Efficacy and Safety of Tofacitinib in the Treatment of NSAIDs Refractory Axial Spondyloarthritis: A Clinical Trial

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Disclosure

Tofacitinib was supplied by:

Globe pharmaceuticals Ltd, Dhaka, Bangladesh

Background

Axial Spondyloarthritis (Axial SpA):

- A chronic inflammatory arthritis
- Involves Spine and sacroiliac joints
- First line treatment: Education, exercise and NSAIDs
- If a patient does not respond to sequential two NSAIDs for at least four wks, then it is called NSAID refractory axial SpA
- ASAS recommends anti TNF (Biologic DMARD) as a treatment option for NSAIDs refractory Ax SpA

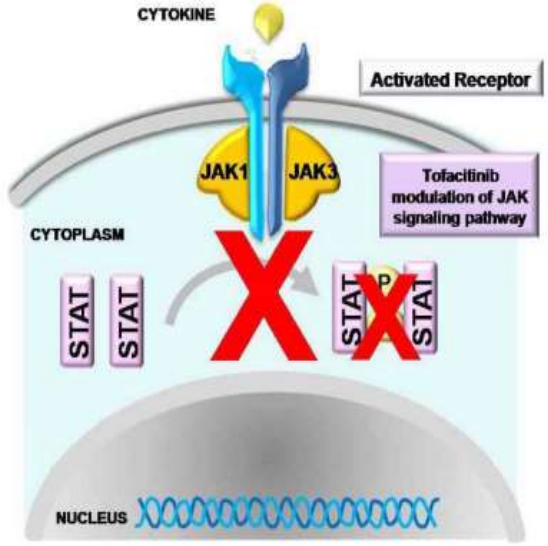
ASAS (Assessment of SpondyloArthritis International Society)

Rationale

- A phase II RCT showed that Tofacitinib is effective in the treament of NSAIDs refractory axial SpA
- Tofacitinib is a cost effective as compared to anti TNF
- It may bring an opportunity to use this agent in axial SpA patients of Bangladesh

Tofacitinib

- It is a targeted synthetic DMARD
- Inhibits JAK-STAT pathway
- ↓ Cytokines (IL-17, 21, 23 and IFN-γ) involved in RA and SpA



JAK=Janus kinase; P=phosphate; STAT=signal transducer and activator of transcription.

- Tofacitinib binds in the catalytic cleft in the kinase domain of JAKs
- Tofacitinib modulates the JAK signaling pathways at the point of JAK, preventing the phosphorylation and activation of signal transducer and activators of transcription (STAT).
- Inhibition of JAK1/JAK3 is expected to block signaling through the common γc -containing cytokine receptors, including those for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; these cytokines are integral to lymphocyte activation, proliferation and function and may thus result in modulation of multiple aspects of the immune response.
- In addition, inhibition of JAK1 may lead to some modulation of additional cytokine receptor signaling, including IFN-α, IFN-β and IL-6

Research Question

Is Tofacitinib safe and effective in the treatment of NSAIDs refractory axial spondyloarthritis ?

Primary Objective

Assessment of the efficacy and safety of tofacitinib in the treatment of NSAIDs refractory axial SpA

Secondary Objectives

- To assess the efficacy of 10 mg and 20 mg tofacitinib in the treatment of NSAIDs refractory axial SpA
- To assess the safety of 10 mg and 20 mg tofacitinib in the treatment of NSAIDs refractory axial SpA

Materials and Methods

- **Study design:** Prospective, open label, interventional study
- **Study place:** Department of Rheumatology, BSMMU
- **Study period:** September, 2017 to February, 2019
- **Sampling:** Samples were taken consecutively

Inclusion criteria

1. Age ≥ 18 yrs
2. Diagnosed axial SpA on the basis of ASAS criteria
3. Failure of response to at least 2 NSAIDs with optimum doses each for at least 2 weeks
4. BASDAI ≥4 and/or ASDAS-CRP>2.1

Exclusion criteria

1. Systemic infections requiring hospital admission during the last 6 months

2. Active infections and/or a history of chronic or recurrent serious infective diseases, opportunistic infections

3. Hb < 9 g/dl, WBC count < 4000/mm3, Neutrophil< 1000/mm3,
Platelet count < 1,00,000/mm3

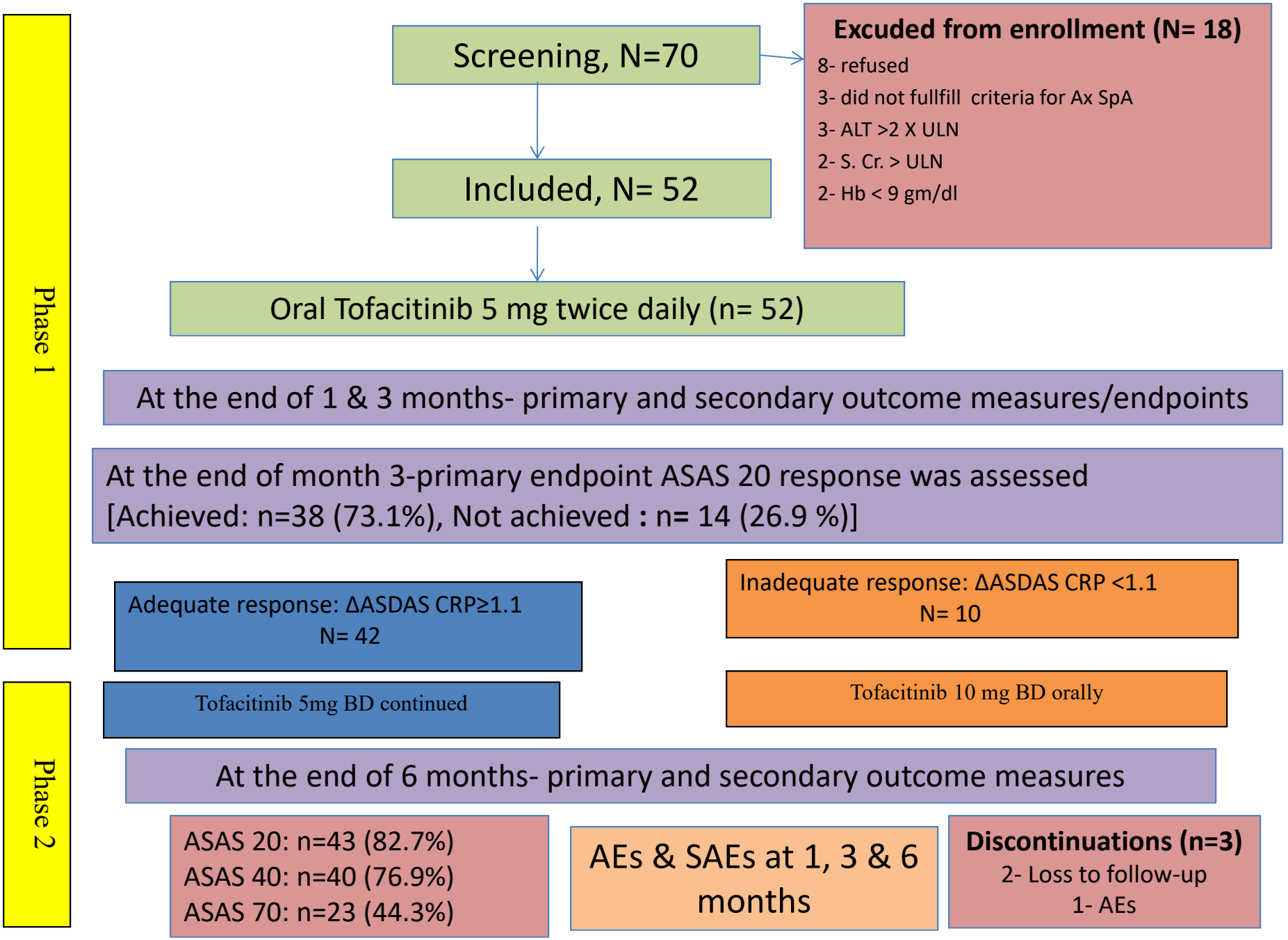
4. Live vaccines within 3 months prior to the first dose

5. S. Cr > ULN or GFR < 50 mL/min

6. ALT > 2 times of ULN

7. Who refused to participate

Study procedure


Phase 1
Screening, N=70
Excuded from enrollment (N= 18)
8- refused
3- did not fullfill criteria for Ax SpA
3- ALT >2 X ULN
2- S. Cr. > ULN
2- Hb < 9 gm/dl
Included, N= 52
Oral Tofacitinib 5 mg twice daily (n= 52)
At the end of 1 & 3 months- primary and secondary outcome measures/endpoints
At the end of month 3-primary endpoint ASAS 20 response was assessed
[Achieved: n=38 (73.1%), Not achieved : n= 14 (26.9 %)]
Adequate response: ΔASDAS CRP≥1.1
N= 42
Inadequate response: ΔASDAS CRP <1.1
N= 10
Tofacitinib 5mg BD continued
Tofacitinib 10 mg BD orally
Phase 2
At the end of 6 months- primary and secondary outcome measures
ASAS 20: n=43 (82.7%)
ASAS 40: n=40 (76.9%)
ASAS 70: n=23 (44.3%)
AEs & SAEs at 1, 3 & 6 months
Discontinuations (n=3)
2- Loss to follow-up
1- AEs

The ASAS Response Criteria

- Developed in 2001
- ASAS 20 is defined as an improvement of at least 20% and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains:
  - Patient global assessment
  - Pain assessment
  - Function (BASFI) and
  - Inflammation (last 2 questions of BASDAI)
- ASAS 40 and 70 are defined as above with improvements of at least 40% and 70% respectively

Results

Baseline demographic characteristics

Demographic characteristics	Mean± SD (n, %))
Age (yrs)	32.94 ± 9.19
Gender	Male (n =41, 78.8%),
	Female (n=11, 21.2%)
BMI (kg/m2)	21.87 ± 2.37
Tobacco use (smoking or chewable)	n=8, 15.4%
Disease duration in years	2.98±1.66
Monthly family income (Taka)	21472 ±42000

SD= Standard deviations, n= Number of patients, %= Percentages of patients

Baseline clinical and laboratory characteristics (n=52)

Characteristics	Mean± SD
BASDAI	5.00± 1.07
BASFI	5.70± 1.26
MASES	1.86± 1.60
ASDAS ESR	4.39± 0.82
ASDAS CRP	4.04± 0.85
ESR	71.27± 35.82
CRP	45.21± 44.85

SD= Standard deviations, n= Number of patients, BASDAI= Bath ankylosing spondylitis disease activity index, BASFI= Bath ankylosing spondylitis functional index, MASES= Maastricht's ankylosing spondylitis enthesitis index, ASDAS= Ankylosing spondylitis disease activity score,ESR= Erythrocyte sedimentation rate, CRP= C- reactive protein

Composite measures and MASES

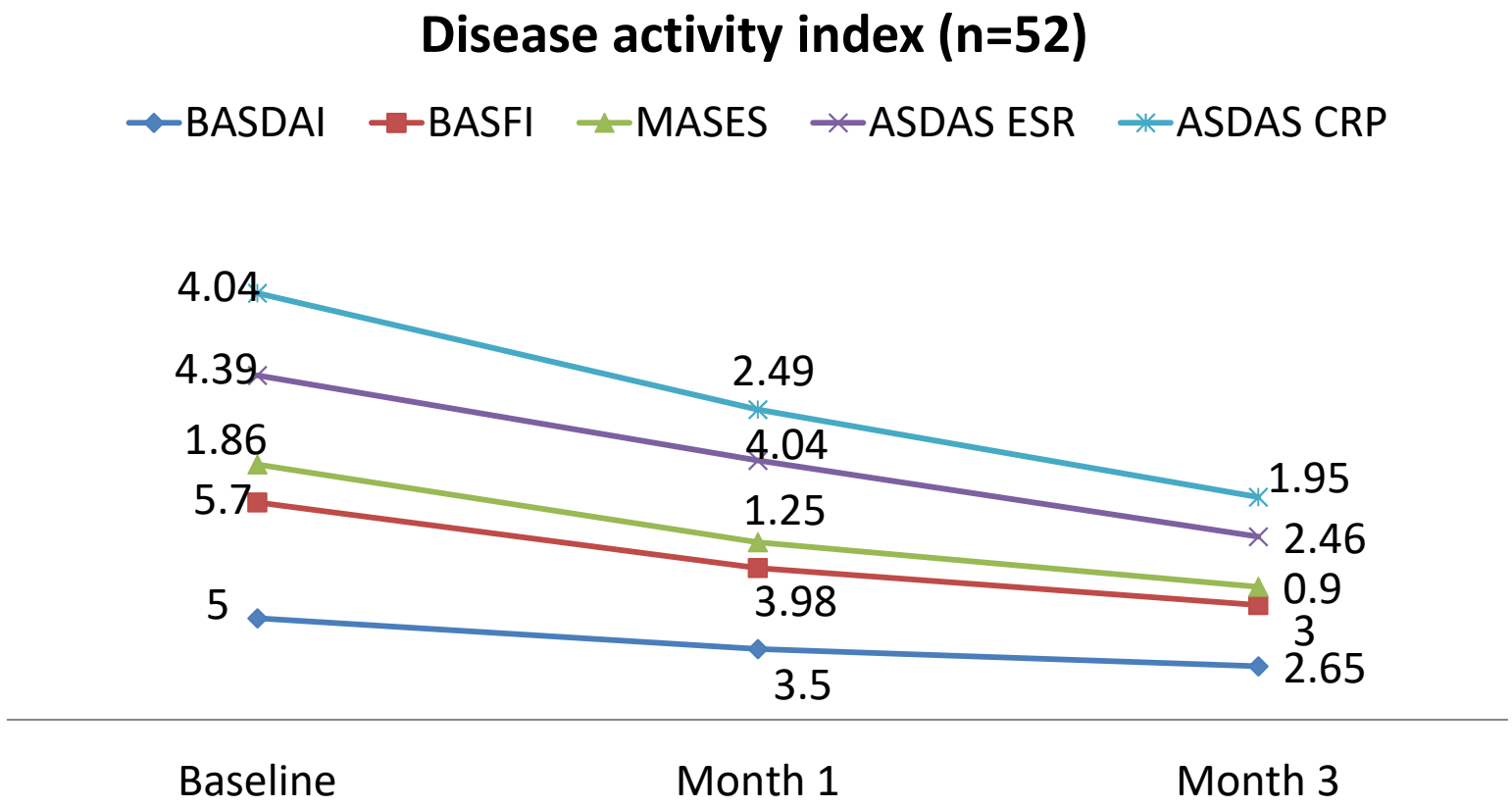


Figure : Disease activity measures, n= Number of patients, BASDAI= Bath ankylosing spondylitis disease activity index, BASFI= Bath ankylosing spondylitis functional index, MASES= Maastricht's ankylosing spondylitis enthesitis index, ASDAS= Ankylosing spondylitis disease activity score, *Paired sample t-test

ESR and CRP improvement

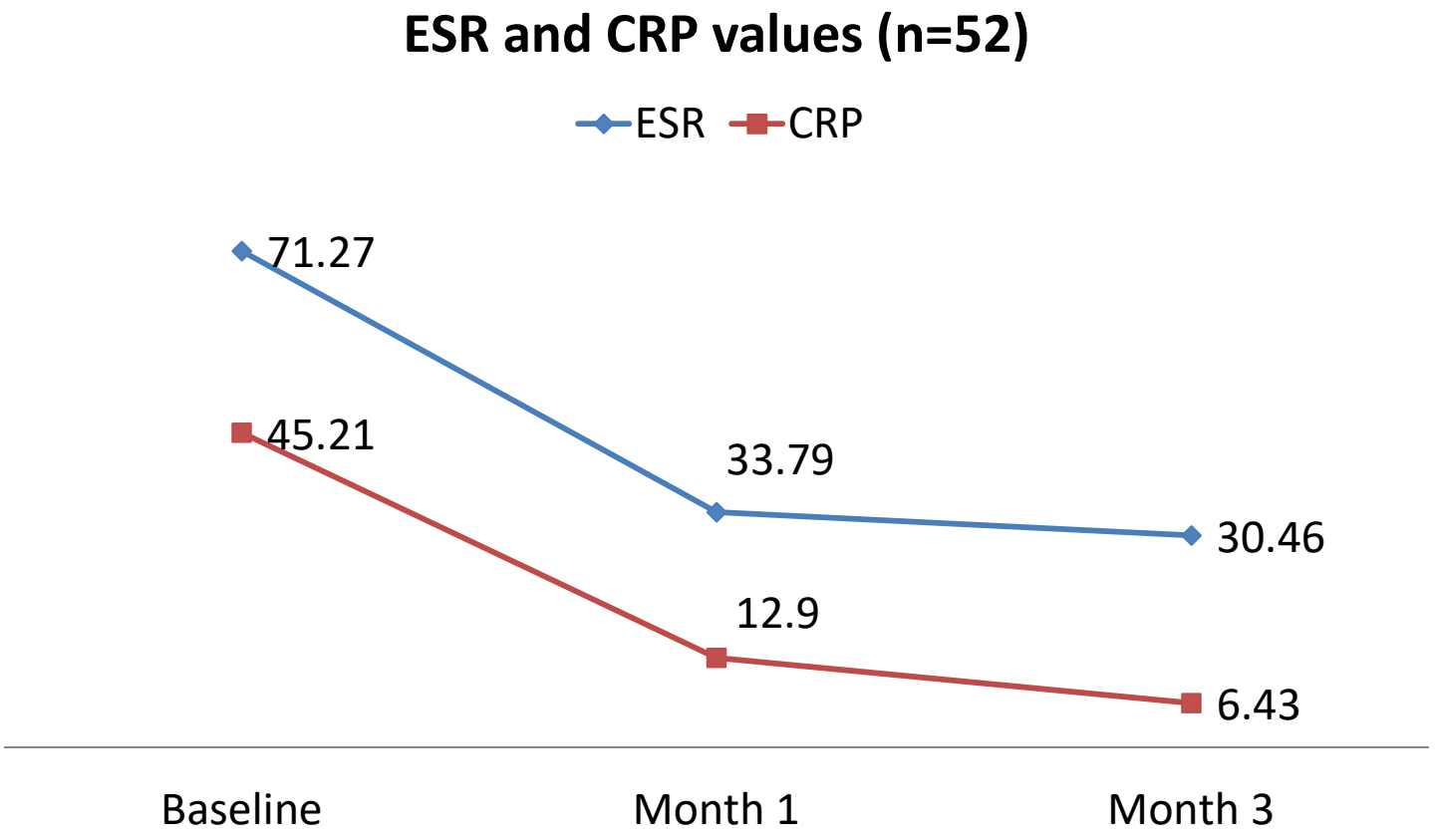


Figure :Inflammatory markers (ESR, CRP),n= Number of patients, ESR= Erythrocyte sedimentation rate, CRP= C- reactive protein, *Paired sample t-test

ASAS response in phase 2

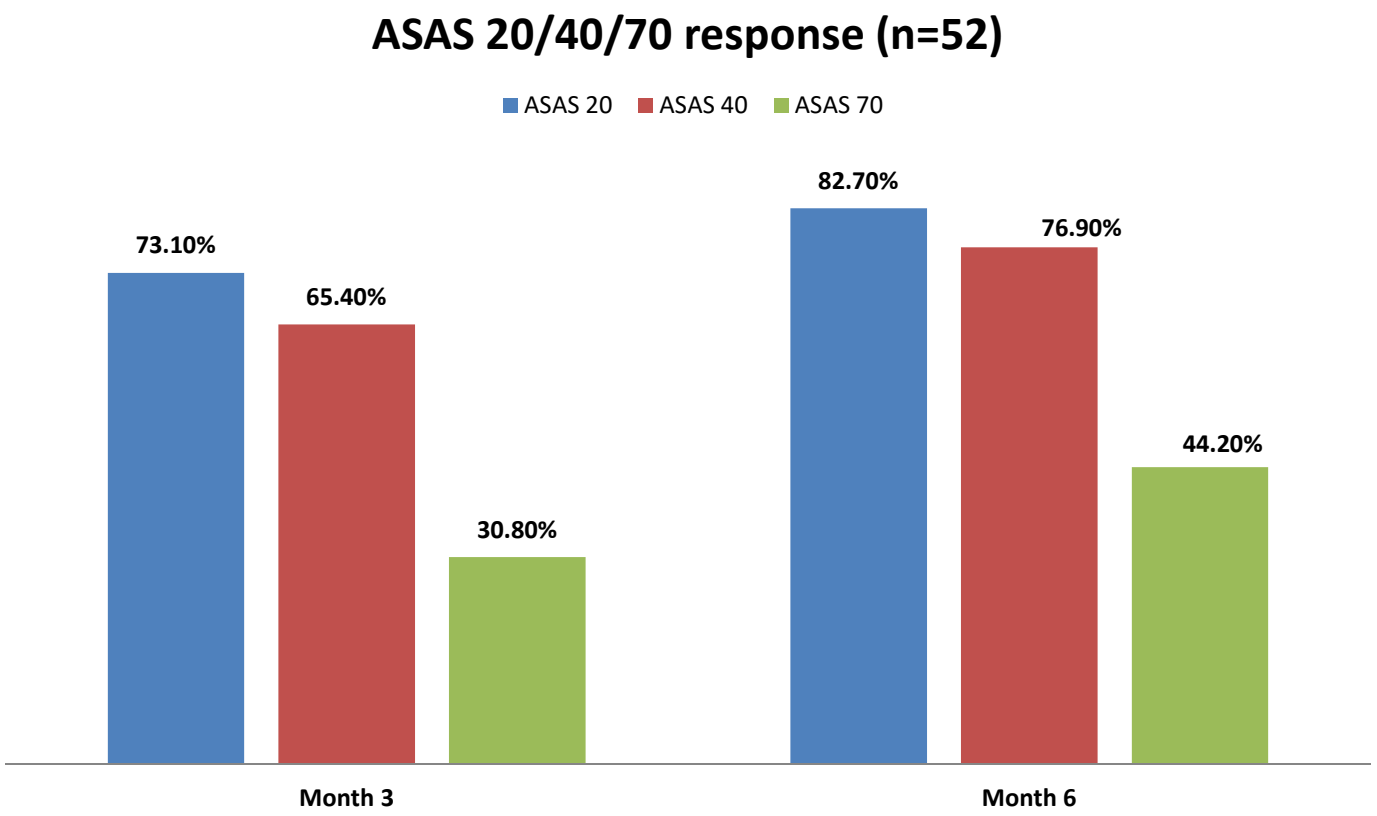


Figure : ASAS response at month 3 and 6, ASAS= Assessement of spondyloarthritis international society, n= Number of patients,%= percentage of patients

Disease activity measures at baseline, month 1 and month 3 & month 6 (n=52)

	Baseline	Month 1		Month 3		Month 6	
	Mean± SD	Mean± SD	P*-value	Mean± SD	P*-value		P*-value
BASDAI	5.00 ± 1.07	3.50 ± 1.42	0.00*	2.65± 1.57	0.00*	1.93±1.24	0.00*
BASFI	5.70 ± 1.26	3.98 ± 1.70	0.00*	3.00 ± 1.90	0.00*	2.26±1.75	0.00*
MASES	1.86 ± 1.60	1.25 ± 1.29	0.00*	0.90 ± 1.03	0.00*	0.63±0.99	0.00*
ASDAS ESR	4.39 ± 0.82	4.04 ± 0.85	0.00*	2.46 ± 1.10	0.00*	2.12±0.82	0.00*
ASDAS CRP	4.04±0.85	2.49 ± 1.05	0.00*	1.95 ± 1.05	0.00*	1.80±0.82	0.00*
ESR	71.27 ± 35.82	33.79 ± 26.13	0.00*	30.46 ± 24.7	0.00*	27.57±22.58	0.00
CRP	45.21 ± 44.85	12.90 ± 18.69	0.00*	6.43 ± 7.48	0.00*	8.38±12.09	0.00

n= Number of patients, SD= Standard deviation, BASDAI= Bath ankylosing spondylitis disease activity index, BASFI= Bath ankylosing spondylitis functional index, MASES= Maastricht's ankylosing spondylitis enthesitis index, ASDAS= Ankylosing spondylitis disease activity score, ESR= Erythrocyte sedimentation rate, CRP= C- reactive protein, *Paired sample t-test

Frequency of adverse events and withdrawal (n=52)

Events	Frequency [n (%)]
Adverse events	33 (63.46%)
Serious adverse events (SAEs)	1 (1.92 %)
Withdrawal due to AEs	1 (1.92 %)

n= Number of patients, SAEs= Serious adverse events,
%= Percentages

Different adverse effects

Common AEs		Others AE	
Nasopharyngitis	12 (23.07%)	Anorexia	1 (1.9%)
Diarrhoea	10(19.23%)	Hypertension	1 (1.9%)
Headache	10 (19.25%)	Abdominal	1 (1.9%)
Fever	9 (17.3%)	pain	1 (1.9%)
Itching	2 (3.8%)	Insomnia	1 (1.9%)
Nausea	2 (3.8%)	Raised s. cr	1 (1.9%)
Herpes zoster	2 (3.8%)	LRTI	1 (1.9%)
Disseminated TB	1 (1.9%)	Recurrent	
Intractable itching	1 (1.9%)	UTI	

Limitations of the Study

- This was an open-label study, had no control group,
- blinding was not done
- There were some AEs and serious AEs
- Three patients were discontinued from the study
- Desired sample size was not achieved due to time frame

Conclusions

- Tofacitinib is effective in NSAIDs refractory axial SpA
- Most of the patients tolerated the drug
- This drug could have a special place in the treatment of NSAIDs refractory axial SpA
- It has also shown effect on enthesitis
- Different types of adverse events including serious adverse events may occur

Recommendations

- A multi-centred, multinational, double blind randomized placebo controlled trial with large sample and for longer duration should be done which might bring better conclusion for use of tofacitinib in the treatment of NSAIDs refractory axial spondyloarthritis
- A comparrison study of tofacitinib with anti TNF may be conducted to detect non inferiority of tofacitinib to anti TNF

Acknowledgement

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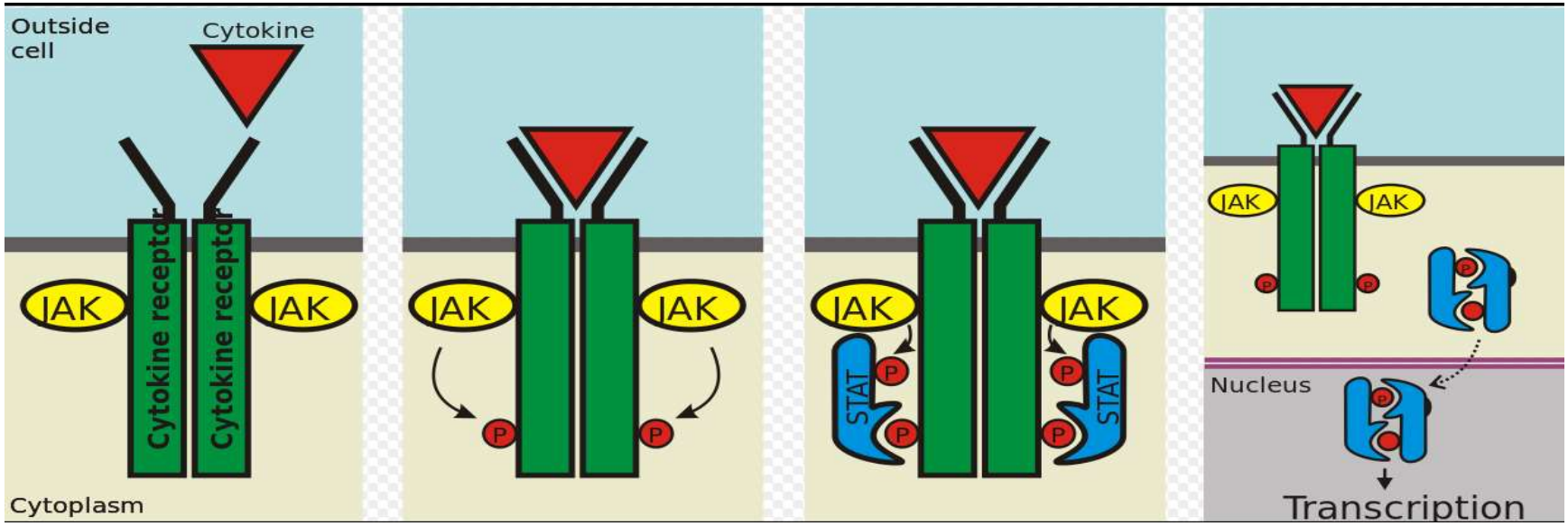
Thank you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