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Current Status of Biological Treatment in Ankylosing Spondylitis Patients and Some Related Factors

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ABSTRACT

Background: Axial spondyloarthritis (axSpA) is a potentially disabling inflammatory arthritis of the spine, usually presenting as chronic back pain typically before the age of 45 years. It is often associated with one or more articular features, including synovitis, enthesitis, and dactylitis. It may also be associated with several non-articular features; these include uveitis, psoriasis, and inflammatory bowel diseases1. **Objective**: The aim of this article is to describe the status of using biological drugs and some related factors in treating ankylosing spondylitis in Vietnam. **Methods:** A joint prospective and retrospective cross-sectional descriptive study was conducted on 161 ankylosing spondylitis patients treated with biological drugs at the Centre for Rheumatology between January 2018 and July 2021. Data were collected at the first dose and after 3, 6, 12, 24, and 36 months, including general characteristics, clinical and para-clinical features, drug use status, and related factors. **Results**: Of the 161 patients, 86.3% were male, with a mean age of 31.1 ± 11.6 years and a mean disease duration of 7.6 ± 6.6 years. Most patients were started on biologics at stage II (46.6%) or III (28.6%). Moreover, 68.9% had active disease based on the Bath Ankylosing Spondylitis Disease Activity Index. The most commonly prescribed first-line therapy was anti-tumor necrosis factor (69.6%), with infliximab the most frequently prescribed drug (44.7%). The rate of biological drug treatment decreased gradually from 100% at the start to 77% after one year and 39.1% after three years. Moreover, 74% of patients changed drugs due to non-response, and 50% discontinued treatment for economic reasons. Age was associated with treatment adherence, and drug change rates were higher in female patients and patients with active disease. Age was significantly associated with drug discontinuation ($p < 0.05$). **Conclusion**: Infliximab was the most commonly prescribed first-line drug. The rate of biological therapy gradually decreased after three years. Most patients changed drugs due to non-response, and many discontinued the drugs for economic reasons. Among the individual and clinical factors, age was associated with treatment adherence.

Keywords: ankylosing spondylitis, biological drugs, bDMARD, treatment adherence.

1. BACKGROUND

Axial spondyloarthritis (axSpA) is a potentially disabling inflammatory arthritis of the spine, usually presenting as chronic back pain typically before the age of 45 years. It is often associated with one or more articular features, including synovitis, enthesitis, and dactylitis. It may also be associated with several non-articular features; these include uveitis, psoriasis, and inflammatory bowel diseases1. Patients with axSpA are classified as having one of two subtypes: ankylosing spondylitis (AS; also termed radiographic axSpA) or non-radiographic axSpA (nr-axSpA). Patients with AS exhibit radiographic abnormalities consistent with sacroiliitis, but such findings are not evident on plain radiography in nr-axSpA. AS affects the spine and can lead to chronic back pain and disability2,3.

The primary goals of managing AS are to reduce symptoms and prevent complications, with initial treatments including nonpharmacologic measures and nonsteroidal anti-inflammatory drugs (NSAIDs)4-8. However, some patients may not respond well to these treatments, and the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) in the early 2000s brought new hope to these patients. These drugs, including tumor necrosis factor (TNF) inhibitors, anti-interleukin (IL)-17 antibodies, and Janus kinase (JAK) inhibitors, have proven effective in treating AS9-15. The Assessment of SpondyloArthritis International Society (ASAS)-European Alliance of Associations for Rheumatology (EULAR) recommendations for managing axSpA recommend NSAIDs, biological drugs, disease-modifying antirheumatic drugs, analgesics, nondrug treatments (e.g., education, exercise, and physical therapy), and surgical intervention to relieve symptoms of AS8.

Following the approval of the first tumor necrosis factor-alpha (TNF-α) inhibitor (TNFi) for use in AS many years ago, TNFi treatment has become the mainstay treatment for active AS. Multiple randomized trials and several meta-analyses of randomized trials have demonstrated the ability of the TNFi to reduce disease activity in patients with AS. The most commonly used TNFi are adalimumab, etanercept, golimumab, and infliximab8. In addition, while the IL-17 axis is the established target of AS treatment, the IL-23/T helper 17 axis has recently attracted attention as a possible inflammation pathway. The use of IL-17A inhibitors (IL-17i) such as secukinumab in treating AS supports the clinical hypothesis that direct and specific inhibition of IL-17 will benefit patients with AS15. There is substantial evidence that patients with AS have high response rates to biological drugs like TNFi/IL-17i, a low likelihood of successful treatment termination, but limited drug retention.

While several reports have assessed drug retention rates for TNFi/IL-17i in AS, few, if any, studies have investigated the actual treatment trajectories at a patient level, including the prescribed first-line biological drugs, subsequent therapy changes (e.g., dose reductions), and discontinuation of individual patients16.

2. OBJECTIVE

This study aimed to describe treatment trajectories in patients with AS using biological drugs, thereby describing the status of using biological drugs and some related factors in these patients.

3. PATIENTS AND METHODS

Participants

The study examined 161 patients diagnosed with AS at the Centre for Rheumatology, Bach Mai Hospital, between January 2018 and August 2021. Participants were diagnosed with AS according to the American College of Rheumatology 1984 criteria and had started treatment with at least one biological drug for at least three months. Patients who met these criteria and were willing to participate in the study were included, while those who did not consent to participate were excluded. All participants provided written informed consent. This study was approved by the Ethics Committee of Hanoi Medical University, Vietnam (decision number: 4149/QĐ- ĐHYHN).

Assessment

This study was a cross-sectional descriptive and longitudinal follow-up study. Data were collected during treatment, including the first dose and follow-up visits at 3, 6, 12, 24, and 36 months after the first dose. Patients' information, clinical and paraclinical features, X-ray images, disease stage, illness duration, combination drugs, drug discontinuation, drug change, reducing dose frequency, adherence/non-adherence to treatment, and causes were collected by reviewing medical records and patient interviews.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used to assess the disease activity level, with high disease activity defined as a BASDAI ≥4.0. Indications for biological drug treatment followed the 2019 ASAS-EULAR recommendations for managing AS. Participants were divided into groups according to the type of bDMARD used at each line of treatment, the proportions of each group, and the duration of bDMARD maintenance.

This study incorporates several concepts. Economic status groups were classified as poor, near-poor, average, and above-average households, based on Prime Minister's Decision No. 59/2015. A patient's response to a bDMARD was assessed as good, bad, or no response, depending on changes in the BASDAI score. Economic reasons refer to patients who could not afford to continue taking a bDMARD as directed. Drug discontinuation refers to patients who have not taken any bDMARD for three consecutive doses or longer after their last dose. Drug change refers to when a patient is given a different biological drug, which is considered drug discontinuation. Treatment adherence was defined as taking the drug as prescribed by the doctor, with patients deemed adherent if they are compliant for ≥80% of the treatment period.

Statistical analysis

Data were analyzed using the SPSS Statistics software (SPSS Inc., Chicago, IL, USA). Tables of descriptive statistics were used to show frequencies, mean values of studied variables, and comparisons between qualitative and quantitative variables. Statistical significance was defined as $p < 0.05$.

4. RESULTS

This study included 161 patients, of which 139 (86.3%) were male. Most patients (67.7%) had a college degree or higher education level. In addition, 87% (140/161) of patients had an average income or higher. All patients (100%) had health insurance. Table 1 summarizes the participants' general characteristics.

The patients' median age was 31.1 years old, and their mean disease duration was 7.6 ± 6.6 years. In addition, 68.9% of patients had active disease at the beginning of their bDMARD treatment (Table 2).

At the start of treatment, 69.6% were prescribed anti-TNF-α biological drugs as their first-line treatment, of which 71 patients (44.7%) were prescribed infliximab,

Characteristic		Number of patients (*n*)	Percentage (%)
Sex	Male	139	86.3
	Female	22	13.7
Education level	High School	52	32.3
	College	38	23.6
	University/ Postgraduate	71	44.1
Income	Poor/Near-poor households	21	13.0
	Not in the above group	140	87.0
Medical insurance	Yes	161	100
	No	0	0

Table 1. Participants' general characteristics.

Variable		Number of patients (*n*)	Percentage (%)
Mean age (years)		31.1 ± 11.6 (min: 17, max: 71)	
Disease duration (year)		7.6 ± 6.6 (min: 1, max: 35)	
Disease activity grade	Active	111	68.9
	Inactive	50	31.1
Treatment duration (week)		80.9 ± 48.1 (min: 24, max: 210)	

Table 2. Participants' clinical and para-clinical features.

26 (16.2%) were prescribed adalimumab, 13 (8.1%) were prescribed golimumab, and one (0.6%) was prescribed etanercept. Fifty (30.4%) patients were prescribed secukinumab as their first-line bDMARD.

Some patients changed drugs once during treatment, while some changed drugs 2–3 times. Secukinumab became the most common drug of choice after the first change, accounting for 45/130 (34.6%) of the patients after the first drug change and 23/63 (36.5%) after the second. At the second drug change, 98 of the 161 (60.9%) patients stopped taking the drugs (Figure 1).

The proportion of patients treated with biological drugs reduced to 77% after one year and 39.1% after three years. The percentage of patients who maintained their initial biological drug was 26.1%, and 11.2% switched to a second biological drug (Table 3).

Disease improvement was assessed using the BASDAI score at various intervals during the study period. At baseline, the mean BASDAI score was 4.1 ± 1.4. A significant improvement in disease activity ($p < 0.05$) was observed after three months, with the mean BASDAI score decreasing to 1.2±1.3. The mean BASDAI score continued to decrease after six (1.0 ± 1.3), 12 (0.8 ± 1.1), 24 (0.7 ± 1.2), and 36 (0.5 ± 0.8) months, indicating further improvements in disease activity.

Regarding the mean duration of treatment with biological drugs for different treatment lines, we observed that the first-line drug was used in 161 patients with the longest mean duration of 66.1 weeks. The second-line drug was used in 44 patients with a mean duration of 43.5 weeks. The third-line drug was administered to only four patients with a mean duration of 39.0 weeks. Finally, the fourth-line drug was used in only two patients with a mean duration of 55.0 weeks.

The rate of drug change due to secondary non-response was the highest, accounting for 50% of cases. The rates of drug change due to primary non-response and side effects were lower, at 24% and 20%, respectively. Only 6% of cases had to change drugs due to a lack of availability.

Of the 98 patients who discontinued the drug during this study, 50% could not pay for treatment. The proportion of patients who stopped treatment due to side effects, primary non-responders, and the COVID-19 pandemic was 14.3%, 13.3%, and 12.2%, respectively. The percentages of patients who stopped taking the drug due to a good response or secondary non-response were both only 4.1%. The percentage of patients who stopped taking the drug due to lack of availability was 2.0%.

Several factors were related to treatment adherence, drug change, and drug discontinuation in patients. Patients aged <25 years had a higher rate of adherence (37.3%) than those in other age groups ($p = 0.037$). Other factors, such as sex, income, or disease activity level, did not significantly affect adherence rates. Female patients had a higher rate of drug change than male patients ($p = 0.010$). Patients with active disease had a higher rate of drug change than those with inactive disease ($p = 0.011$). Patients aged <25 years had a lower rate of drug discontinuation (45.8%) than those in other age groups ($p = 0.011$). Other factors did not significantly affect drug discontinuation rates (Table 4).

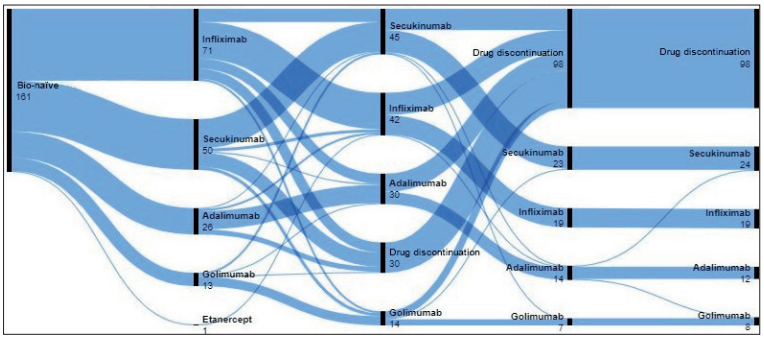

Figure 1. Drug change or drug discontinuation during the study period.

Time (months)	1st bDMARD (%)	2nd bDMARD (%)	3rd bDMARD (%)	4th bDMARD (%)	Stop drug (%)
0	100	0	0	0	0
6	91.9	8.1	0	0	0
12	64	13	0	0	23
24	38.5	9.9	1.3	0.6	49.7
36	26.1	11.2	0.6	1.2	60.9

Table 3. Percentage of patients treated with biological drugs over time (N = 161).

5. DISCUSSION

The mean disease duration of study participants was 7.6 ± 6.6 years, shorter than previous studies by Lindstrom et al. and Lie et al.16,17, possibly due to this study's shorter period. The mean treatment time was 80.9 ± 48.1

Factors		Percentage of patients with treatment adherence (%)	p	Percentage of patients with drug change (%)	p	Percentage of patients with drug discontinuation (%)	p
Age (years)	<25 (*n* = 59)	37.3	0.037	11,86	0.117	45.8	0.011
	25–45 (*n*= 8 0)	21.2		31.2		68.8	
	>45 (*n* = 22)	13.6		36.4		72.7	
Sex	Male (*n* = 139)	23.7	0.363	23.7	0.010	59.7	0.449
	Female (*n* = 22)	18.2		50		68.2	
Income	Poor/near-poor households (*n* = 21)	28.6	0.781	33.3	0.508	47.6	0.182
	Above average (*n* = 140)	25.7		26.4		62.9	
Disease activity grade	Active	24.3	0.448	33.3	0.011	59.5	0.585
	Inactive	30.0		14.0		64.0	

Table 4. Factors related to the participants' treatment process.

weeks, much lower than in previous studies, possibly due to the earlier indications for treatment in this study.

Regarding drug choice, bDMARDs were the preferred choice for anti-TNF-α drugs over IL-17i drugs, consistent with the 2019 ASAS-EULAR recommendation. Infliximab was the preferred drug for initial treatment (44.7%), consistent with the findings of Glintborg et al.18. The main reasons for this preference were its status as the first biological drug introduced19 and its relatively low cost in Vietnam. Additionally, infliximab treatment scheduling was seen to have minimal impact on the patient's current work.

The percentage of patients continuing treatment gradually decreased yearly, with only 39.1% maintaining biological drugs by the end of the study period. This persistence rate is lower than in Machado et al.20, possibly due to differences in economic and health insurance payments across countries and the impact of the COVID-19 pandemic on patients' lives during the study period.

The baseline mean BASDAI score was 4.1±1.4, lower than in Lie et al. and Glintborg et al.17,19, indicating that the indication for bDMARD treatment at Bach Mai Hospital was earlier than in those studies. This difference could be attributed to the hospital's reputation as a leading center for rheumatologic diseases, providing patients with access to the best available treatment. Disease activity improved gradually over time, with the most significant improvement observed after the first six months of biological therapy. However, the BASDAI score was highly dependent on the patient's subjective perception of the disease, and patients often felt more secure with the best and most expensive therapy. Additionally, Vietnamese people generally have a high pain tolerance, which could also introduce bias when evaluating the BASDAI score.

Among the study patients, 27.3% and 11.2% switched to a second drug after one and three years, respectively. These rates were higher than those reported by Lindstrom et al.16. Of the 50% of patients who had to switch drugs, 74% were due to no response, including primary or secondary non-response. Furthermore, side effects accounted for 20% of such cases. This finding highlights the need for further research to identify prognostic factors for response or non-response to treatment and for developing new medications. Of the 98 patients who discontinued treatment in this study, 50% did so for financial reasons, underscoring the need for policies to improve patient access to treatment, such as increasing health insurance coverage and producing bioequivalent drugs. This issue has also been highlighted in recent studies, including Kvien et al.21. Additionally, 12.2% of the patients in this study stopped treatment due to the impact of the COVID-19 pandemic. Lessons learned during this period can help the healthcare system mitigate similar issues in the future.

Patients aged <25 years had a higher adherence rate (37.3%) than the other age groups. Typically, these young patients were students and financially dependent on their parents, who provided significant support in accessing the best treatment. However, economically self-sufficient patients had to manage their own finances and support their families, often resulting in an inability to afford treatment. Consequently, some patients even discontinued biological therapy despite disease progression. The rate of drug change was significantly higher in females (50%) than in males (23.7%; $p < 0.05$), similar to Rusman et al.'s 2018 study on 122 patients22. Interviews with patients showed that females had a lower pain threshold and higher anxiety levels than males, leading to a higher likelihood of switching to a second drug. Additionally, patients with active disease had a higher rate of drug change than those with inactive disease since they experienced more inflammation and joint pain. Consequently, if the first biologic failed to provide a therapeutic response, these patients often sought a second drug in the hope of achieving better outcomes. Among individual factors, age was significantly associated with drug discontinuation ($p < 0.05$), with adult (68.8%) and middle-aged (72.7%) patients having higher rates than younger patients (45.8%). Patients aged >25 years were often responsible for supporting their families, leading to a greater likelihood of discontinuing treatment.

This study had some limitations. Its study period was relatively short. In addition, it was only conducted at the Centre for Rheumatology of Bach Mai Hospital, and its participants may not be representative of patients with AS taking biological drugs in Vietnam. We hope to expand this into a multi-center study with more patients

and a longer study period to clarify the status of using biological drugs in patients with AS.

6. CONCLUSION

A TNFi is the standard therapy for patients with active AS, with approximately 70% prescribed anti-TNF-α biological drugs as their first-line treatment. The proportion of patients treated with biological drugs gradually decreased after three years. At the second drug change, approximately 61% of patients stopped taking the drugs. Most patients changed drugs due to non-response, and many discontinued the drugs for economic reasons. These findings show that the maintenance rate of biological drugs used to treat AS in Vietnam remains a challenge.

- **Ethics statement:** This study was approved by the Ethics Committee of Hanoi Medical University, Vietnam (decision number: 4149/QĐ- ĐHYHN).
- **Pateient Consent Form:**Informed consent was obtained from all participants.
- **Data availability statement:**Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- **Author's contribution:** Study concept and design: Bui Hai Binh and Le-Thi Bich Phuong; acquisition of data: Bui Hai Binh and Le-Thi Bich Phuong; analysis and interpretation of data: Bui Hai Binh, Nguyen Ngoc Trung, Nguyen-Van Hung, Nguyen-Thi Ngoc Yen, Nguyen-Thi Nhu Hoa, Nguyen Thanh Hiep, Nguyen Minh Duc, and Le-Thi Bich Phuong; drafting of the manuscript: Bui Hai Binh and Le-Thi Bich Phuong; critical revision of the manuscript: Bui Hai Binh and Le-Thi Bich Phuong; study supervision: Bui Hai Binh confirm the authenticity of all the raw data. All authors read and approved final version of this manuscript.
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