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Comparative Efficacy of Targeted Therapies in Treating Multiple Domains of Psoriatic Arthritis - A Single Center Study

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Abstract: ***Targeted therapies are commonly used in the management of Psoriatic arthritis (PsA). The Objective of our study is to investigate the comparative efficacy and safety of adalimumab (A), secukinumab(S) and tofacitinib(T) for patients with active PsA.A 3-year single centre study was conducted among PsA patients treated with either A/S/T. Primary objective was major clinical improvement (ACR50 and ASAS40) at week 24 and improvement in other domains (enthesitis, dactylitis and skin) were studied as secondary objectives. Disease activity scores (PASDAS, PASI, BASDAI) were computed. 79 patients with a were included. Adalimumab may be preferable for treating arthritis. Secukinumab shows significantly better response in treating axial symptoms, enthesitis and dactylitis. High CRP (>10.8), smoking and baseline BASDAI were predictors of clinical response.***

Keywords: Psoriatic arthritis, Adalimumab, secukinumab, Tofacitinib

1. Introduction

PsA is a chronic, immune-mediated disease with a global average incidence of 83 per 100,000 per year, affecting men and women equally [1]. The manifestations of PsA are heterogeneous and involve the peripheral and axial skeleton along with enthesitis and dactylitis [2]. In addition, there is an increased prevalence of hypertension, obesity, metabolic syndrome and cardiovascular disease among patients with PsA [3]. Over time, PsA is associated with joint deformity, reduction of life quality and expectancy [4].

Targeted therapies revolutionized the treatment of inflammatory arthritis and PsA is no exception. Biological therapies used for the treatment of psoriasis include TNF inhibitors, interleukin (IL)−12/IL-23 inhibitor ustekinumab, IL-17A inhibitors secukinumab and ixekizumab, IL-23 inhibitor guselkumab and selective T-cell costimulation modulator abatacept, as well as non-biological treatments such as phosphodiesterase 4 inhibitor apremilast and the Janus kinase (JAK) inhibitors tofacitinib and upadacitinib [5] with recent guidelines suggesting their appropriate use; although nearly all the proposed recommendations were conditional since the quality of evidence was most often low or very low, and occasionally moderate [6]. A network meta-analysis comparing the various biologicals concluded that there is insufficient statistical evidence to demonstrate clear differences in effectiveness between majority of the available biologic agents for PsA [7], but they have some differences in the outcomes of other domains of PsA [8]. Also, biologicals show racial differences in efficacy, safety and adherence all of which will have an impact in treatment outcome [9]. Hence head-to-head comparative methodologically well-conducted studies in a diverse population are necessary to help physicians and decision-makers in making appropriate decisions [10].

This study is performed in Indian patients with psoriatic arthritis to assess the comparative clinical efficiency of different biological agents on different domains of PsA when used in real-world settings.

2. Methodology

This was a single center 3 year retro-prospective study with data being extracted from our adult (>18 years) psoriatic arthritis cohort. Patients diagnosed as having active PsA based on CASPAR criteria [11] treated with either Adalimumab (A)/ Secukinumab (S)/ Tofacitinib(T) were included and patients with incomplete data, lost to follow-up, medication non-adherence were excluded. All the patients receiving A/S/T also received background methotrexate 10mg/once weekly [12]. Demographic data, comorbidities, clinical presentation, disease activity scores (PASDAS, PASI, BASDAI [13]) and biochemical data at the initiation and during follow-up were recorded and retrieved. Primary objective was the proportion of patients achieving major clinical improvement (ACR50 and

ASAS40) at week 24 [14]; secondary objectives were change in disease activity scores and mean response time to primary objective at week 24.

Continuous and categorical variables were reported as mean (SD) and number of observations (%), respectively. T test, chi square test were performed where appropriate. Multivariate cox regression analysis was performed to determine the predictors and receiver operator characteristic (ROC) curves were analyzed for an optimal cut-off if required. A p value of <0.05 was considered significant. All the statistical analyses were performed by AZR software.

3. Results

During the study period a total of 113 patients with PsA were treated with either A/S/T of which 79 patients were included in the study. The mean age of study population was 42.6 years (males: 62%). Baseline comorbidities were shown in **Table 1.**Oligo-arthritis was the predominant form (74.7%:59/79) of peripheral arthritis. Skin, axial involvement, enthesitis and dactylitis were seen in 89.9%(71), 58.2%(46), 33% (26) and 20.2%(16) of patients respectively. Biochemical data and mean disease activity in different domains of PsA at presentation are shown in **Table 2.** 44.3%(35), 29.1% (23) and 26.5% (21) of patients were treated with A, S and T respectively.

Table 1 and 2: Clinical, demographic and biochemical characteristics of the study population

Variable	Adalimumab group (A) (n = 35)	Secukinumab group (S) (n = 23)	Tofacitinib group (T) (n = 21)	p
Males (N)	20	12	17	0.10
Age (years)	41.8 +/- 4.5	44.3 +/- 5.1	43.4 +/- 3.9	0.76
Hypertension (N)	12	8	3	0.21
Diabetes mellitus (N)	4	3	3	0.95
Obesity (N)	10	8	6	0.86
PsA duration (months)	5.3 +/- 2.4	7.8 +/- 3.1	5.9 +/- 2.8	0.43
Oligoarthritis (N) PASDAS	25 5.6 +/- 1.7	18 5.9 +/- 2.1	16 5.1 +/- 1.8	0.82 0.46
Axial involvement (N) Sacroiliitis only BASDAI	25 13 (52%) 4.8 +/- 2.1	15 7 (46.7%) 4.5 +/- 1.9	16 5 (31.3%) 4.1 +/- 1.9	0.72 0.42 0.87
Skin involvement (N) Plaque psoriasis PASI	34 30 (88.2%) 13.5 +/- 7.6	22 21 (91.3%) 12.9 +/- 6.4	14 10 (71.4%) 9.1 +/- 7.2	**0.004** 0.10 **0.041**
Dactylitis (N)	9	3	4	0.49
Enthesitis (N)	10	10	6	0.44
Eye involvement (N)	1	1	1	0.92
ESR (mm/hr)	58.6 +/- 11.4	62.1 +/- 8.7	55.8 +/- 14.2	0.71
CRP (mg/dl)	1.53 +/- 0.21	1.78 +/- 0.42	1.66 +/- 0.34	0.56
WBC (10^3/dl)	7.2 +/- 2.3	8.4 +/- 3.1	6.7 +/- 3.2	0.32
Hb (gm/dl)	10.8 +/- 2.2	10.4 +/- 1.9	11.1 +/- 2.1	0.43
RF +ve	2	2	1	0.84
Anti-CCP +ve	1	2	1	0.60

mean rank of the following pair is significantly different: A-T and S-T.

PASDAS- Psoriatic Arthritis Disease Activity Score, BASDAI – Bath Ankylosing Spondylosis Disease Activity Index
PASI – Psoriasis Area and Severity Index ,ESR – Erythrocyte Sedimentation Rate , CRP – C-reactive Protein , WBC – White Blood cell count , HB – Hemoglobin , RF – Rheumatoid factor , Anti CCP – Anti – Cyclic citrullinated peptide.

ACR50-24W was seen in 42.8%, 39.1%, 38% of patients treated with A,S,T respectively with no statistical difference. ASAS40-24W was seen in 56%, 66.6% and 43.8% of patients treated with A,S,T respectively with significantly lower response with tofacitinib. At 24W mean change in PASDAS among three groups was similar statistically, however, reduction in BASDAI and PASI scores was significantly higher with secukinumab and also proportion of patients free from enthesitis and dactylitis was higher with secukinumab. Mean time to ACR50 was lowest with adalimumab but to ASAS40, it was significantly higher with Tofacitinib.

On multivariate cox regression analysis, CRP (AUROC:0.702, optimal cutoff >14.5 , overall accuracy of 70.1%, **Figure 1**), baseline BASDAI score and smoking status were identified as predictors of response at 24W with targeted therapies in patients with peripheral arthritis, axial PsA and psoriasis respectively. **Table 4**

Table 3: Comparative performance of different agent across disease spectrum of PsA

Variable	Adalimumab group (A)	Secukinumab group (S)	Tofacitinib group (T)	p
Skin involvement	34	22	14	
Mean PASI change	8.6 +/- 4.2	8.3 +/- 4.1	4.4 +/- 4.3	0.002*
PASI 75-24W	25 (73.5%)	18 (81.8%)	5 (35.7%)	0.010*
Time to PASI 75-24W	15.7 +/- 3.9	14.6 +/- 4.8	18.2 +/- 5.2	0.014*
Axial involvement	25	15	16	

Mean BASDAI change	2.2 +/- 2.0	3.7 +/- 2.4	1.9 +/- 2.9	0.042^
ASAS40-24W	14 (56%)	10 (66.6%)	7 (43.8%)	0.432
Time to ASAS 40-24W	17.8 +/- 6.6	13.2 +/- 4.3	19.2 +/- 6.2	0.013^
Psoriatic arthritis	35	23	21	
Mean PASDAS change	2.4 +/- 2.2	2.3 +/- 1.9	2.0 +/- 1.9	0.861
ACR50-24W	15 (42.8%)	9 (39.1%)	8 (38%)	0.921
Time to ACR50-24W	15.1 +/- 4.8	19.2 +/- 6.5	18.26 +/- 5.6	0.044#
Dactylitis at presentation	9	5	2	
Dactylitis at 24 weeks	4	1	1	
% improvement	55.50%	80%	50%	0.042
Enthesitis at presentation	11	10	5	
Enthesitis at 24 weeks	6	3	3	
% improvement	45.50%	70%	40%	0.038

*mean rank of the following pair is significantly different: A-T and S-T.
^mean rank of the following pair is significantly different: A-S and S-T.
#mean rank of the following pair is significantly different: A-T and A-S Mean change in scores are depicted in absolute numbers (change actually represent "-").

Table 4: Multivariate cox regression analysis

Variable	β	OR	95% CI	p
ACR-50-24W				
CRP	1.76	3.27	1.17-7.82	0.017
smoking	3.51	1.82	1.10-11.94	0.042
ASAS-40-24W				
CRP	1.22	2.11	0.12-11.67	0.191
BASDAI	-4.20	0.25	0.00-0.76	0.039

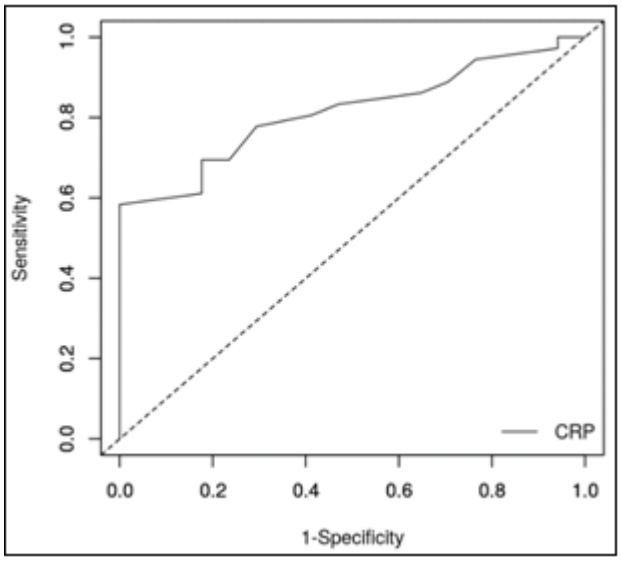

Figure 1: Multi-variate cox regression analysis

4. Discussion

To the best of our knowledge this is the first study that is conducted on Indian PsA patients receiving b/tsDMARDs. We also reported the impact of these therapies on various domains of PsA including axial symptoms and thus tried to make our results meaningful in clinical decision making.

Age, male predominance, oligo-arthritis as major presentation has been noted similarly in other studies in our region [15]. Around 88% of the patient population in our study had preceding diagnosis of psoriasis. 29% (23/79), 30.3% (24/79) and 12.6%(10/79) of patients were hypertensive, obese and diabetic respectively, which is similar to Indian rheumatological patients [16] and also in concordance with the global PsA data [17].

There are no or few head-to-head comparative trials among b/ts- DMARDs in PsA. As per the available RCTs and indirect comparison [18] through network meta-analysis [19-21] GRAPPA had suggested that TNF inhibitors, IL-17 inhibitors and JAK inhibitors are equally effective and had given a strong recommendation as 1st line therapy in patients with peripheral arthritis [22]. ACR50 response with A/S/T was around 35-40% and statistically similar among patients treated with any of the 3 agents. Meta-analytic data suggested a response rate (ACR50 at 24 weeks) of around 30-40%, 35-45%, 30% for A/S/T respectively. Mean change in PASDAS score at 24W was also similar but interestingly time required to achieve the primary response was significantly lower among patients treated with adalimumab indicating that it may be more efficient compared to the other two drugs and this in part may be explained by their superiority in preventing radiographic progression [22].

Data assessing the b/tsDMARD effectiveness in psoriatic spondylitis (AxPsA) is very limited. EULAR, ACR, GRAPPA strongly recommends [23,24] the use of TNFi/IL-17i/ JAKi in AxPsA based on the data from Axial SpA; However, it still remains to be defined whether results regarding the therapeutic efficacy can be extrapolated from AxSpA to axial-PsA; this is important because post hoc analyses from the trials of ustekinumab and guselkumab in patients who have had axial symptoms suggest that these agents might be effective in axial PsA but not in axial SpA [25]. Even recently, data suggest that axSpA and PsA with axial involvement are distinct entities, so extrapolation of treatment data from randomized trials in axSpA should be performed with caution [26]. In our study both adalimumab and secukinumabwere equally efficacious but secukinumab found to be more effective (lesser time to ASAS40 response and higher mean change in BASDAI). ASAS40 response rate at 24 weeks with secukinumab was around 60% and was slightly higher than the MAXIMISE trial [27] results. Patients treated with tofacitinib showed least response among the three agents. Though the preliminary data points towards comparative response with JAK inhibitors in patients with axial PsA [28], trials like PASTOR [29] are needed to truly uncover their effectiveness in this population sub-group. As per our knowledge, this is a new finding and needed to be evaluated in larger studies.

26% and 21% of our study population hadenthesitis and dactylitis which is slightly lower than the global meta-analysis data [30]. Secukinumab was more effective statistically in treating dactylitis and enthesitis in our study population but available literature points to conflicting results with one meta-analysis [31] suggesting that anti-TNF-α agents have the same efficacy as other biological agents whereas the other [32] suggests that IL-17 inhibitors offer preferential efficacy for treating enthesitis and dactylitis. There is no RCT to date to analyze the comparative data to resolve this issue and will be of future interest.

Skin involvement as quantified by PASI showed significant improvement with secukinumab compared to tofacitinib. Even meta-analytic data suggest that in general, IL-17A and IL23 inhibitors being more effective than anti-TNF-α agents (except infliximab) [33,34] which in turn perform better than apremilast and tofacitinib [34]. This is because psoriasis is a Th17-mediated inflammatory disorder and IL-23 is the 'master regulator' due to its critical role in production of cytotoxic Th17 cells that produce pro-inflammatory cytokines including IL-17 and IL-22 [35].

Regression analysis had suggested that high CRP, lower baseline BASDAI score and non-smoking status were associated with good response with targeted therapies in patients with peripheral arthritis, axial PsA and psoriasis respectively. There are no known consistent predictors among PsA patients treated with targeted therapy and this might be due to diversity in study population, domain specific patho- physiology and thus drug effects making theragnostics difficult among all domains of PsA. Available evidence suggests that CRP, active smoking status, young age, obesity, baseline activity predict the treatment response in different subsets of PsA patients [36-38].

Our Study has five main limitations. This was a single-center study that may affect the generalizability of results and it includes a small sample population selected retrospectively thus affecting its validity. Second, the impact of targeted therapies on nail, eye, bowel involvement was not made. Another limitation is that there was no proper protocol followed for drug titration. Fourth, the comparative effect of these drugs on patients with prior exposure to b/tsDMARDs was not assessed. Finally an important question relevant to resource-limited settingsand cost effectiveness was left unanswered.

5. Conclusion

Our South Indian cohort of PsA patients shows that Adalimumab or Secukinumab or Tofacitinib are equally efficacious in improving arthritis symptoms. But adalimumab may be more efficient for improving arthritis symptoms. Tofacinitib is least effective for treating skin psoriasis and axial symptoms. Interestingly, secukinumab shows significantly better response in treating axial symptoms, enthesitis and dactylitis. Drug tolerability was similar. High CRP (>10.8), non- smoking status and lower BASDAI were associated with good clinical response.

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