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LONG-TERM RETENTION RATE OF CERTOLIZUMAB PEGOL IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS: DATA FROM THE TURKBIO REGISTRY

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Abstract

Aim: Selecting the most effective treatment plan for a patient represents one of the most challenging issues in contemporary rheumatology. Clinicians must consider the long-term retention rate and the reasons for discontinuing candidate drugs.This study aimed to assess the drug survival of certolizumab pegol (CZP) in patients with axial spondyloarthritis (ax-SpA) and identify predictors for discontinuation.

Material and Methods: Data on patient characteristics, demographics, diagnosis, disease duration, treatment, and outcomes have been collected from the Turkish Biological (TURKBIO) Registry since 2011. By December 2020, 410 ax-SpA patients, treated with CZP, were included. Assessment of disease activity parameters was conducted at baseline and at regular follow-up intervals throughout the study period. Additionally, drug retention rates were evaluated through Kaplan-Meier survival analysis over the observation period.

Results: The analysis revealed that CZP demonstrates a high long-term retention rate in ax-SpA. At 36 months, the retention rate of CZP among patients with ax-SpA was 71.5%. During follow-up, 92 (22.4%) patients discontinued CZP treatment, with inefficacy being the main reason for discontinuation (58.7% of patients who discontinued therapy, n=54). Patients who discontinued CZP had significantly higher health assessment questionnaire, bath ankylosing spondylitis (AS) functional index, and bath AS disease activity index values compared to those who continued with CZP. They were relatively older, had longer symptom duration, and had a higher prevalence of

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uveitis. Compared to patients who continued with CZP, those who discontinued CZP were more frequently co-treated with non-steroidal anti-inflammatory drugs (NSAIDs) (68.5% vs. 53.1%), methotrexate (24.1% vs. 6.9%), sulfasalazine (38.9% vs. 12.6%), and leflunomide (5.6% vs. 0.6%). However, co-treatment with NSAIDs or conventional synthetic disease-modifying anti-rheumatic drugs did not increase the retention rate of CZP.

Conclusion: Real-world data from the TURKBIO registry reveal that CZP exhibits a high long-term retention rate in patients diagnosed with ax-SpA.

Keywords: Axial spondyloarthritis, certolizumab pegol, drug survival, tumor necrosis inhibitors, biological therapy

INTRODUCTION

Axial spondyloarthritis (ax-SpA) is a chronic inflammatory condition affecting the sacroiliac joints and vertebral column that can lead to irreversible disabilities (1,2). Tumor necrosis factor (TNF)-α has been demonstrated to play a significant role in ax-SpA pathogenesis (1,2). Consequently, TNF-α inhibitors (TNFi) are widely used in ax-SpA treatment (1-3). Certolizumab pegol (CZP), adalimumab, golimumab, infliximab, and etanercept represent the available TNFi options. The efficacy of these drugs has been demonstrated in randomized controlled trials (RCTs) meeting strict inclusion and exclusion criteria (1-3). However, in routine clinical practice, the presence of various comorbidities, concomitant medications, and atypical disease manifestations leads to the emergence of different patient phenotypes (4,5). Consequently, diverse sources of information are needed to confirm RCT findings.

These findings can offer valuable insights for healthcare professionals, particularly in developing effective treatment strategies for patients with ax-SpA. This topic is of particular concern for physicians due to various factors affecting the efficacy, safety, and adherence of selected therapeutic agents. Consequently, further investigation into the characteristics of patients exposed to TNFi, treatment adherence, and response rates to TNFi, is needed.

CZP has been documented to be both effective and safe in the treatment of ankylosing spondylitis (AS) and non-radiographic ax-SpA (nr-ax-SpA). Additionally, available long-term extension data of CZP in ax-SpA have been reported (6-8). The aim of this study was to evaluate drug survival of CZP in patients with ax-SpA and to determine the reasons and predictors for treatment discontinuation.

MATERIAL AND METHODS

Study Population

The Turkish Biological (TURKBIO) registry system is the Turkish version of the Danish rheumatological database (DANBIO), established in 2011. In this database, data on rheumatology patients, who will be initiated on biological treatment by many tertiary rheumatology centers across the country, are collected.

Patient characteristics, demographic features, diagnosis, disease duration, treatment, and outcome data have been collected in the TURKBIO registry system since 2011. Data extraction was performed in December 2020. Patients with ax-SpA diagnosis, ≥18 years of age, who were prescribed CZP between January 2011 and December 2020 in 11 tertiary centers of TURKBIO, were included. Approval was obtained from the Dokuz Eylül University Clinical Research Ethics Committee (approval number: 2024/02-79, date: 08.02.2024), and the study was performed in compliance with the principles outlined in the Declaration of Helsinki. All patients signed informed consent to be included in the TURKBIO registry system. The diagnosis of ax-SpA was established according to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria. This study included both radiographic ax-SpA (r-ax-SpA) and nr-ax-SpA patients, with AS specifically classified according to the modified New York criteria (9,10).

Outcome Measures

The main outcome was the retention rates of CZP for ax-SpA at one, two, and three years. Reasons for discontinuing CZP were categorized as inefficacy (primary and secondary lack of response), adverse events, remission, desire for pregnancy, and patient preference. Assessment of disease activity parameters was conducted at baseline and at regular follow-up intervals throughout the study period. Disease activity and functional status were evaluated using validated assessment instruments. The bath AS disease activity index (BASDAI) was utilized to assess disease activity on a scale of 0-10, where higher scores indicate greater disease activity. This self-reported instrument encompasses six questions addressing fatigue, spinal pain, peripheral joint pain, enthesitis, and morning stiffness (both severity and duration). The bath AS functional index (BASFI) was employed to evaluate functional limitations across 10

activities related to daily living, with scores ranging from 0-10; where higher scores reflect greater functional impairment. The health assessment questionnaire (HAQ) was used as a measure of disability, consisting of 20 questions across eight domains of physical function (with scores ranging from 0-3), where higher scores indicate increased disability. All questionnaires were administered in their validated Turkish versions.

Statistical Analysis

Summary descriptive statistics were presented as means with standard deviations, medians with interquartile ranges, and percentages, as appropriate. The likelihood of survival of CZP treatment was assessed using the Kaplan-Meier survival analysis. Statistical analysis was performed using international business machines (IBM) Statistical Package for the Social Sciences Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). The statistical significance threshold was defined as $p<0.05$, and all p-values were two-sided.

RESULTS

A total of 410 ax-SpA patients were enrolled in the study, with a median follow-up duration of 54 months. At 36 months, the retention rate of CZP among patients with ax-SpA was 71.5% (Figure 1). The long-term efficacy of CZP treatment was demonstrated by continuous improvements in ASDAS responses, BASDAI, and BASFI scores (Figure 2).

During follow-up, 92 (22.4%) patients discontinued CZP treatment. The main reason for treatment discontinuation (58.7% of patients who discontinued therapy) was inefficacy (n=54). Reasons included adverse events (n=6), surgery (n=4), pregnancy (n=3), transfer to other centers (n=3), neglect (n=3), and other reasons (n=17). Baseline characteristics of patients who continued with CZP and those who discontinued due to inefficacy are shown in Table 1.

Patients who discontinued CZP had significantly higher HAQ, BASFI, and BASDAI values compared to those who continued with CZP (Table 1). They were relatively older, had longer symptom duration, and had a higher prevalence of uveitis, compared to patients who continued with CZP.

CZP was the first biological disease-modifying anti-rheumatic drug (bDMARD) for 253 patients (61.7%), while 157 (38.3%) patients had previously used other bDMARDs. CZP was switched from adalimumab in 54 patients, etanercept in 53 patients, infliximab in 39 patients, and golimumab in 11 patients (Table 2). CZP retention rates were calculated as 77.8% for patients switching from adalimumab, 75.5% for those switching from etanercept, 63.6% for those switching from golimumab, and 89.7% for those switching from infliximab.

Compared to patients who continued with CZP, those who discontinued CZP were more frequently co-treated with non-steroidal anti-inflammatory drugs (NSAIDs) (68.5% vs. 53.1%), methotrexate (24.1% vs. 6.9%), sulfasalazine (38.9% vs. 12.6%), and leflunomide (5.6% vs. 0.6%), in addition to CZP (Table 2). However, co-treatment with NSAIDs or conventional synthetic DMARDs (csDMARDs) did not increase the retention rate of CZP. The risk of discontinuing the drug was higher when CZP was co-administered with NSAIDs or csDMARDs compared to CZP alone. This finding may be due to physicians attempting to add NSAIDs and/or csDMARDs to improve treatment adherence in anticipation of potential bDMARD treatment failure.

DISCUSSION

ax-SpA is a type of spondyloarthritis that can affect the sacroiliac joints and vertebral column, potentially leading to long-term impairments (1,2). Reducing patient complaints and preventing disabilities are the two main objectives of ax-SpA medical care. It involves the use of anti-cytokine drugs that target TNF-α and interleukin-17, as well as NSAIDs (3). The current study, which documents practical experience, indicates that CZP, a TNFi, is effective in treating ax-SpA over a considerable period.

RCTs and open-label extension studies have shown that CZP is effective in treating ax-SpA (7,8). Additionally, one-year follow-up data from a Turkish tertiary center on CZP treatment for ax-SpA was published by Bilgin et al. (6). In the first year, the CZP retention rate was 72.5%. The CZP retention rates for the study's first, second, and third years were 83.3%, 76.1%, and 71.5%, respectively. Our real-world experience demonstrates that CZP has a high retention rate in patients with ax-SpA, and that this rate holds steady over time.

The main reasons for stopping treatment were both the primary and secondary inefficacy of the medication. Because CZP was ineffective, patients who stopped taking it had significantly lower HAQ, BASDAI, and BASFI scores than those who continued to take it. These findings imply that patients with higher degrees of disability are more likely to stop their treatment. Tracking ax-SpA, including identifying patients who are appropriate for bDMARDs, is commonly done using patient-reported outcome (PRO)-based indices like HAQ, BASDAI, and BASFI (11). Furthermore, Krabbe et al. (12) demonstrated that ax-SpA patients with poor PROs had lower TNFi retention rates. It is important to keep in mind that PROs, because they can alter ax-SpA due to competing conditions like depression, fibromyalgia, and degenerative disc disease, are not pathognomonic (12,13).

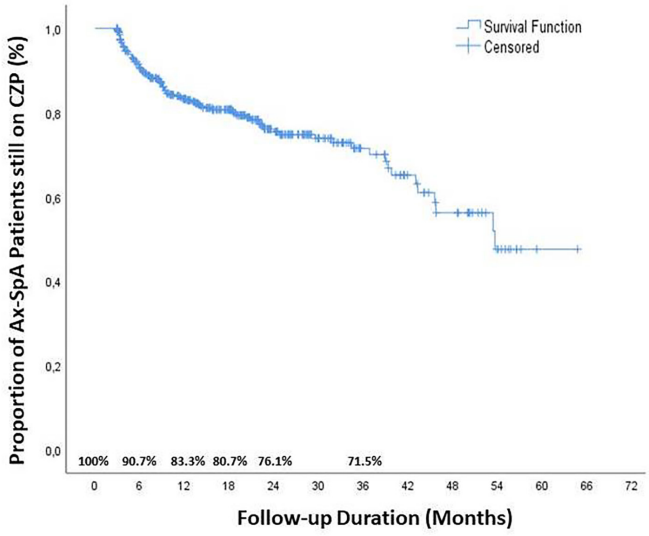

Figure 1. Drug survival of CZP in patients with ax-SpA. Kaplan-Meier survival curve showing drug retention of certolizumab pegol in 410 ax-SpA patients. The retention rate at 36 months was 71.5%. Vertical lines indicate censored data
CZP: Certolizumab pegol, ax-SpA: Axial spondyloarthritis

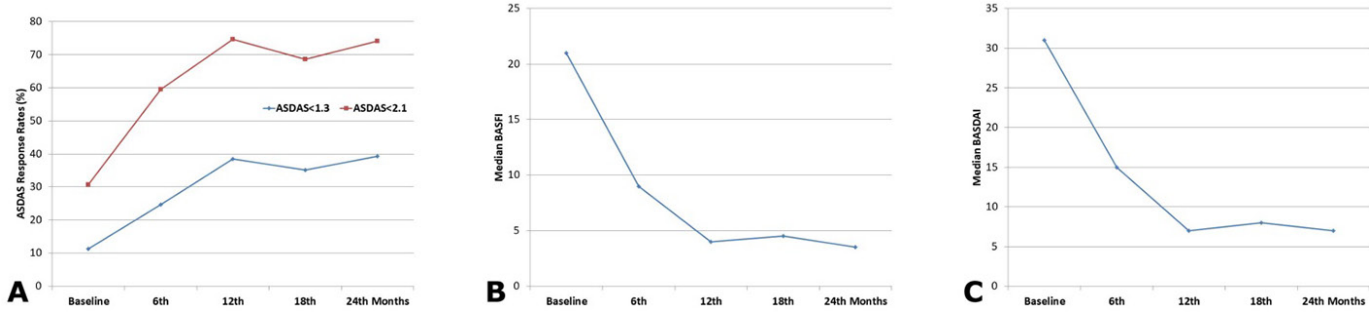

Figure 2. Clinical responses in patients with ax-SpA treated with CZP. Sustained improvements in BASDAI, BASFI and ASDAS scores in ax-SpA patients treated with CZP. Baseline BASDAI score decreased from 5.8±1.3 to 2.1±1.6 at month 36, BASFI score from 5.3±1.5 to 2.0±1.4, and ASDAS score from 3.7±0.9 to 1.8±0.8 ($p<0.001$ for all comparisons)
CZP: Certolizumab pegol, ax-SpA: Axial spondyloarthritis, BASDAI: The bath ankylosing spondylitis disease activity index, BASFI: The bath ankylosing spondylitis functional index, ASDAS: Ankylosing spondylitis disease activity score

Along with the efficacy shown in controlled clinical trials, our examination of CZP retention rates provides valuable information about the treatment's actual efficacy in ax-SpA. Landewé et al. (14) RAPID-axSpA study, was crucial in demonstrating the efficacy of CZP, as it showed significant improvements at 24 weeks in patients with both r-ax-SpA and nr-ax-SpA. Notably, only 38.3% and 19.8% of patients treated with a placebo received ASAS20 and ASAS40 responses, compared to 57.7% and 43.1% of patients treated with CZP, respectively.

Additional supporting information is provided by Deodhar et al. (8), who conducted a 52-week randomised placebo-controlled study with an emphasis on nr-ax-SpA. Their study found that by week 52, 47.2% of patients treated with CZP had significantly improved their ASDAS scores (ASDAS-MI), compared to only 7.0% of the placebo group. As a result, even in the early stages of ax-SpA, CZP is now thought to be helpful.

In our study, patients who had more functional limitations were more likely to stop taking CZP. The findings of López-Medina et al. (15), who observed that certain comorbidities, specifically fibromyalgia and depression, were linked to lower TNFi survival in ax-SpA patients across European registries, seem to be consistent with these observations. The authors of the study proposed a "comorbidity burden index" as a possible instrument to assist physicians in determining the probability of TNFi persistence in patients with ax-SpA.

Table 1. Baseline characteristics of ax-SpA patients who continue and discontinue to CZP

	All patients (n=410)	Continue to CZP (n=318)	Discontinue to CZP‡ (n=54)	p-value
Females, n (%)	185 (49.7)	157 (49.4)	28 (51.9)	0.736
Age*, years	42 (34-49)	41 (34-49)	45 (34-54)	0.064
Disease duration*, years	8 (5-12)	8 (5-12)	8 (6-14)	0.128
Symptom duration*, years	11 (7-17)	11 (6-16)	12 (8.5-20)	0.054
HLA-B27, n (%)	150 (63.8)	129 (64.5)	21 (60)	0.609
Enthesitis, n (%)	228 (61.3)	201 (63.2)	27 (50)	0.065
Dactylitis, n (%)	40 (10.8)	34 (10.7)	6 (11.1)	0.927
Uveitis, n (%)	38 (10.2)	29 (9.1)	9 (16.7)	0.090
IBD, n (%)	20 (6)	15 (5.2)	5 (10.6)	0.177
ESR*, mm/h	21.5 (10-37)	21 (10-37)	23 (10-34)	0.999
CRP*, mg/dL	7 (3-20)	7 (3-20)	7 (3-22)	0.727
HAQ*	**0.63 (0.25-0.94)**	**0.5 (0.25-0.88)**	**0.75 (0.38-1.25)**	**0.009**
VAS-physicians*	20 (10-40)	19 (10-40)	25 (10-36)	0.468
VAS-patient global*	50 (21-70)	50 (20-70)	54 (36-70)	0.156
VAS-patient pain*	50 (20-70)	50 (20-70)	51 (40-73)	0.080
VAS-patient fatigue*	50 (20-70)	48 (17.5-70)	50 (27-70)	0.223
BASFI*	21 (7-45)	20.5 (6-41)	31 (13-58)	0.011
BASDAI*	30.5 (13-52)	30 (12-50)	43 (23-61.5)	0.002
ASDAS*	2.7 (1.8-3.7)	2.7 (1.8-3.6)	2.9 (2.3-4)	0.062

‡Discontinue due to inefficacy. *Data are expressed as median (IQR1-IQR3). ASDAS: Ankylosing spondylitis disease activity score, ax-SpA: Axial spondyloarthritis, BASDAI: The bath ankylosing spondylitis disease activity index, BASFI: The bath ankylosing spondylitis functional index, CRP: C-reactive protein, CZP: Certolizumab pegol, ESR: Erythrocyte sedimentation rate, HAQ: Health assessment questionnaire, HLA: Human leukocyte antigen, IBD: Inflammatory bowel disease, IQR: Interquartile range; VAS: Visual analog scale

Table 2. Previous bDMARDs and co-administered treatments in ax-SpA patients who continue and discontinue CZP

	All patients (n=410)	Continue to CZP (n=318)	Discontinue to CZP* (n=54)	p-value
Previous bDMARDs, n (%)				
Adalimumab	54 (14.5)	42 (13.2)	12 (22.2)	0.082
Etanercept	53 (14.2)	40 (12.6)	13 (24.1)	0.025
Golimumab	11 (3)	7 (2.2)	4 (7.4)	0.060
Infliximab	39 (10.5)	35 (11)	4 (7.4)	0.425
Co-treated drugs, n (%)				
NSAID	206 (55.4)	169 (53.1)	37 (68.5)	0.036
Analgesics	136 (36.6)	113 (35.5)	23 (42.6)	0.319
Methotrexate	35 (9.4)	22 (6.9)	13 (24.1)	<0.001
Sulphasalazine	61 (16.4)	40 (12.6)	21 (38.9)	<0.001
Leflunomide	5 (1.3)	2 (0.6)	3 (5.6)	0.023
Glucocorticosteroids	12 (3.2)	8 (2.5)	4 (7.4)	0.080

ax-SpA: Axial spondyloarthritis, bDMARDs: Biological disease-modifying antirheumatic drugs, CZP: Certolizumab pegol, NSAID: Non-steroidal anti-inflammatory drug

In comparison with patients who continued to receive CZP, those who ceased treatment were more likely to be co-treated with NSAIDs, methotrexate, sulfasalazine, and leflunomide. However, concomitant treatment with NSAIDs or csDMARDs did not result in an increased retention rate of CZP. For ax-SpA, the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network advises against the routine prescription of csDMARDs (3). However, physicians may elect to administer NSAIDs and/or csDMARDs in cases where they predict that bDMARD treatment will prove ineffective.

This observation gives rise to a number of significant inquiries regarding treatment strategy. The most recent ASAS-European League Against Rheumatism recommendations (16), reaffirm the absence of sufficient evidence to support the conventional co-prescription of csDMARDs alongside TNFi in cases of axial illness. In addition to the use of combinations of pharmaceuticals, the results of the present study emphasise the importance of the patient's previous treatment history in the prediction of outcomes. The observations presented herein are in alignment with the existing research, which has indicated that prior treatment response and disease activity are associated with the long-term retention of biological agents. A study conducted by Glintborg et al. (17) utilised the DANBIO registry system to analyse 432 individuals with AS. The objective of the study was to investigate parameters influencing clinical response and medication survival after switching TNFi therapy. The findings demonstrated that the survival rate of a second TNFi was significantly reduced in patients who discontinued the first TNFi due to inefficacy, in contrast to those who terminated it due to adverse effects.

Lie et al. (18) indicated that concomitant administration of csDMARDs, such as methotrexate and sulfasalazine, correlated with improved retention of TNFi therapy in AS. A recent study indicated that concurrent methotrexate administration was linked to a reduced likelihood of medication discontinuation in psoriatic arthritis, but not in ax-SpA (19). Sepriano et al. (20) reported that the co-administration of csDMARDs or NSAIDs was not linked to the drug survival of TNFi in the treatment of ax-SpA. Methotrexate and leflunomide may be favoured due to their anticipated effects on immunogenicity, which is regarded as a factor contributing to the inefficacy of bDMARDs. Sulfasalazine has been demonstrated to have no influence on immunogenicity and has been found to be efficacious in the treatment of peripheral spondyloarthritis, but not in ax-SpA. In the present investigation, concomitant use of CZP with sulfasalazine, methotrexate, and leflunomide did not correlate with enhanced retention rates of CZP in ax-SpA.

The findings of the present study are in alignment with those of recent research conducted by Ørnbjerg et al. (5), which examined over 24,000 biologic-naïve ax-SpA patients from 12 European registries within the EuroSpA collaboration. The study revealed that prior TNFi treatment correlated with diminished drug survival rates and responses to subsequent TNFi therapies. This suggests that the quantity of previously unsuccessful TNFi treatments serves as a significant predictor of future treatment outcomes. Furthermore, Ciurea et al. (21) established that the failure mechanism of the prior TNFi, whether primary or secondary, is crucial in ascertaining the efficacy of transitioning to an alternative TNFi. Their research on ax-SpA patients from the Swiss Clinical Quality Management Cohort indicated that those with primary non-response exhibited markedly reduced response rates to a subsequent TNFi compared to those with secondary non-response.

The immunogenic nature of CZP necessitates particular consideration when analysing the findings of this study. CZP is a polyethylene glycosylated fragment antigen-binding fragment of a humanised anti-TNF monoclonal antibody, which may influence its immunogenicity profile. Nesbitt et al. (22) demonstrated that CZP exhibits lower immunogenicity relative to other monoclonal antibody TNFi treatments, which may partially elucidate the favourable retention rates noted in this group. The absence of the fragment crystallized region in CZP may be responsible for its reduced immunogenicity profile, as demonstrated in vitro comparisons with other anti-TNF alpha drugs.

The results of the present study carry significant implications for clinical practice. The three-year retention rate of CZP in ax-SpA patients is 71.5%, indicating that CZP may serve as a viable long-term treatment option. The observations made in this study indicate a potential relationship between baseline disease activity, functional limitations, and treatment outcomes. These observations suggest that early intervention with appropriate therapy may help prevent progressive functional decline. The patterns observed in the present study subtly emphasise the possible advantages of prompt therapeutic interventions in preserving patient functionality over time. A treat-to-target strategy that seeks low disease activity or remission within the initial 3-6 months, as proposed by Landewé et al. (23), may enhance long-term outcomes. The observation that co-treatment with csDMARDs did not enhance CZP retention suggests that clinicians must thoroughly assess the risk-benefit ratio associated with combination therapy. This is of particular

significance when considering the findings of Sepriano et al. (16), whose prospective cohort study on this topic demonstrated variable outcomes associated with the combination of TNFi and csDMARDs in patients with spondyloarthritis. The combination of these treatments may offer potential benefits for patients with peripheral involvement; however, the addition of csDMARDs has demonstrated only limited net clinical advantages in cases of purely axial disease. It is imperative that potential adverse effects be taken into consideration during risk-benefit evaluations.

If bDMARD treatment for ax-SpA does not yield the desired results or causes adverse effects, switching to an alternative bDMARD option is recommended (3). While the optimal bDMARD selection is yet to be determined, this presents a significant opportunity for clinicians to refine their decision-making processes. As is thoroughly documented, the efficacy and retention rates of bDMARDs can vary according to the number of previous treatments.

Limitations

This study has several limitations due to its observational design, including potential selection bias and unmeasured confounders. The registry lacks comprehensive data on certain variables, such as socioeconomic factors, that may influence treatment adherence. In addition, the sample size limited the robustness of subgroup analyses, and radiographic progression data, critical for assessing structural outcomes, were not available.

CONCLUSION

A multitude of positive factors influence drug retention, including long-term efficacy, safety, patient adherence, and ease of administration. A study of real-world data from the nationwide TURKBIO registry in Türkiye has demonstrated that CZP exhibits a noteworthy long-term retention rate in patients diagnosed with ax-SpA. The analysis indicates that baseline disease activity and functional status are pertinent factors in assessing treatment patterns involving CZP. The findings of this study indicate that the combination of NSAIDs and csDMARDs may not enhance CZP retention rates in patients exhibiting difficult prognostic indicators. These insights have the potential to refine clinical approaches and inform future discussions regarding individualised treatment planning for patients with ax-SpA.

Ethics

Ethics Committee Approval: The data for this study were sourced from the TURKBIO registry, which serves as the Turkish equivalent of the DANBIO. The TURKBIO database project has been designated as a Phase IV observational study by the Dokuz Eylül University Clinical Research Ethics Committee (approval number: 2024/02-79, date: 08.02.2024). This ensures that the project adheres to the ethical norms that are in place for clinical research.

Informed Consent: A written informed consent was obtained from the participants.

Footnotes

Authorship Contributions

Concept: A.K., Design: A.K., Data Collection or Processing: A.K., Y.P., S.A., S.Ş., A.A.G., Ö.S.G., A.Y., S.Y., N.İ., G.Y.Ç., M.P.A., F.Ö., Analysis or Interpretation: A.K., R.P.S., Literature Search: A.K., R.P.S., Writing: A.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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