearly absent (prevalence of HLAB27 <1%) in African blacks and Japanese (4). In Iraq the prevalence of AS is 0.07% of the population and HLA-B27 is positive in 2% of normal controls and in 84% of Iraqi AS patients (5).

The AS pathogenesis is not fully understood but it almost certainly immune mediated, tumor necrosis factor- α (TNFα) is a major inflammatory mediator of the disease, and the dramatic response to TNFα inhibitors indicates that it plays central role in the pathogenesis. CD4, CD8 T cells and macrophage in the inflamed sacroiliac joint shows high level of TNFα (6). The AS is dull chronic low back pain (lasting longer than 3 months), insidious in onset, usually in the buttocks (or hips, as interpreted by the patient). It is worse in the early part of the morning, when it is associated with morning stiffness lasting at least 30 minutes; is relieved with exercise or activity and/or a hot shower; is worsened by rest; and usually is improved by the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)(7).

Enthesitis is inflammation of the origin and insertion of ligaments, tendons, aponeuroses, and joint capsules. Inflammation may occur at any enthesis in AS, although it is most common in the entheses of the lower limbs, especially at the insertion of the Achilles tendon and the insertion of the plantar fascia onto the calcaneus (8).

The shoulders and hips are involved in up to 50% of patients with AS, and their involvement is more common than the involvement of the more distal joints. Peripheral arthritis in AS is usually an asymmetric oligoarthritis presenting predominantly in the lower extremities (9).

Current or history of anterior uveitis can be found in 30–40% of AS patients. Flares of uveitis are reported in 15–20% of AS patients per year. Uveitis is typically anterior, sudden in onset (painful red eye), acute, self-limiting, and unilateral but alternating from one eye to the other (10).

Diagnosis of AS must rest on the combination of clinical features, radiological findings, and laboratory results. There are no established diagnostic criteria for AS. On the other hand, classification criteria, used for the purpose of categorizing patients in research studies, are available. The most widely used classification criteria for AS are the modified New York criteria. Although the New York criteria are useful in established disease, their heavy reliance on the demonstration of radiographic sacroiliitis diminishes their applicability in patients with early disease (11).

Delayed diagnosis has been suggested as one of the several factors affecting the prognostic outcomes in AS. This is especially important since this disease has the longest diagnostic delay among other rheumatic diseases (12).

Recent studies showed that patients with shorter disease duration have better response to treatment compared with patients with longer disease duration (13). Therefore, early diagnosis and treatment before irreversible changes occur are crucial for managing patients with AS. However, the diagnosis of AS is typically delayed. An average diagnostic delay of 8–11 years has been reported by studies on ankylosing spondylitis (AS) (14-15). A number of factors potentially associated with the delayed diagnosis of AS have been reported, including female gender, absence of human leukocyte antigen (HLA)-B27, absence of a family history of AS among first-degree relatives, juvenile onset AS (onset age less than 17 years), presence of extra-articular disease and/or the absence of peripheral arthritis as an initial symptom (16-17). Improved knowledge about diagnostic delay status and associated factors in different regions of the world may help clinicians diagnose AS in earlier stages. Earlier diagnosis and efficient treatments with anti-tumor necrosis factor agents may prevent disabilities and improve the outcomes as well as decrease the government healthcare and nonhealthcare costs.

The aims of this study are find out the mean delayed time for diagnosis of ankylosing spondylitis among Iraqies and to evaluate the effect of delayed diagnosis

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on prognostic outcomes and Patients" response to treatment.

Methods

Patients

A retrospective cohort study was conducted at the Rheumatology Unit of Baghdad Teaching Hospital, a tertiary referral center in Iraq, during the period between October 2016 and May 2017. Data were collected using a pre-designed data collection form from face-to-face interviews, reviews of medical records and physician assessments of disease status.

A total of 108 consecutive patients diagnosed as having AS according to the modified New York criteria were included in the study. The patients who received Infliximab or etanercept for at least three months were included in this study, those who didn't receive treatment on schedule due to inavailability of the drug or absence of patient from attendance to take treatment, or incomplete data of their disease history and laboratory investigations were excluded from the study. The collected data included patient demographics and disease characteristics such as age and symptoms at disease onset, age at diagnosis of ankylosing spondylitis, the symptoms during the disease course ,the presence of family history or any history of smoking and the number of doctors each patient visited, as well as the alternative diagnoses before the diagnosis of ankylosing spondylitis was made.

Age at disease onset was defined as the date of the first appearance of AS-related symptoms. These symptoms included Inflammatory Back Pain (IBP) and peripheral symptoms as arthritis or enthesitis as well as uveitis. IBP was defined according to the ASAS criteria appendix (2). Diagnostic delay was defined as the duration (years) between symptom onset and time of diagnosis. Assessments of patients' disease status were made using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The Bath Ankylosing Spondylitis Functional Index (BASFI). Inflammatory markers such as serum C reactive protein (CRP) in mg/l, the erythrocyte sedimentation rate (ESR) in mm/h,were recorded. The patients then, were classified into early and late diagnosis groups based on the median interval of the diagnostic delay. We compared multiple clinical parameters between the early and late diagnosis groups.

To identify factors related to the delayed diagnosis of AS, comparisons between the groups were made for demographic and clinical variables including gender, family history of AS, history of arthritis and the educational levels. The patients, also, were categorized into two groups; the first group patients were already on treatment with biological agents and the second group patients received first dose and followed for 3 months of biological therapy. So all patients studied were on treatment for at least 3 months. A comparison then, was made between both groups to assess the outcome and response to treatment. Ten patients from the second group (received the first dose only) were excluded from comparison because they didn't accomplish the minimum 3 months therapy, but they were included in demographic data and delay diagnosis factor part of the study.

Ethical issue, approval and official permission:

Prior to data collection, a signed consent from each of the participants was obtained after explaining the purpose of the study and ensuring privacy of the data. The study protocol was reviewed; approval and official permission were obtained from the Ministry of Higher Education and Scientific Research, Baghdad University, College of Medicine to conduct the present study. At last ,although the ASAS criteria(appedix5) was modified for earlier diagnosis of axial spondyloarthropathy we chose the modified New York criteria for our patients selection; as our study was designed for only AS patients while the axial spondyloarthritis according to ASAS criteria involves psoriatic arthritis, reactive arthritis, enteropathic arthritis in addition to AS. However the modified New York criteria still used according to the last update of the ASAS-EULAR management recommendations for axial spondyloarthritis (18).

Statistical analysis

Demographic and clinical characteristics were analysed using descriptive statistics. A paired t test was performed to evaluate changes in clinical features before and after diagnosis. The patients were classified into two groups according to the median duration of the diagnostic delay. Univariate analyses were performed to compare demographic, clinical

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and biochemical variables between the early and late diagnosis groups. The comparisons were made using the $\chi 2$ test or Fisher's exact test for categorical variables and the independent student's t test for continuous variables. The entire analysis was performed using the Statistical Package for the Social Sciences for Windows version 21.0 (SPSS).Statistical significance was $p<0.05$.

Results

Patient demographics and disease characteristics

There was predominance of male (83.4%). The average of current age was 38.8 years (range16-63 years) , the average of disease duration was 12.8 years (range1-29 years). The average of age at disease onset was 25 years (range12-46 years) and average of age at time of diagnosis was 32.9 years (range15-54 years). All patients had history of Inflammatory Back Pain (IBP), (41%) of patients complained from history of arthritis, while the percentage of uveitis and enthesitis from history was(23%) , (37%) respectively. The average of delayed diagnosis was 6.9 years (range1-25 years) and the median was 7 years, on that basis our patients classified into early diagnosed group (<7 years) and delay diagnosed group (≥7years)(Table 1).

Alternative diagnosis before the definite diagnosis of AS

The number of physicians (NOP) were visited by patients before definitive diagnosis were made are shown in figure (1). Most patients visited five physicians for diagnosis (37.04%), followed by three physicians (24.07%). Mechanical back pain was the most common diagnosis prior to AS diagnosis (36%), followed by disc prolapsed (20%),osteoarthritis(11%). Nonspecific pain (patient didn't remember) (7%) and rheumatoid arthritis (6%). Twenty percent were diagnosed as AS and all of them were from the early diagnosed group (Fig. 2).

Factors related to the delayed diagnosis of AS

Comparisons of selected demographic and clinical variables were made between the early and late diagnosis groups to identify factors related to the delayed diagnosis of AS. Patients without articular involvement experienced a significantly longer delay in diagnosis compared to patients with articular involvement (29.1% late diagnosis group vs early diagnosis group 54.7%,p=0.001). The presence of family history of AS appeared to be associated with earlier diagnosis (early 9.2% vs late 4.6%) although these were not statistically significant (p=0.17).Other factors female gender, education level and smoking history were included in assessment but no significant differences were detected as shown in table (2).

Outcomes of delayed diagnosis in AS

The patients were classified into early and late diagnosis groups on the basis of median diagnostic delay of 7 years. The median of early diagnosis group was 2 years (range 1-6 years) while the median of late diagnosis group was 11 years (range 7-25 years). Compared a number of clinical parameters between the early and late diagnosis groups was performed as shown in table (3). At the time of diagnosis all parameters included in study were worse in late diagnosis group compared to the early diagnosis group, although none of the differences were statistically significant. After 3 months of treatment, BASDAI and BASFI scores were significantly worse in delayed diagnosis group compared to early diagnosis group. (p=0.01).

Patients in our study were also classified into two groups, the first group patients were already on treatment and the second group patient received first dose of biological therapy and followed after 3 months, both groups were assessed and compared before and after treatment and the results of both BASDAI and BASFI were significantly improved (p=0.001) after therapy as shown in figure3 (a and b). It is worth to mention that (25%) of patients in our study were used DMARDS, while(58,33%)were used NSAID.as shown in figure 4(a and b). Interestingly, patients knowledge of AS specific exercise and its performance were assessed; (56%) of patients don't know exactly what are AS specific exercises and only (33%) of patients claimed regular performance of these exercises.

Discussion

We noted in our study that delayed diagnosis among AS patients in Iraqi population was 6.9 years, and this come in accordance with what was reported in other studies which showed delayed in diagnosis of AS ranging from 6 to 10 years (19). In the past, delayed diagnosis of AS did not significantly impact

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disease outcome as there were no effective treatment options to prevent or delay the disease progression. Currently, however, TNF inhibitors demonstrate prompt and impressive effects on many aspects of AS, including pain, fatigue, spinal mobility, peripheral arthritis, and enthesitis which will effect the patients outcome if not started early (20).

Our study confirmed that the delayed diagnosis of AS was significantly linked to worse outcomes in disease activity, (BASDAI), function (BASFI) at the time of investigation in the late compared to those in the early diagnosis group (p =0.01); however this observation was not definite at the time of diagnosis, in addition the treatment response was less favorable among patients with delayed diagnosis than in those with early diagnosis, and this was similar to a study done in south Korea (21), which showed that AS patients with shorter disease duration are more likely to respond to anti- TNF agents than patients with long-standing disease. Also they reported that the patients with delayed diagnosis showed less favorable treatment responses according to the Bath Ankylosing Spondylitis Disease Activity Index and the rate of radiographic progression in a series of 105 patients.

In our study,(80%)of the patients with AS had prior diagnoses other than AS. Diseases with MBP (36%) were the most frequent, although all the patients involved in our study had IBP. The IBP is a primary symptom in most patients with AS and is relevant for its diagnosis (22). However, IBP is often ignored by doctors as well as patients because non-inflammatory MBP is common in the community and is typically benign (23).

Distinguishing IBP from MBP can be often difficult. Patients with IBP who developed AS, particularly those without any other peripheral or extra-articular manifestations, can be incorrectly diagnosed as having MBP (24). Marked variations in the clinical presentation of AS (16, 25) could be pointed out for the diagnostic delay. Some patients showed high disease activity with both spinal and peripheral joint involvements but others showed only mild symptoms. Garrett et al. (25) showed the widely distributed disease activity among the patients with AS and no correlation between the disease duration and its activity.

In this study, patients with articular involvement experienced a significantly shorter delay in diagnosis compared to patients without articular involvement (54.7%early vs. 29.1late, p=0.001), this finding was similar to study done in Japan (26), Authors found patients with articular involvement had a significantly shorter delay in diagnosis compared to patients without articular involvement (5.2 years vs. 8.9 years, p¼ 0.03). In other word, the diagnosis would be possibly delayed in patients with limited lesions to spine and sacroiliac joints.

Our results, also showed different clinical symptoms between the genders; women had peripheral arthropathies more often than did men.(female 45% vs male 40%).

However, the diagnostic delays did not differ statistically between genders (p=0.667), although delays were longer among women than among men (7.5 years vs. 6.8 years). Gender differences in clinical features might affect the timely diagnosis of AS. Roussou et al (16), reported that women with AS had greater delays in diagnosis and different presenting symptoms and main problems compared with men. Slobodin et al (17), reported that widespread pain was common in female patients with AS, and it nearly doubled the delay in the diagnosis.

A gender effect in delayed diagnosis was not evident in our study. Nevertheless, the possible longer delays in diagnosing AS in women should be taken into consideration. The delayed appearance of radiographic sacroiliitis must be one of the causes of delayed diagnosis of AS. It is suggested that the absence of radiographic changes should not be used to rule out the diagnosis of AS if the patient has inflammatory musculoskeletal pain (20). Moreover, radiographic sacroiliitis has been shown to have lower sensitivity and specificity compared to MRI (27). Currently, MRI is thought to be the most sensitive technique for detecting sacroiliitis and therefore new classification criteria by The Assessment of SpA International Society (ASAS) have used MRI for early diagnosis of SpA including AS (28).

The limitations of our study are attributable to its retrospective design in a single tertiary centre and the gathering of some data based on patient recall. Thus, there are the possibilities of selection and recall bias to consider when interpreting the data. There is a

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limitation in our study because it relied heavily on patients' memories to determine symptom onset and diagnosis time, although these were based on medical records as much as possible. One previous study reported that the majority of patients with AS remembered their ages at disease onset, although accuracy was unknown (29).

The cornerstone of nonpharmacologic treatment of patients with AS is patient education and regular exercises even Home exercises are effective. Physical therapy with supervised exercises, land or water based, individually or in a group, should be preferred as these are more effective than home exercises (30). Knowledge and regular exercise performance by Iraqi patients were low (performance was 33%) as compared in a study done in Korea (21)(performance was 60%) ,so patients education about exercise importance for their disease must be improved.

In conclusion; patients with delayed diagnoses of AS showed less favourable treatment response in terms of activity and function scores. Articular involvement may make the diagnosis of AS earlier.

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Table (1): Patients demographics and disease characteristics*

Demographics characterization	No.
Female	16.6 (n=18)
Current age (years)	38.8 (16-63)
Age at onset (years)	25 (12-46)
Age at diagnosis (years)	32.9 (15-54)
Disease duration (years)	12.8 (1-29)
Diagnosis delay (years)	6.9 (1-25)
History of	(%)
IBP	100%
Arthritis	41%
enthesitis	37%
Uveitis	23%

*value are expressed as mean (range), while Inflammatory back pain(IBP),arthritis uveitis, enthesitis are expressed as percentage(%).

Table (2): Factors related to the delayed diagnosis of AS *

Factors	Early	Delayed	P value
Female	7.4	9.2	0.667
Family Hx	9.2	4.6	0.17
Smoking Hx	25.9	29.6	0.219
Education	31.4	29.6	0.14
Arthritis	54.7	29.1	0.001

*The data are presented as % of the patients, statistically significant was $p<0.05$;

Family HX; Family history: Smoking HX; Smoking history

Table (3): Comparison of the outcomes between the early and late diagnosis groups in ankylosing spondylitis*

Factors	Early <7 years (n=53)	Late >_7 years (n=55)	P.value
BASDAI	5.77 (4.3-7.9)	6.2 (4.2-9)	0.83
BASFI	5.3 (2.2-7.5)	5.8 (2.1-9)	0.22
ESR(mm/h)	28.6 (2-105)	34 (1-105)	0.98
CRP(mg/l)	9.7 (3-33)	13.2 (2-48)	0.64
After 3 months of treatment			

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BASDAI	2.3 (1-4.2)	3.6 (0.9-6.5)	0.01
BASFI	2.1 (1-3.9)	4.3 (1.2-6.8)	0.01
ESR(mm/h)	12.9 (2-27)	13.6 (1-55)	0.49
CRP(mg/l)	4 (1-11.5)	6.2 (1-18.6)	0.45

*the data present the mean of compared parameters+(range) At the time of diagnosis and after 3 months of treatment BASDAI, Bath Ankylosing Spondylitis Disease Activity Index BASFI, Bath Ankylosing Spondylitis Functional Index ESR, Erythrocyte Sedimentation rate,and CRP,C reactive protein.

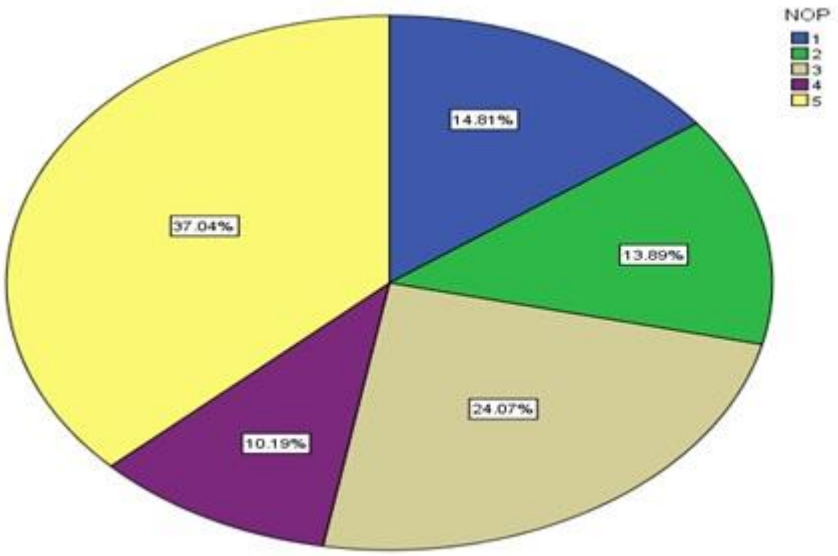

Figure (1): Number of Physicians (NOP) prior to diagnosis of AS(1to ≥5) in relation to percentage of patients visited the physicians.

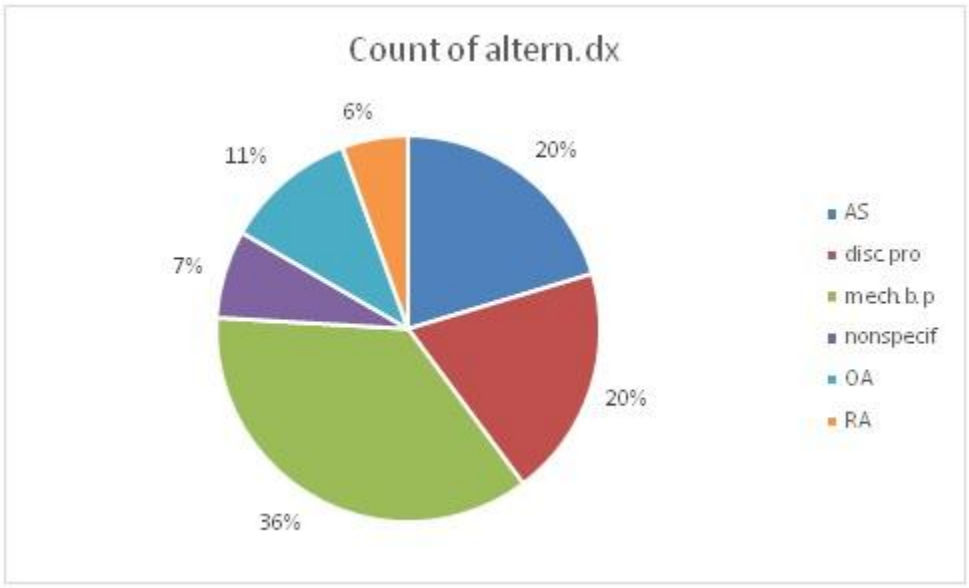

Figure (2): Count of alternative diagnosis with percentage, ankylosing spondylitis (AS), disc prolapse(disc.pro), Mechanical Back Pain (MBP), OsteoArthritis (OA),Rheumatoid Arthritis(RA) and non specific pain.

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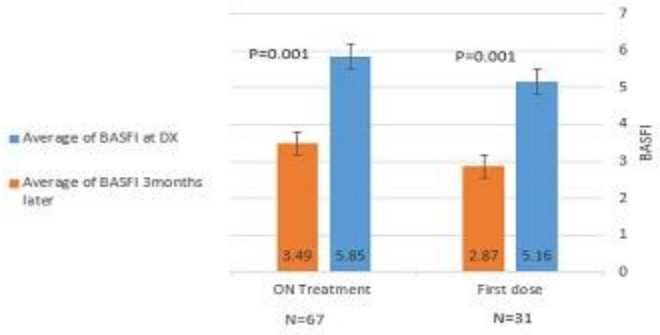

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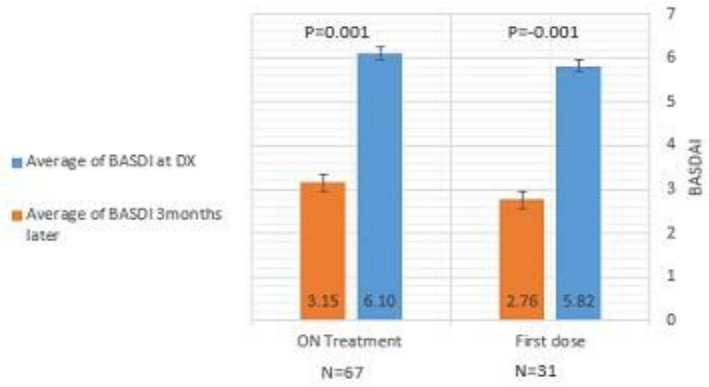

B

Figure (3): (a) BASDAI, (Bath Ankylosing Spondylitis Disease Activity Index) compared in between first group (on treatment) and second group(1st dose)(p=0.001): (b)BASFI,(Bath Ankylosing Spondylitis Disease Function Index) The 1st group (on treatment) compared to the 2nd group(1st dose)(p=0.001)

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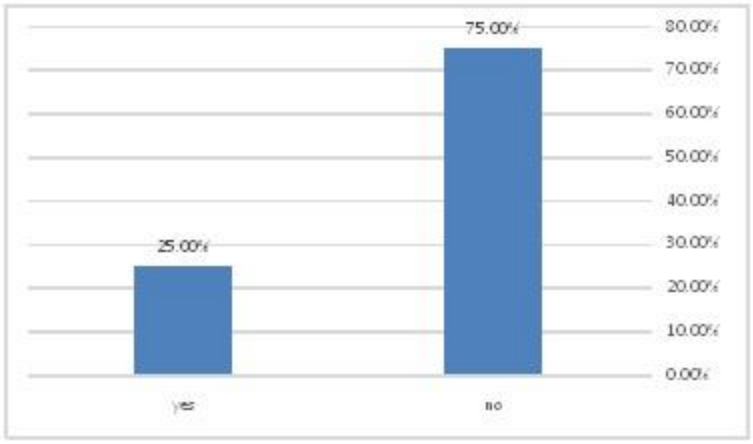
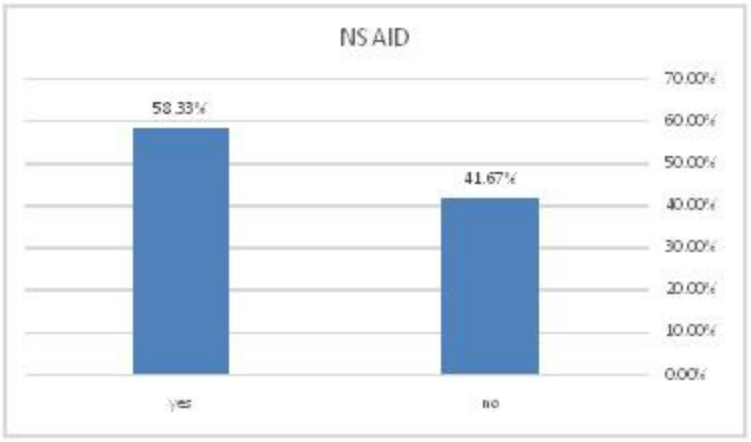


A



B

Figure (4): (a) percentage of patients used DMARD: (b) percentage of patients used NSAID

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