Clinical Rheumatology (2023) 42:3251–3255
https://doi.org/10.1007/s10067-023-06724-3

ORIGINAL ARTICLE

Cause analysis of conversion to biologics in spondyloarthritis patients with poor response to conventional treatment

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Received: 6 March 2023 / Revised: 4 July 2023 / Accepted: 25 July 2023 / Published online: 23 September 2023

Abstract

Objective We sought to investigate the reasons why spondyloarthritis (SpA) patients failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) and the influences of different initial cDMARDs on the likelihood of a switch to biologics.

Methods SpA patients were divided into a conventional drug maintenance group and a biologics conversion group to determine the causes of conversion to biologics. Then, we divided all patients into three groups according to different initial cDMARDs, NSAID monotherapy, NSAID + (sulfasalazine or thalidomide) double combination, and NSAID + sulfasalazine + thalidomide triple combination therapy groups, to clarify the influence of initial treatment on later conversion to biologics.

Results This study includes 202 patients, including 97 patients in the conventional drug maintenance group and 105 patients in the biologics conversion group. The mean age of the conventional drug maintenance group was higher than that of the biologics conversion group (40.8 ± 14.3 vs. 33.8 ± 12.3 years, $P < 0.05$). Uveitis (OR 5.356, $P < 0.05$) is positively correlated with conversion to biological therapy, while age (OR 0.940, $P < 0.05$) is negatively correlated. The proportion of NSAID monotherapy, double combination, and triple combination groups converted to biological agents was 80%, 51.1%, and 23.2%, respectively ($P < 0.05$).

Conclusion Age and uveitis are related to conversion to biologics therapy. The early combination of sulfasalazine and thalidomide with NSAIDs may lower the probability of conversion to biologics therapy in the later stage and offer a new option for patients with limited use of biologics in SpA patients.

Key Points
- *Patients' move to biologics may be caused mostly by inadequate disease control by conventional oral medications.*
- *Regardless of axial vs. peripheral joint involvement, combination drug therapy was superior to single drug therapy in controlling SpA and decreasing the probability of conversion to a biological agent.*
- *For SpA patients who are not candidates for biologics due to contraindications or other reasons, early combination application of NSAIDs, sulfasalazine, and thalidomide may be a new choice.*

Keywords Biologics · Conventional synthetic DMARDs · NSAIDs · Spondyloarthritis

Introduction

In 2009, the Assessment of SpondyloArthritis International Society (ASAS) published the classification criteria for axial spondyloarthritis (SpA). The new definition for inflammatory back pain and active sacroiliitis on MRI as one of the imaging parameters was the most remarkable part. Based on the high sensitivity and specificity of the entire set of the new criteria, it was applied widely for SpA in the clinic once it was published. SpA is an autoimmune disease marked by chronic axial and peripheral joint inflammation and may be complicated by extra-articular manifestations, like uveitis and inflammatory bowel disease. When disease progression is halted, inflammation tends to rebound and worsen. Inflammatory factors such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) may rise during the active stage of the disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) and functional

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exercise are the first-line initial treatments; sulfasalazine (SSZ) can be used for peripheral SpA. If they are ineffective or intolerable, biological agents, such as TNF-α inhibitors (TNFi) and interleukin-17A (IL-17A) inhibitors, should be considered [1]. Due to the efficacy of biologics, they are commonly used in the clinic. However, biologics usage by some individuals is restricted due to cost, infection risk, malignancy, or serious heart conditions. To provide new ideas for selecting clinical treatment schemes, this paper used the new SpA classification criteria recommended by the ASAS in 2009 and describes a retrospective study to investigate which clinical characteristics are associated with conversion to a biological agent and to clarify the impact among different initial conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) on that conversion.

Methods and patients

This study retrospectively screened SpA patients hospitalized from January 2015 to December 2021 in The Second Affiliated Hospital of Chongqing Medical University who met the ASAS classification criteria for axial SpA in 2009. The disease activity index referred to the patient's visual analogue pain scale (VAS) score. All the patients had sacroiliitis, and some of them also had peripheral arthritis. NSAIDs with or without cDMARDs were the initial treatment. cDMARDs included only sulfasalazine and thalidomide (THD) because these two drugs were the most common drugs we used. The patients who used other cDMARDs have been eliminated. We collected clinical data from the initial visit and followed up with the patients. If patients responded well to conventional drugs, which effectively controlled disease, and continued on maintenance therapy, they were included in the conventional drug maintenance group. Patients whose VAS score decreased less than 50% and who switched to biologics after over 6 months of conventional drug administration were included in the biologics conversion group. This paper compares the clinical data of the two groups and then conducts a binary logistic regression correlation analysis to determine the causes of conversion to biological agents. To explore the impact of different initial treatments on conversion to biological agents, we divided patients into three groups according to the conventional drug regimen: NSAID monotherapy group, NSAID + (SSZ or THD) double combination group, and NSAID + SSZ + THD triple combination group. We compared the proportion of patients converted to biologics in these three groups. All patients have been approved by the Ethics Committee at The Second Affiliated Hospital of Chongqing Medical University and have therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

General data and laboratory tests

We collected the age; sex; disease duration; peripheral joint involvement of limbs, hip, and sternoclavicular joints; laboratory examinations; bone mineral density; uveitis; and medication regimen of all patients when they were admitted to our hospital for the first time and follow-up. Inflammatory bowel disease was not included because of the small number of patients in this group. Laboratory tests included HLA-B27, ESR, CRP, TNF-α, and IL-6 at the first visit. Bone mineral density (BMD) decreases were defined as a T or Z value of <-1.

Statistical analysis

Statistical analysis was performed by SPSS version 23.0, and $P < 0.05$ indicated statistical significance. The discrete data were analyzed using a chi-square test and expressed as numbers and percentages. Continuous variables were expressed as mean ± standard deviation ($\overline{\chi} \pm s$). When the variance was homogeneous, an independent samples t-test was adopted. When the variance was uneven, a two-independent samples nonparametric test Mann-Whitney U test was adopted. Binary logistic regression was adopted to analyze the correlation, and $P < 0.05$ indicated a significant relationship between clinical features and conversion to biologics. The odds ratio was expressed by OR value and 95% confidence interval (OR, 95% CI).

Results

This study included 202 patients. For the comparison of clinical indexes between the conventional drug maintenance group and the biologics conversion group, 97 patients were in the conventional drug maintenance group, with an average age of 40.8 ± 14.3 years, and 105 patients were in the biologics conversion group, with an average age of 33.8 ± 12.3 years, of which 99 patients (94.3%) were treated with a TNFi and six patients (5.7%) with an IL-17A inhibitor. Patients in the conventional drug maintenance group were older than those in the biologics conversion group ($P < 0.05$). There were no significant differences between the two groups in sex; disease duration; the proportion of peripheral joint involvement, including limb joints, hip joints, and sternoclavicular joints; the incidence of uveitis; BMD decrease; HLA-B27 positivity rate; ESR, CRP, TNF-α, and IL-6 ($P > 0.05$). The details are shown in Table 1.

This study adopted a binary logistic regression analysis between the two groups to verify a correlation between clinical indicators and patients' conversion to biologics. We observed that uveitis was positively correlated with the

Table 1 Comparison of clinical characteristics between the traditional medicine maintenance group and the conversion to biological agent group

	Traditional medicine maintenance group (*n*=97)	Biological agent conversion group (*n*=105)	*P*
Gender (male/female)	61/36	75/30	0.196
Age (years), mean ± S.D	40.8 ± 14.3	33.8 ± 12.3	0.001*
Disease duration (month), median (25%, 75%)	36 (6, 120)	48 (12, 120)	0.408
Limbs joint involvement, *n* (%)	43 (46.1%)	50 (6.9%)	0.639
Hip joint involvement, *n* (%)	30 (31.4%)	26 (23.9%)	0.328
Sternoclavicular joint involvement, *n* (%)	7 (6.9%)	9 (9.7%)	0.473
BMD decreased, *n* (%)	28 (29.4%)	31 (29.2%)	0.918
Uveitis, *n* (%)	9 (8.8%)	18 (17.7%)	0.101
HLA-B27 positive, *n* (%)	83 (87.3%)	96 (91.2%)	0.19
ESR (mm/h), mean ± S.D	31.2 ± 25.4	32.3 ± 25.9	0.748
CRP (mg/l), mean ± S.D	20.5 ± 25.2	21.9 ± 22.4	0.693
TNF-α (pg/ml), mean ± S.D	165.9 ± 179.9	153.8 ± 127.8	0.435
IL-6 (pg/ml), mean ± S.D	22.8 ± 28.1	24.7± 29.3	0.728

**P*-value was less than 0.05

conversion to biologics (OR 5.356, $P < 0.05$), and the probability of conversion to biologics in patients with uveitis was 5.356 times that in patients without uveitis. Age (OR 0.940, $P < 0.05$) was negatively correlated with conversion to biologics ($P < 0.05$), and the probability decreased by 6% with per year of advancing age. Sex, peripheral joint involvement, BMD decrease, HLA-B27 positivity, and inflammatory factors did not correlate with conversion to biological agents. The details are shown in Table 2.

This study divided all patients into three groups based on different initial conventional drug schemes to determine the statistical differences in the proportion of patients converted to biologics. We obtained the following results. Initial treatment with NSAIDs alone was given to 60 patients; 48 (80%) were later converted to biological agents. Double combination treatments with NSAIDs + (SSZ or THD) were given to 86 patients; 44 (51.1%) were later converted to biologics. Triple combinations were given to 56 patients; only 13 (23.2%) were later converted to biologics. The proportion of patients who converted to biologics in the three different initial schemes was different ($P < 0.05$), and the comparison of any two groups was also different ($P < 0.05$), as shown in Table 3.

Discussion

In recent years, because of the decreased cost of biological agents and the availability of medical insurance, biologics have become widely used for SpA patients with inadequate response to NSAIDs. The efficacy of biologics has been universally acknowledged; however, their application in patients with severe cardiopulmonary disorders,

Table 2 Binary logistic regression correlation analysis of conversion to biological agent therapy

	OR (95%CI)	*P*
Gender	0.926 (0.372–2.308)	0.869
Age	0.940 (0.900–0.983)	0.006*
Peripheral joint involvement	1.405 (0.552–3.577)	0.476
BMD decreased	2.161 (0.666–7.011)	0.200
Uveitis	5.356 (1.347–21.296)	0.017*
HLA-B27 positive	1.123 (0.277–4.552)	0.871
ESR	0.994 (0.970–1.018)	0.624
CRP	1.010 (0.989–1.031)	0.371
TNF-α	0.999 (0.996–1.002)	0.518
IL-6	0.997 (0.982–1.013)	0.736

**P*-value was less than 0.05

Table 3 Comparison of three initial traditional oral medication regimens converted to biological agents

	NSAIDs *n*=60	NSAIDs + (SSZ or THD) *n*=86	NSAIDs + SSZ + THD *n*=56	*P*
Traditional medicine maintenance therapy	12 (20%)	42 (48.9%)	43 (76.8%)	<0.001
Biological agent conversion therapy	48 (80%)	44 (51.1%)	13 (23.2%)	

$P < 0.05$ indicates that the proportion of patients converted to biological agents in the three medication groups is statistically different. The probability of any two medication methods being converted to biological agents is different, and the difference is statistically significant ($P < 0.05$)

autoimmune diseases, prior or latent tuberculosis infections, and malignancies is restricted [1]. Therefore, it is crucial to find the characteristics of patients who can maintain conventional drug treatment. According to our data, the age was older in the conventional drug maintenance group compared to the biologics conversion group and was negatively correlated with conversion to biological therapy. The risk of converting to a biological agent decreased by 6% per year of advancing age. The disease activity of SpA may reduce gradually with age [2, 3], a trend that can be somewhat improved by oral conventional drugs. The progressive decline in disease activity may be connected to the decreasing likelihood of conversion to a biologics therapy over time.

SpA has only recently been defined. Therefore, the literature is limited. The recommendations for axial and peripheral SpA were largely extrapolated from evidence in AS. The most prevalent extra-articular symptom of AS is uveitis. Approximately 50% of AS patients will suffer recurrent uveitis [4], and 13–19% of AS [5] patients with uveitis are resistant to local ocular treatments. Chronic uveitis will develop as a consequence of recurrent uveitis and medication resistance. Conventional drugs have a poor curative effect on uveitis, whereas TNFi can reduce joint inflammation and significantly reduce the recurrence of uveitis and significantly enhance visual recovery [6, 7]. In this investigation, a chi-square test revealed no statistically significant difference between the proportion of patients with uveitis in the conventional drug maintenance group and the biologics conversion group (8.8% vs. 17.7%, $P > 0.05$). However, binary logistic correlation analysis revealed a link between uveitis and the conversion of patients to biologics (OR 5.356, $P = 0.017$). The chi-square test examines a single factor; the binary logistic analysis is a multivariate analysis that retains statistical significance in the presence of additional variables. Therefore, we refer to the results of a binary logistic analysis that uveitis positively correlated with conversion to biological therapy. All the 18 uveitis patients who converted to biological treatments used TNFi. Patients may switch from conventional drugs to biologics due to the recurrent nature of uveitis, drug resistance to local treatment, impact on patients' vision, and good responsiveness to TNFi.

According to studies, sulfasalazine may potentiate adenosine receptor-mediated anti-inflammatory effects in joints [8]. The digestive tract may be the primary site of antigen stimulation in inflammatory joint disorders [9]. Sulfasalazine alters the intestinal flora and inflamed tissues in rheumatic disease to have therapeutic effects [10, 11], although its exact mechanism in SpA is as yet unknown. In previous studies on the efficacy of sulfasalazine or comparisons with other medications, nearly all used sulfasalazine alone [12–14], and there is a dearth of evidence on combination treatments. Only a small sample randomized double-blind controlled trial confirmed that NSAIDs combined sulfasalazine were more effective than NSAIDs alone in axial SpA patients [14]. The guideline of 2010 Chinese Society for Rheumatology for the Diagnosis and Treatment of Ankylosing Spondylitis recommended thalidomide to refractory AS. Thalidomide was commonly used in the triple combination therapy with NSAIDs and sulfasalazine for many years. In patients with active AS, thalidomide may work by reducing the levels of TNF-α, M-CSF, and TGF-β, thereby reducing inflammation, controlling the immune system, and decreasing bone remodeling [15]. Multiple open, randomized, controlled studies have demonstrated that thalidomide is beneficial for both axial and peripheral joints [16–18]. In addition to ameliorating the physical symptoms of AS patients, thalidomide can also ameliorate their psychosocial symptoms and sleep difficulties [19]. Long-term use of thalidomide has been demonstrated to be both safe and effective in AS, with cumulative effects as treatment duration increases [20]. The major side effects were drowsiness, constipation, dry mouth, dizziness, and dandruff, which improved after drug withdrawal. However, due to the lack of randomized controlled studies on thalidomide in the treatment of AS and SpA, the therapeutic effect has not been fully recognized, and the drug has not been approved for use in this indication, so it has not been widely used in the clinic. At present, the first-line initial treatment for SpA patients is still NSAIDs alone, while sulfasalazine is only recommended for patients with prominent peripheral joint symptoms [1]. To clarify the influences of the combined application of conventional drugs on the later conversion to biologics, we divided patients into three groups. The results show that the combination of NSAIDs with sulfasalazine and thalidomide significantly reduced the proportion of patients converted to biologics ($P < 0.05$). The triple combination treatment group had the lowest proportion (23.2%) of patients who converted to biologics compared to the two-drug treatment and the NSAID alone groups. Axial involvement was detected in every subject examined for this paper. There was no statistical significance in the involvement of peripheral joints between the conventional drug maintenance group and biologics conversion group. This implied that regardless of axial vs. peripheral joint involvement, combination drug therapy was superior to single drug therapy in controlling SpA and decreasing the probability of conversion to a biological agent. Patients' move to biologics may be caused mostly by inadequate disease control by conventional oral medications. For SpA patients who are not candidates for biologics due to contraindications or other reasons, early combination application of NSAIDs, sulfasalazine, and thalidomide may, through various mechanisms of action, improve the curative effect, reduce inflammation, and maintain the stability of SpA. These findings offer patients

who cannot or are unwilling to adopt biologics an empirical basis for choosing conventional medications.

We used the ASAS classification criteria for SpA in 2009. Therefore, we covered patients who were diagnosed by MRI, which is sensitive for SpA, and patients were in the early stage of the disease. However, this paper is just a retrospective study. We did not present the differences between the NSAID + sulfasalazine group and the NSAID + thalidomide group because the number of patients varies dramatically. There are a dearth of randomized controlled studies that demonstrate the effectiveness of combination therapy, even in AS. Data are urgently needed to support the efficacy of combined medications, and the practical utility justifies further exploration for SpA.

Conclusions

Uveitis, youth, and poor response to conventional treatment were most closely correlated with conversion to biologics in SpA patients. Compared to NSAID monotherapy, early combined application of sulfasalazine and thalidomide with NSAIDs may enhance the curative effect, alleviate inflammation, maintain disease stability, and reduce the probability of conversion to biologics. However, more reliable data must be urgently generated to provide new options for SpA patients who have limited access to biological agents.

Funding This work was supported by grant no. 81771738 from the National Natural Science Foundation of China.

Compliance with ethical standards

Disclosures None.

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