Journal of Medicine in Scientific Research

Volume 4 | Issue 3 Article 6

Subject Area: Rheumatology

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Recommended Citation

Abdelrahman, Sherry K. and M. Mostafa, Taghreed F. (2021) "Interrupted course of antitumor necrosis factor alpha therapy versus combined nonsteroidal anti-inflammatory drug therapy and physiotherapy in patients with ankylosing spondylitis: A comparative study," *Journal of Medicine in Scientific Research*: Vol. 4: Iss. 3, Article 6.
DOI: https://doi.org/10.4103/JMISR.JMISR_106_20

Interrupted course of antitumor necrosis factor alpha therapy versus combined nonsteroidal anti-inflammatory drug therapy and physiotherapy in patients with ankylosing spondylitis: A comparative study

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Abstract

Aim
The aim was to evaluate the efficacy of interrupted course of antitumor necrosis factor alpha (TNF-α) blocking agents (etanercept and adalimumab) as 3-month-on-and-3-month-off regimen versus combined regimen of physiotherapy and NSAIDs in patients with ankylosing spondylitis (AS) within a 2-year period.

Patients and methods
A total of 60 patients who fulfilled the Modified New York Criteria for AS were enrolled in the current study and divided into two equal groups: one received interrupted course of anti-TNFα agents and one received NSAIDs plus physiotherapy. Both groups were subjected to follow-ups at 6, 12, 18, and 24 months. To assess the response, Ankylosing Spondylitis Disease Activity Scores (ASDAS-ESR and ASDAS-CRP) were used, in addition to Bath Ankylosing Spondylitis Disease Activity Index (BASDI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath AS Metrology Index (BASMI). Modified stock Ankylosing Spondylitis Spine Score (M-SASSS) was used to assess the radiological progression.

Results
The authors found significantly higher improvement in the patient group treated by intermittent course of anti-TNFα agents relative to the other group regarding inflammatory markers, disease activity, and functional index during follow-up. Although there was a significant radiographic progression regarding M-SASSS values in anti-TNFα therapy patients, these values were lower than NSAID patient group.

Conclusion
Patients with AS can follow regular intermittent course (3 months on and 3 months off) of anti-TNFα blocking agents such as etanercept and adalimumab with possible efficacy and safety. This regimen was found to be successful in improving disease activity and functional impairment in those patients when compared with patients maintained on NSAIDs and physiotherapy.

Keywords: Ankylosing spondylitis, antitumor necrosis factor alpha agents, interrupted course

Introduction

Ankylosing spondylitis (AS) is one of closely related group of rheumatic diseases termed spondyloarthropathies, which are associated with significant disability and increased socioeconomic costs [1].

The primary pathology includes enthesopathy and inflammation of the region of the bony attachment of tendons, ligaments, or

Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/JMISR.JMISR_106_20

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Submitted: 06-Oct-2020 **Revised:** 13-Oct-2020 **Accepted:** 02-Jun-2021 **Published:** 17-Sep-2021

How to cite this article: Abdelrahman SK, MostafaTF. Interrupted course of antitumor necrosis factor alpha therapy versus combined nonsteroidal anti-inflammatory drug therapy and physiotherapy in patients with ankylosing spondylitis: A comparative study. J Med Sci Res 2021;4:210-6.

joint capsules. Typically, this occurs in the spines; if unchecked, exuberant new bone formation may result in ankylosis, or spinal fusion [2].

The disease starts early in life; therefore, the lifetime individual effect of AS can be high [3].

Different treatment strategies were used to deal with patients with predominant axial disease, including full doses of NSAIDs coupled by physiotherapy aiming to improve spinal mobility and functional disability. However, the new era of antitumor necrosis factor (TNF) blocking therapy making dependence on the usual treatment is questionable [4].

Despite the great success of anti-TNFα agents in improving the outcome of AS, long-term effects of maintenance regimen of these agents needed to be further reviewed regarding adverse effects and economic issues.

More recently, dose reduction and spacing strategies were tried in some works for achieving the lowest doses maintaining the remission [5–7]

However, what about patients who cannot follow continuous course of these agents for a long period of time even with lower doses, like patients who are not covered by medical insurance or patients experiencing severe side effects, for those patients, another regimen could be tried.

So, the aim of this work was to evaluate the efficacy of interrupted course of anti-TNFα blocking agents (etanercept and adalimumab) as 3-month-on and 3-month-off versus combined regimen of physiotherapy and NSAIDs in patients with AS within a 2-year period.

Patients and methods

A total of 60 patients who fulfilled the Modified New York Criteria for AS[8] were enrolled in this longitudinal observational study. The study started from January 2016 till June 2018. Recruitment of all cases started within the first 6 months. All patients were not covered by medical insurance. A written and verbal consent was taken from them before the beginning of the study according to the Helsinki Declaration[9] and after approval from Institutional Ethics Committee. They were assigned to following assessment: Bath Ankylosing Spondylitis Disease Activity Index (BASDI) [10], Bath Ankylosing Spondylitis Functional Index (BASFI) [11], Bath AS Metrology Index (BASMI) [12], and Ankylosing Spondylitis Disease Activity Scores (ASDAS-ESR and ASDAS-CRP)[13]

Radiographies of spines were done for all patients to obtain the Modified stock Ankylosing Spondylitis Spine Score (M-SASSS)[14]

All patients who had predominant axial manifestations, persistent high disease activity, BASDI greater than or equal to 4 plus high ESR/positive CRP, and positive MRI/radiogrraphy for sacroiliitis (during the past 3 months) were subjected to two treatment courses: the first group of patients (30 patients) who could not afford the standard course of anti-TNF blocking agents were treated with interrupted course of anti-TNFα therapy (15 patients treated by etanercept and 15 patients treated by adalimumab) as 3-month-on-and-3-month-off regimen for 2 years. The other group of patients (30 patients) who were unable to continue this biological treatment (due economic causes or due to side effects) were maintained on conventional therapy of full doses of NSAIDs, physiotherapy (in the form of range of motion and stretching exercises of spines, hips, knees, and shoulders), and hydrotherapy three times per week. The patients treated by interrupted course of anti-TNFα therapy were subjected to the same conventional treatment during drug-off period.

Both groups (group of interrupted course of anti-TNF therapy and who were maintained on NSAIDs) were subjected to a follow-up every 3 months. In addition to baseline assessment of BASDI, BASFI, BASMI, ASDAS-ESR, and ASDAS-CRP, the aforementioned data were also documented at 6, 12, 18, and 24 months of treatment. Modified stock Ankylosing Spondylitis Spine Score (M-SASSS) was used to assess the radiological progression during the same follow-up period.

The following patients were excluded: patients younger than 18 year; pregnant and lactating women; and patients with predominantly peripheral arthritis, inflammatory bowel disease, uveitis, other autoimmune diseases, fibromyalgia, acute or chronic infectious diseases, including viral hepatitis and tuberculosis, in addition to malignant diseases. Patients who showed exacerbation of disease activity at any time during the study were also excluded.

Statistical analysis

The collected data were tabulated and analyzed using SPSS version 20 software (SPSS Inc., Chicago, Illinois, USA). Categorical data were presented as number and percentages. χ^2 test was used to analyze them. Quantitative data were analyzed for normality using Shapiro–Wilks test, assuming normality at expande P value more than 0.05. Quantitative data were expressed as mean and SD, and t-test was used for assessment if normally distributed, whereas they were expressed as median and interquartile range if not normally distributed. Mann–Whitney U test (ZMWU) was used to analyze not normally distributed variables among oktwo independent groups. Matched variables were analyzed by Friedman's test. $P \leq 0.05$ was considered significant.

Results

This study was performed on 60 male patients with AS, and their ages ranged from 20 to 45 years. Among the 60 patients involved in the study, 55 (91.7%) patients were positive for HLAB27 testing, whereas only 5 (8.3%) patients showed negative tests. The patients were divided into two groups, and by comparing them regarding HLAB27 positivity, no significant difference was described ($\chi^2 = 1.96$, $P = 0.16$).

Regarding disease duration of the patients, the first group that received interrupted course of anti-TNF drugs showed

disease duration ranged from 4 to 7 years, with a mean ± SD of 4.67 ± 1.269 years, whereas in the second group that underwent usual treatment, the mean disease duration was 4.87 + 1.167 years, with no significant difference detected (t = 0.64, *P* = 0.53).

By comparison of the study groups regarding the baseline clinical, laboratory, and radiographic characteristics, including, CRP, BASDI, BASFI, (M-SASSS), BASMI, ASDAS-ESR, and ASDAS-CRP, we reported insignificant results (P > 0.05) (Tables 1–6).

During the follow-up period, the patients who underwent interrupted course of anti-TNF therapy showed significant lower values of CRP when compared with the other group (P < 0.001) [Table 1].

Related to disease activity, both patient groups were compared regarding BASDI during follow-up; there were significant differences between them recorded at 12 months (P = 0.008), as well as during the second year of follow up (P < 0.001), with the lower values being in a anti-TNF therapy group [Table 2]. Similar results were reported regarding ASDAS-ESR and ASDAS-CRP (P < 0.001) [Table 3].

Regarding BASMI during periods of follow-up, a highly significantly higher number of patients showed improvement in spinal mobility in the group treated by anti-TNFα than the other group beginning at the end of the first year and throughout 18 months, and at the end of the second year, a higher number of patients showed grade 0 of BASMI [29 (96.7%) vs. 2 (6.7%), *P* = 0.002] [Table 4].

Radiologically, the patients treated by interrupted course of anti-TNF therapy showed lower grades of M-SASSS when compared with the other group of patients at 12 months (P = 0.025), at 18 months (P = 0.014), and at 24 months (P = 0.001) [Table 5].

The current study also showed better functional scores measured by BASFI in patients treated with anti-TNFα course when compared with patients treated by NSAIDs at the end of 18 and 24 months (P < 0.001) [Table 6].

Table 1: Comparison of CRP value (mg/l) between the study groups during the follow-up period

	Group	*n*	Median	IQR	Z_{MWU}	*P*
Baseline	AS (antiTNF	30	14.54	12.4-16.6	0.68	0.49 NS
	AS (NSAIDs	30	14.47	12.4-15.6		
At 6 m	AS (antiTNF	30	9.47	8.5-10.5	6.2	<0.001**
	AS (NSAIDs	30	14.4	10.7-16.5		
At 12 m	AS (antiTNF	30	7.14	6.4-7.5	5.83	<0.001**
	AS (NSAIDs	30	14.5	10.5-18.1		
At18m	AS (antiTNF	30	7.33	6.5-8.3	6.65	<0.001**
	AS (NSAIDs	30	16.4	14.5-18.5		
At 24 m	AS (antiTNF	30	7.11	6.4-8.1	6.66	<0.001**
	AS (NSAIDs	30	16.2	14.1-18.1		

IQR, interquartile range; Z_{MWU}, *Z* value of Mann-Whitney U test.
**Highly significant.

Within the anti-TNFα therapy group, the patients showed highly significant improvement in the most studied variables throughout the study (P < 0.001) (Table 7). Although there was a significant radiographic progression regarding M-SASSS values in anti-TNFα therapy patients [Table 7], these values were lower than NSAID patient group [Table 5].

Within both groups, no patients were excluded from the study because of acute exacerbation of the disease.

Discussion

AS is a chronic inflammatory disorder that affects mainly sacroiliac joint and spines and ends finally in impairment of spinal mobility and significant functional deficit[15]

TNFα is the main cytokine found in the joints of patients with AS, and it has been suggested to be involved in the pathogenesis of a wide range of inflammatory diseases, such as rheumatoid arthritis (RA) and other types of spondyloarthropathy [15]. So, this study aimed to evaluate the effectiveness of interrupted course of anti-TNF (etanercept and adalimumab) in patients with AS versus patients treated by conventional strategies in the form of NSAIDs and physiotherapy.

In this work, we found highly significantly better values in most of the study parameters in patients on intermittent course of anti-TNFα agents when compared with patients remained on conventional course during the study.

These results are opposite to the concepts that the interrupted treatment with anti-TNFα may be associated with either loss of efficacy or development of hypersensitivity reactions leading to discontinuation.

In a study conducted by Esposito *et al*. [16], no differences were found in safety between the continuous and intermittent regimens of adalimumab, but decrease in response with withdrawal associated with development of autoantibodies

Several studies were reviewed regarding this issue taking into consideration safety and efficacy of different anti–TNFα agents, mostly infliximab in different diseases.

Laharie *et al*.[17] assessed the efficacy of retreatment with infliximab in 61 patients with Crohn's disease after 38 weeks following an induction regimen; during this interval, the patients were maintained on immunomodulatory drugs. Efficacy was achieved in most of the patients. However, 12 patients exhibited no clinical benefit: seven of them showed acute hypersensitivity reactions and five showed loss of response. They concluded that retreatment with infliximab in Crohn's disease in patients who responded primarily to an induction regimen has good efficacy and is well-tolerated when performed within the first 50 weeks. If performed later, it is associated with intolerance and lack of response. This reinforced our results in the current study, in which intermittent dosing regimen gave clinical responses in patients receiving conventional treatment as maintenance, suggesting possible drug holiday; however, shorter bridge (3 months)

Table 2: Comparison of BASDI between both groups during follow-up periods

	Group	*n*	Median	IQR	Z_{MWU}	*P*
BASDI/baseline	AS (antiTNF	30	6.4	5.5-7.3	0.68	0.49
	AS (NSAID)	30	6.4	5.4-7.3		NS
BASDI/6 m	AS (antiTNF	30	4.4	3.5-5.5	1.07	0.28
	AS (NSAIDs)	30	4.7	3.5-5.5		NS
BASDI/12 m	AS (antiTNF)	30	3.0	2.5-3.1	2.66	0.008*
	AS (NSAIDs)	30	3.5	3-3.9		
BASDI/18 m	AS (antiTNF	30	2.8	2.3-3.9	3.58	<0.001**
	AS (NSAIDs)	30	3.9	3.5-4.1		
BASDI/24 m	AS (antiTNF	30	2.4	1.6-2.5	6.29	<0.001**
	AS (NSAIDs)	30	4.1	3.5-4.5		

BASDI, Bath Ankylosing Spondylitis Disease Activity Index. *Significant. **Highly significant.

Table 3: Comparison of ASDAS-ESR and ASDAS-CRP between both study groups during follow-up periods

Variables	Group	*n*	Median	IQR	Z_{MWU}	*P*
DAS ESR/baseline	AS (antiTNF)	30	2.48	2.47-3.44	0.98	0.32 NS
	AS (NSAIDs)	30	2.49	2.48-3.41		
DAS ESR/6 m	AS (antiTNF)	30	2.13	1.49-2.47	4.14	<0.001**
	AS (NSAIDs)	30	2.9	2.57-3.0		
DAS ESR/12 m	AS (antiTNF)	30	1.25	1.11-1.47	4.2	<0.001**
	AS (NSAIDs)	30	2.25	1.44-2.55		
DAS ESR/18 m	AS (antiTNF)	30	1.32	1.11-1.5	4.35	<0.001**
	AS (NSAIDs)	30	2.3	1.5-3.33		
DAS ESR/24 m	AS (antiTNF)	30	1.12	1-1.22	4.51	<0.001**
	AS (NSAIDs)	30	2.25	1.19-3.14		
DAS CRP/baseline	AS (antiTNF)	30	2.97	2.67-3.32	1.55	0.25 (NS)
	AS (NSAIDs)	30	2.8	2.64-3.32		
DAS CRP/6 m	AS (antiTNF)	30	1.96	1.92-2.63	5.06	<0.001**
	AS (NSAIDs)	30	3.0	2.63-3.2		
DAS CRP/12 m	AS (antiTNF)	30	1.36	1.28-1.44	5.87	<0.001**
	AS (NSAIDs)	30	2.36	2.28-2.44		
DAS CRP/18 m	AS (antiTNF)	30	1.36	1.28-1.44	6.74	<0.001**
	AS (NSAIDs)	30	2.93	2.5-3.0		
DAS CRP/24 m	AS (antiTNF)	30	1.25	1.18-1.32	6.75	<0.001**
	AS (NSAIDs)	30	2.8	2.5-3.1		

ASDAS, Ankylosing Spondylitis Disease Activity Score. **Highly significant.

and different drugs were used in the current work (etanercept and adalimumab).

Similarly, Lee *et al*.[18] reported that retreatment with infliximab after a 'drug holiday' of at least 1 year was found to be successful whether the patients had initial response to infliximab or not. The main limiting factor was the development of infusion reactions owing to development of anti-infliximab antibodies. Conversely, the titers of antibodies to infliximab were found to decline to undetectable levels within 1 year after cessation of infliximab in most patients in a study conducted by Ben-Horin *et al*.[19]

The benefit of induction with infliximab followed by maintenance with immunomodulating agents such as azathioprine had been reviewed in two controlled studies in patients with Crohn's disease. The authors found that an induction regimen with the three infliximab infusions showed clinical remission and steroid sparing in 64 and 83% of patients, respectively, and patients with azathioprine remained on clinical remission without steroid use at the end the first year [20,21].

ECCO (European Crohn's and Colitis Organisation) group recommended the regimen of infliximab induction that was followed by azathioprine or methotrexate maintenance strategy alternative to infliximab alone. However, the researchers did not demonstrate long-term effects of this regimen [22]. However, other studies reported that the proportion of responders to this strategy decreases with time, and additional infliximab infusions may be considered [23].

The previous reports showed that discontinuation and drug readministration of anti-TNFα blocking agents such as infliximab, in different diseases, is associated with established remission and absence of intolerance. These supported

the concept of the current study, in which intermittent usage (3 months on and 3 months off) regimen were tried with other anti-TNFα blocking agents.

Regarding adalimumab, Tanaka *et al*.[24] investigated the possibility of discontinuation of adalimumab (ADA) for 1 year and elucidated possible factors enabling patients with RA to remain ADA free. Patients with RA who were treated by ADA and exhibited deep remission were subjected to evaluation for 1 year to investigate the concept of a 'biologic treatment holiday.' The researchers found that ADA can be withdrawn without flare in 79% of patients who showed deep remission, with similar results in the ADA continuation group, and those patients with DAS28-ESR ok less than 3.2 showed no functional impairment or structural progression. The authors stated that retreatment with ADA for patients with flare during ADA discontinuation was effective and safe. The study confirmed that 'adalimumab treatment holiday' can be applied to patients with RA with long-term remission, deep remission, and in patients without needs to steroid therapy [24].

This finding was also supported by the results of another study in Japanese patients treated with ADA. Of the 52 patients who agreed to discontinue ADA, 22 showed remission for 1 year [25].

Regarding axial spondyloarthropathy, etanercept treatment was tried in several studies in patients with active disease, and after achieving disease remission or low disease activity, the treatment was withdrawn, and the patients underwent long-term follow-up for 1 year. Brandt *et al*.[26] reported that disease relapse occurred after 36 weeks in 100% of patients, whereas in another study, 70% of patients showed disease relapse after 52 weeks [27], and this is different from shorter interval (12 weeks) of drug discontinuation in the current work.

Table 4: Comparison of BASMI between both study groups during follow-up periods

Time	Groups, *n* (%)			χ^2	*P*
	BASMI grades	Anti-TNF	NSAIDs		
At base line	1	6 (20)	6 (20)		1.0 (NS)
	2	24 (80)	24 (80)	0	
At 6 months	1	24 (80)	18 (60)		
	2	6 (20)	12 (40)	0.86	0.09 (NS)
At 12 months	0	4 (13.3)	0		
	1	24 (80)	18 (60)	12	0.002*
	2	2 (6.7)	12 (40)		
At 18 months	0	28 (93.3)	2 (6.7)		
	1	2 (6.7)	24 (80)	45.15	0.002*
	2	0	4 (13.3)		
At 24 months	0	29 (96.7)	2 (6.7)		
	1	1 (3.3)	23 (76.7)	45.16	0.002*
	2	0	5 (16.7)		

BASMI, Bath Ankylosing Spondylitis Metrology Index. *Significant.

Table 5: Comparison of M-SASSS between both study groups during follow-up periods

	Group	*n*	Median	IQR	ZMWU	*P*
(M-SASSS) baseline	AS (antiTNF)	30	4.5	2-7	1.51	0.13 (NS)
	AS (NSAIDs	30	5.5	0-7		
(M-SASSS)/6 m	AS (antiTNF)	30	4.5	2-7	1.51	0.13 (NS)
	AS (NSAIDs	30	5.5	0-7		
(M-SASSS)/12 m	AS (antiTNF)	30	6	2-8	2.25	0.025*
	AS (NSAIDs	30	7.5	4-10		
(M-SASSS)/18 m	AS (antiTNF)	30	7	2-8	2.43	0.014*
	AS (NSAIDs	30	8	4-10		
(M-SASSS)/24 m	AS (antiTNF	30	7.5	2-9	3.4	=0.001**
	AS (NSAIDs	30	9	6-10		

M-SASSS, modified Stoke Ankylosing Spondylitis Spinal Score. *Significant. **Highly significant.

Table 6: Comparison of BASFI between both study groups during follow-up periods

	Group	*n*	Median	IQR	ZMWU	*P*
BASFI/baseline	AS (antiTNF)	30	6.7	5.8-7.7	0.91	0.36
	AS (NSAIDs	30	6.7	5.9-7.7		NS
BASFI/6 m	AS (antiTNF)	30	5.2	4.2-5.9	0.36	0.71
	AS (NSAIDs)	30	5.0	4.2-5.9		NS
BASFI/12 m	AS (antiTNF)	30	3.7	2.8-4.5	1.46	0.14
	AS (NSAIDs)	30	3.7	2.7-4.5		NS
BASFI/18 m	AS (antiTNF)	30	3.7	2.8-4.5	5.91	<0.001**
	AS (NSAIDs)	30	4.7	4.5-4.8		
BASFI/24 m	AS (anti-TNF	30	3.2	2.4-3.9	5.68	<0.001**
	AS (NSAIDs	30	4.9	4.2-5.2		

BASFI, Bath Ankylosing Spondylitis Functional Index. **Highly significant.

Table 7: Comparison of CRP, BASDI, ASDAS-ESR, ASDAS-CRP (M-SASSS), and BASFI within anti-TNFα drug group at baseline, 6, 12, 18, and 24 months

Items	No	Friedman' test	*P*
CRP	30	92.6	<0.001(HS)
BASDI	30	91.7	<0.001(HS)
ASDAS-ESR	30	92.6	<0.001(HS)
ASDAS-CRP	30	118.4	<0.001(HS)
M-SASSS	30	64.3	<0.001(HS)
BASFI	30	117.1	<0.001(HS)

ASDAS, Ankylosing Spondylitis Disease Activity Score BASDI:Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; HS, highly significant; M-SASSS, Modified stock Ankylosing Spondylitis Spine Score; TNF, tumor necrosis factor.

Another work concluded that etanercept readministration after a period of withdrawal is effective and safe in patients with AS; in this work, about 88% of the participants completed the study and remained on etanercept. Most of them showed improvement of disease activity and partial remission with only one patient discontinued the drug owing to serious adverse effects [28].

These data reinforced the results of our study, as none of patients showed serious drawbacks or lack of response, suggesting effectiveness of our regimen.

Different explanations were supposed to clarify the reasons behind clinical remission observed in patients with subtherapeutic doses of anti-TNFα blockers with low or undetectable drug level. First, lower level of the drug needed for remission or remission became not reliant on those agents, and these data were detected in two studies performed on patients with IBD [29,30]

However, certain predictors should be taken into consideration for maintaining long-term disease remission following the drug holiday including deep remission parameters rather than low disease activity as well as normal inflammatory markers, so the decision to apply a 'drug holiday' must be strictly evaluated and individualized [31].

More recently, in one study, different tapering regimens were reviewed in patients with axial spondyloarthropathies who achieved remission after etanercept therapy for 6 months. The tapering schedule was followed by increasing the drug injection interval by 25 or 50% every 3 months for 2 years, and those patients showed longer periods of remission than patients within the discontinuation group [5]. Similar results with other anti-TNFα blockers were reported by Gratacós *et al*. [7]. However, this regimen may be problematic for patients experiencing adverse effects or cannot afford the drug, so interrupted regimen may be more reasonable for those patients.

Finally, for safety and economic issues, modification of dosing strategies of anti-TNFα agents should be tried, and this can be accomplished by either by lowering the dose of these drugs or by stoppage–retreatment of them following the intermittent noncontinuous treatment courses. Patients on the intermittent strategy should be treated periodically (regular on and off courses) rather than episodically (when needed). It must be emphasized that carful close monitoring of the patients is needed so as to avoid disease reactivation by early re-introduction of these drugs for achieving remission in those patients on intermittent course [32].

Despite the encouraging results of the current study, it was limited by available small sample size, and to put those results as a recommendation, it needs a larger sample size and longer periods of follow-up.

We concluded that patients with AS can follow regular intermittent course (3 months on and 3 months off) of anti-TNFα blocking agents such as etanercept and adalimumab with possible efficacy and safety. This regimen was found to be successful in improving disease activity and functional impairment in those patients when compared with patients maintained on NSAIDs and physiotherapy. This treatment course is conceivable owing to cost-effective implications. This treatment strategy can be considered as an economic course, in addition to decreasing the risk of adverse effects, including infections and malignancy. However, this cannot be considered as a recommendation on the basis of the present data in this study owing to small sample size. Further larger works are needed to clarify this issue.

Conflicts of interest

There are no conflicts of interest.

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