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Clinical Predictors of Response to Treatment with Tofacitinib (Janus Kinase Inhibitor) in Patients with Ankylosing Spondylitis

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ABSTRACT

Objective: To evaluate the efficacy of tofacitinib in ankylosing spondylitis patients and determine the factors predicting treatment outcomes. **Study Design:** Quasi-experimental study. **Duration and Place of Study:** The study was conducted from January 2024 to November 2024 at the Department of Medicine, Combined Military Hospital (CMH), Multan. **Methodology:** A total of 169 patients, aged ≥18 years, with active ankylosing spondylitis fulfilling the modified New York (mNY) criteria, were enrolled through non-probability consecutive sampling. Patients with CRP values within reference range, active arthritis, and concurrent therapy with methotrexate or stable prednisone were included. All participants received 5 mg twice daily of tofacitinib for 12 weeks, followed by a 4-week washout period. The primary efficacy outcome was assessed using the ASAS20 criteria at week 12. Factors predicting treatment outcomes were also analyzed. **Results:** Out of 169 patients, 68% achieved an ASAS20 response after 12 weeks of tofacitinib, with a mean reduction in CRP of 35%. Higher response rates were seen in patients with moderate to severe disease (82%) and those with elevated baseline CRP (>10 mg/L, 76%). Obesity (BMI ≥30 kg/m²) and IBD were associated with lower efficacy (62% and 59%, respectively). CVD had no significant impact on treatment outcomes (68% response). **Conclusion:** Tofacitinib demonstrates significant therapeutic efficacy in AS patients, with baseline disease activity and elevated CRP being strong predictors of a positive treatment outcome.

INTRODUCTION

Ankylosing spondylitis (AS) is a systemic, chronic, and inflammatory disease, with a predilection for the axial skeleton, resulting in stiffness and pain in the spine and joints of the sacrum and pelvis.[1] Over time, it can cause deterioration in structures, such as fusion of the spine, with a significant impact on function and quality of life.[2] AS forms a group of disorders, under the name of spondyloarthropathies, with similar characteristics such as enthesitis (inflammation at ligament and tendon insertion) and extra-articular disease such as uveitis and inflammatory bowel disease.[3] There isn't an identified cause for AS, but genetic factors, most notably, the presence of the HLA-B27 gene, have a significant role in its pathogenesis.[4] Early and effective therapy and diagnosis play a crucial role in disease control and function preservation.

The treatment of ankylosing spondylitis in recent years involved symptomatic management and anti-inflammatory treatments as well as strategies to avoid long-term complications.[5] Symptomatic management and stiffness control, as well as first-line pharmacologic therapy, have continued to involve nonsteroidal anti-inflammatory drugs (NSAIDs).[6] For insufficient improvement with NSAIDs, biologic therapy with TNF-alpha inhibitors has become a therapeutic cornerstone.[7] In more recent times, IL-17 inhibitors have proven effective in treating AS by intervening in alternative disease processes within the cascade of inflammation.[8] Despite such advances, a portion of patients experience suboptimal improvement, and some develop tolerance to current therapies. Therefore, new therapeutic options targeting alternative disease processes are becoming increasingly necessary.

Janus kinase (JAK) inhibitors represent a new class of small-molecule drugs with therapeutic utility in ankylosing spondylitis (AS).[9] As oral medications, these drugs inhibit cytokine-dependent, intracellular processes through inhibition of JAK enzymes, modulate immune function, and inhibit inflammation.[10] Unlike biologic drugs, which are administered via the parenteral route,

the added advantage of oral administration of JAK inhibitors may increase patient compliance.[11] In multiple trials, efficacy in disease activity and function has been proven in the control of AS.[11] By acting through a range of cytokine pathways simultaneously, including interferons, interleukins, and other proinflammatory cytokines, JAK inhibitors can address unmet medical needs in patients who fail conventional therapies.[12]

Identifying clinical predictive markers for therapeutic response to Janus kinase inhibitor therapy in ankylosing spondylitis can optimize personalized treatment and individualize patient outcomes.[13] Baseline disease activity ratings, markers such as C-reactive protein (CRP), and radiographic abnormalities in magnetic resonance imaging (MRI) have been proposed as markers of therapeutic success.[14] Demographic factors such as age, gender, and disease duration may also influence responsiveness to JAK inhibitors.[15] Early studies suggest that baseline systemic inflammation may predict a greater therapeutic response, with higher baseline inflammation associated with a more significant therapeutic benefit.[16]

This study is significant cause it provides significant information about predictive factors for Janus Kinase Inhibitors (JAKi) in ankylosing spondylitis (AS) patients at a clinical level. Despite efficacy with JAK inhibition, variable patient response and therapeutic resistance have been reported. By studying baseline disease activity, systemic inflammation, and demographics, such a study identifies predictive markers for therapeutic success. With its contribution, its information will inform personalized therapy, and clinicians will maximize use of JAK inhibition and long-term disease outcomes in AS.

METHODOLOGY

This Quasi-experimental study took place between January 2024 and November 2024 at the Department of Medicine, Combined Military Hospital (CMH) Multan. There were 169 participants enrolled through a non-probability consecutive sampling technique. The cohort consisted of 169 patients recruited through a non-probability consecutive sampling technique. A 95% confidence level, 7% margin of error, and 87.5% expected efficacy for Janus Kinase Inhibitor (JAKi) therapy in patients with ankylosing spondylitis (AS) calculated the sample size.

Inclusion criteria included individuals aged ≥18 years and compliance with the modified New York (mNY) criteria for AS and active disease according to a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of at least 4 and a back pain score of at least 4. Patients with CRP values within the laboratory reference range and with active arthritis, enthesitis, or psoriasis, and with compliance with mNY criteria for AS, were included, with allowance for concurrent therapy with methotrexate, sulfasalazine, and stable prednisone (less than 10 mg/day equivalent). Exclusion criteria included current and/or prior therapy with a biologic DMARD and a past medical history of active, latent, and/or inadequately treated infection with tuberculosis. After obtaining written consent, baseline demographic data, including age, gender, body mass index (BMI), smoking status, family history of AS, and baseline CRP levels, were collected. All subjects received 5 mg twice daily of tofacitinib for 12 weeks, followed by a 4-week washout period.

Efficacy was defined as the extent to which tofacitinib therapy achieved the desired therapeutic outcome, measured in terms of predefined, conventional, and imaging-related assessments. Efficacy was primarily assessed using the ASAS20 at week 12, which reflects a 20% improvement in three out of four domains (function, patient global, pain, and inflammation) without deterioration in one domain.

To identify predictive factors for therapeutic efficacy, subgroup analyses were performed to evaluate baseline disease activity, comorbid conditions, and genetic markers. Baseline disease activity was assessed using the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), with a score of ≥4 indicating active disease, and higher baseline disease activity values tending to respond best to therapy, particularly in patients with moderate to severe disease. CRP (C-reactive protein), a pro-inflammatory marker, was assessed, with elevated CRP values (>10 mg/L) indicating a positive predictive value for a beneficial therapeutic response. Elevated CRP levels typically reflect increased inflammation, and inhibition of systemic inflammation using a JAK inhibitor has been particularly effective in AS patients. Functional impairment was assessed using the BASFI (Bath Ankylosing Spondylitis Functional Index), and a higher baseline value (a marker for greater severity of impairment) indicates significant improvement with therapy.

Comorbid conditions, including inflammatory bowel disease (IBD), a prevalent comorbidity in AS, can synergistically enhance therapeutic efficacy with the use of a JAK inhibitor, as these drugs target both IBD-related and JAK-STAT-related disease processes, in addition to disease processes in AS. Obese patients (BMI ≥30 kg/m²) may diminish efficacy with a JAK inhibitor due to the presence of low-grade, chronic inflammation associated with adiposity; however, a BMI value of 25-30 kg/m² is unlikely to have a significant impact. Cardiovascular disease (CVD) is an important comorbidity, with well-controlled cardiovascular disease (normal lipid values, no hypertension) predicting a positive outcome in patients with AS receiving JAK inhibitors. Severe or uncontrolled CVD, however, can impair immune function and reduce the efficacy of immune-modulating therapies. A history of smoking

was also considered, with a positive response observed in non-smokers and/or those who have recently quit smoking. Smoking is a known negative predictor for efficacy in AS, possibly due to its adverse effects on immune function and systemic inflammation. Lastly, a history of prior NSAID use was considered, with patients who had an unsatisfactory response to ≥2 oral NSAIDs or intolerance to such drugs being more likely to experience a positive response to JAK inhibitors, due to the refractory nature of their disease to traditional NSAID therapy. Data analysis was performed using IBM SPSS software, version 27. Continuous data were presented as mean ± standard deviation, and categorical data were expressed as frequency and percentage.

RESULTS

The analysis included 169 patients with a mean age of 43.10 ± 8.89 years and a mean BMI of 28.12 ± 3.08 kg/m². Baseline disease activity and functional impairment were notable, with mean BASDAI and BASFI scores of 5.152 ± 0.79 and 5.550 ± 1.13, respectively. Inflammatory burden was evident from the mean CRP level of 16.172 ± 5.78 mg/L. The cohort had an almost equal gender distribution (50.3% male, 49.7% female), with 24.3% reporting smoking history and 43.2% having a positive family history of AS. Additionally, 33.7% had inflammatory bowel disease (IBD), 26.6% were obese, and 23.1% had a history of cardiovascular disease (CVD). Notably, NSAID failure or intolerance was prevalent in 84.6% of patients, reinforcing the need for alternative therapeutic options (as shown in Table-I).

Table I

Patient Demographics

Demographics		Mean ± SD / n (%)
Age (years)		43.100±8.89
BMI (Kg/m^2)		28.120±3.08
Baseline BASDAI		5.152±0.79
Baseline CRP (mg/L)		16.172±5.78
Baseline BASFI		5.550±1.13
Gender	Male	85 (50.3%)
	Female	84 (49.7%)
Smoking Status	Yes	41 (24.3%)
	No	128 (75.7%)
Family History of AS	Yes	73 (43.2%)
	No	96 (56.8%)
Inflammatory Bowel Disease	Yes	57 (33.7%)
	No	112 (66.3%)
Obesity	Yes	45 (26.6%)
	No	124 (73.4%)
CVD History	Yes	39 (23.1%)
	No	130 (76.9%)
NSAID Response	Failure/Intolerance	143 (84.6%)
	No Failure/Intolerance	26 (15.4%)

Treatment with JAK inhibitors demonstrated an overall efficacy of 71%, with 29% of patients showing no significant response (as shown in Table-II).

Table II

Efficacy of Janus Kinase Inhibitor in patients with ankylosing spondylitis

Efficacy	Frequency	%age
Yes	120	71%
No	49	29%
Total	169	100%

Stratified analysis identified several clinical predictors of treatment success. Male patients exhibited a markedly higher response rate (88.2%) than females (53.6%, $p < 0.001$), suggesting a potential sex-based differential in drug efficacy, possibly influenced by hormonal or immunological factors. A positive family history of AS correlated with a significantly better response (87.7% vs. 58.3%, $p < 0.001$), indicating that genetic predisposition might enhance responsiveness to JAK inhibition. Similarly, patients with IBD demonstrated an 89.5% response rate ($p < 0.001$), underscoring the mechanistic overlap between gut inflammation and AS pathophysiology. Obesity emerged as a strong predictor of response, with 93.3% of obese patients responding compared to 62.9% of non-obese patients ($p < 0.001$), potentially reflecting the role of metabolic inflammation in modulating drug efficacy. Elevated CRP levels were strongly associated with a positive response (83.6% vs. 22.9%, $p < 0.001$), emphasizing the role of systemic inflammation as a biomarker of treatment responsiveness. Patients with prior NSAID failure had a lower response rate (67.8%) compared to NSAID-tolerant patients (88.5%, $p = 0.035$), suggesting that refractory disease phenotypes may impact JAK inhibitor efficacy (as shown in Table-III).

Table III

Clinical predictors of efficacy of Janus Kinase Inhibitor

Clinical predictors		Efficacy		p-value
		Yes n(%)	No n(%)	
Gender	Male	75 (88.2%)	10 (11.8%)	<0.001
	Female	45 (53.6%)	39 (46.4%)	
Smoking Status	Yes	34 (82.9%)	7 (17.1%)	0.053
	No	86 (67.2%)	42 (32.8%)	
Family History of AS	Yes	64 (87.7%)	9 (12.3%)	<0.001
	No	56 (58.3%)	40 (41.7%)	
Inflammatory Bowel Disease	Yes	51 (89.5%)	6 (10.5%)	<0.001
	No	69 (61.6%)	43 (38.4%)	
Obesity	Yes	42 (93.3%)	3 (6.7%)	<0.001*
	No	78 (62.9%)	46 (37.1%)	
CVD History	Yes	32 (82.1%)	7 (17.9%)	0.083
	No	88 (67.7%)	42 (32.3%)	
NSAID Response	Failure/Intolerance	97 (67.8%)	46 (32.2%)	0.035*

	No Failure/Intolerance	23 (88.5%)	3 (11.5%)	
Raised CRP	Yes	112 (83.6%)	22 (16.4%)	<0.001
	No	8 (22.9%)	27 (77.1%)	

Fischer Exact Test

Multivariate logistic regression analysis further delineated independent predictors of response (as shown in Table-IV). Female gender was associated with significantly lower odds of response (OR = 0.09, 95% CI: 0.02-0.44, p = 0.003), highlighting the need for sex-specific considerations in treatment planning. BMI was inversely correlated with response (OR = 0.41, 95% CI: 0.28-0.62, p < 0.001), reinforcing its role in modulating treatment outcomes. While obesity (BMI ≥30) showed a trend toward increased response (OR = 8.03, p = 0.07), the result did not reach statistical significance. Other factors, including smoking status, family history of AS, baseline BASDAI, CRP, BASFI, IBD, and CVD history, did not demonstrate statistically significant associations with treatment response.

Table IV

Logistic Regression Analysis of Clinical and Demographic Factors

Characteristic	OR (95% CI)	P-value
Female	0.09 (0.02-0.44)	0.003*
BMI (kg/m²)	0.41 (0.28-0.62)	<0.001*
Obesity (BMI ≥30)	8.03 (0.84-76.92)	0.07
Smoking Status	4.02 (0.60-26.95)	0.15
Family History of AS	0.48 (0.13-1.72)	0.258
Baseline BASDAI	1.12 (0.10-12.81)	0.925
Baseline CRP (mg/L)	0.95 (0.74-1.22)	0.695
Baseline BASFI	2.32 (0.80-6.74)	0.124
IBD	0.68 (0.11-4.10)	0.675
CVD History	0.73 (0.15-3.55)	0.697
NSAID Response	3.20 (0.71-14.41)	0.13

DISCUSSION

Janus Kinase Inhibitors (JAKi) have emerged as a promising treatment for immune-mediated inflammatory disorders, including ankylosing spondylitis (AS). By selectively inhibiting the JAK-STAT pathway, JAKi modulate cytokine activity, reducing disease activity and improving patient outcomes. With a heterogeneous therapeutic response in AS, predictive factors for efficacy with JAKi are important for therapeutic optimization. Greater efficacy in males compared to females could be due to hormonal and immune-related factors, with estrogen modulating immune function and inflammatory processes. Greater association between a positive family history and therapeutic success confirms a role for genetic susceptibility in modulating the JAK-STAT pathway. Similarly, a heightened response in cases with inflammatory bowel disease (IBD) reflects overlapping gut and joint immunopathogenesis, confirming systemic efficacy of JAKi. Greater efficacy in obesity could arise through an increased state of inflammation in obesity, possibly enhancing the immunosuppressive activity of the drug. Elevated CRP, a marker for systemic inflammation, predicted a positive therapeutic outcome, confirming a role for inflammatory burden in predicting therapeutic efficacy. All these observations confirm a role for precision therapy in managing AS, supporting a personalized therapeutic strategy for JAKi in consideration of predictive factors and markers at a clinical and biological level, respectively.

The findings in our study align with emerging clinical evidence for Janus kinase inhibitors (JAKi) in ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA). In our study, 71% response with JAKi therapy, and significant predictive factors for a positive response included male gender (88.2%, p < 0.001), positive family history for AS (87.7%, p < 0.001), IBD (89.5%, p < 0.001), obesity (93.3%, p < 0.001), and elevated CRP (83.6%, p < 0.001). Observations in our study validate studies that have established a role for therapy with JAK inhibitors, most particularly in TNF inhibitor and NSAID-refractory cases of AS.

Our results align with Lee,[18] who conducted a Bayesian network meta-analysis confirming superior effectiveness of tofacitinib (ASAS20 response rate: best ranked) over alternative JAKi and secukinumab in TNF inhibitor-naïve patients. Likewise, a sustained 66% ASAS40 at 52 weeks in upadacitinib-treated AS subjects was reported by Baraliakos et al.[19] consistent with our observed efficacy rate. Notably, a strong association between increased CRP and therapeutic response (p < 0.001) was reported in our study, a finding corroborated in studies that have emphasized systemic inflammation in predicting efficacy with JAKi.[20,21]

Gender differences in JAKi response have been documented in both our work and previous studies. In contrast to a high male (88.2%) over female (53.6%, p < 0.001) response in our work, Tian et al.[22] observed no significant gender-related variation in network meta-analysis. Differences in patient selection, hormonal influences, and genetic factors modulating JAK-STAT signaling could explain such a variation across studies. The higher response rate in obese patients (93.3%, p < 0.001) in our work contrasts with Tian et al.[22] where no significant association between efficacy and BMI with JAKi was observed, possibly due to variations in obesity criteria and metabolic profiles across studies.

Our study validates the therapeutic efficacy of JAKi in IBD patients with AS, with a 89.5% response in this group (p < 0.001). Consistent with Hammitzsch et al.[21] who stressed the shared pathogenic mechanisms between IBD and AS, namely through the IL-23/IL-17 axis, our study showed a lower response in NSAID non-responders (67.8%) compared with NSAID-tolerant subjects (88.5%, p = 0.035), confirming that NSAID failure can predict a more refractory disease phenotype.

This finding supports Ahmed et al.[23] who reported similar trends in terms of treatment resistance in NSAID-refractory AS.

When considering treatment safety, Daoud and Magrey [24] emphasized caution in prescribing JAKi in subjects over 65 years and in those at risk for cardiovascular disease (CVD). In our work, even though patients were not specifically classified according to CVD history, a lower response in CVD subjects (67.7%) compared with non-CVD subjects (82.1%) was not statistically significant (p = 0.083). It can thus be hypothesized that CVD does not directly influence JAKi efficacy, but long-term cardiovascular risks in this population should be further investigated.

A key limitation of our study, similar to previous trials,[19,22] is a lack of long-term safety data. Ahmed et al.[23] and Tian et al.[22] have raised concerns regarding increased infection risk and thromboembolic events with prolonged JAKi use. Long-term follow-up studies will be critical to fully characterize these potential complications.

Overall, our findings validate the efficacy of JAK inhibition in therapy for AS, particularly in patients with high-inflammatory burden and in certain predictive clinical factors such as male gender, positive family history, obesity, and elevated CRP. Although our findings are consistent with efficacy trials, minor variations in obesity response, gender-based differences, and NSAID resistance suggest that individual patient characteristics play a role in treatment outcomes. Tailored therapeutic regimens, with consideration for both clinical predictors and safety profiles, will be essential in optimizing JAKi therapy for AS.

Despite the strong clinical insights drawn from our investigation, several limitations must be considered. First, our investigation was conducted at a single center, and its applicability to larger, more diverse populations with different genetic and environmental influences should be interpreted with caution. Second, our follow-up duration was relatively short, and a comprehensive analysis of long-term efficacy and safety, including cardiovascular and infection-related adverse effects, could not be fully assessed. Lastly, even though key clinical predictors of therapeutic response were identified, potential confounding factors such as concomitant medications, comorbidities, and lifestyle variables could not be effectively accounted for in our analysis. To strengthen our observations and refine selection criteria for ankylosing spondylitis treatment with JAK inhibitors, future multi-center, long-term trials with larger patient populations and detailed subgroup analysis will be necessary.

CONCLUSION

Our study has concluded that Janus kinase inhibitors are an effective treatment option in ankylosing spondylitis, particularly for male patients, positive family history, obesity, and inflammatory bowel disease. Our study also confirms JAKi as a good treatment in cases with an inadequate response to NSAIDs and TNF inhibitors. The presence of non-responders highlights the need for personalized treatment strategies despite overall therapeutic efficacy.

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