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Efficacy of TNF-α inhibitors in the treatment of ankylosing spondylitis

Ocena skuteczności inhibitorów TNF-α w leczeniu zesztywniającego zapalenia stawów kręgosłupa

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Abstract

Purpose: The study aimed to evaluate and compare the efficacy of TNF-α inhibitors in the treatment of ankylosing spondylitis in everyday medical practice. **Materials and methods:** We analysed the data of 106 patients with ankylosing spondylitis treated in 2012–2019 with TNF-α inhibitors (etanercept, adalimumab or golimumab) under the drug program of the National Health Fund. The observation period for each patient was 18 months. The disease activity was assessed at 3-month intervals on the basis of BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score). **Results:** The study covered 80 men and 26 women. The mean age of the patients was 37 years. The group receiving etanercept included 50 patients, adalimumab – 39 patients, and golimumab – 17 patients. Due to coexisting off-axial symptoms such as uveitis (n = 20/106) and peripheral arthritis (n = 39/106), some patients were simultaneously receiving classic disease-modifying antirheumatic drugs, i.e. methotrexate (n = 32/106), sulfasalazine (n = 8/106), cyclosporine (n = 5/106), and glucocorticosteroids (n = 14/106). All subgroups showed a significant clinical improvement in the form of a decrease in inflammatory markers and a decrease in disease activity after 3 months of treatment, increasing up to the 6th month. The biological drug was discontinued due to remission (according to BASDAI) in 20/48 patients taking etanercept and in 19/36 patients receiving adalimumab. The observation period following drug discontinuation for both groups was similar and lasted about 7 months. The remission time (according to BASDAI) without treatment was short; 3.55 ± 2.28 months for etanercept vs. 5.21 ± 2.53 months for adalimumab (p = 0.038). **Conclusions:** The inclusion of TNF-α inhibitors in patients with an unsatisfactory response to treatment with non-steroidal anti-inflammatory drugs resulted in a major reduction of disease activity. There was no statistically significant difference in treatment efficacy between individual TNF-α inhibitors, i.e. etanercept, adalimumab, and golimumab. The group treated with adalimumab was found with a trend towards longer-lasting remission after drug discontinuation, but it was short-lived and a return to treatment was necessary.

Keywords: ankylosing spondylitis, AS, TNF-α inhibitors, spondyloarthropathy

Streszczenie

Cel: Badanie miało na celu ocenę i porównanie skuteczności inhibitorów TNF-α w leczeniu zesztywniającego zapalenia stawów kręgosłupa w codziennej praktyce. **Materiał i metody:** W badaniu przeanalizowano dane 106 chorych na zesztywniające zapalenie stawów kręgosłupa leczonych w latach 2012–2019 inhibitorami TNF-α (etanerceptem, adalimumabem lub golimumabem) w ramach programu lekowego Narodowego Funduszu Zdrowia. Okres obserwacji dla każdego chorego wynosił 18 miesięcy. Aktywność choroby oceniano w odstępach 3-miesięcznych na podstawie wskaźników BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) i ASDAS (Ankylosing Spondylitis Disease Activity Score). **Wyniki:** Badaniem objęto 80 mężczyzn i 26 kobiet. Średni wiek pacjentów wyniósł 37 lat. W grupie przyjmującej etanercept znajdowało się 50 osób, leczonej adalimumabem – 39 chorych, stosującej golimumab – 17 pacjentów. Ze względu na współistniejące objawy pozaosiowe, takie jak zapalenie błony naczyniowej oka (n = 20/106) i zapalenie stawów obwodowych (n = 39/106), część chorych przyjmowała równocześnie klasyczne leki modyfikujące przebieg choroby, tj. metotreksat (n = 32/106), sulfasalazynę (n = 8/106), cyklosporynę (n = 5/106) oraz glikokortykosteroidy (n = 14/106). We wszystkich podgrupach zaobserwowano istotną poprawę stanu klinicznego pod postacią spadku wykładników stanu zapalnego oraz zmniejszenia aktywności choroby już po 3 miesiącach leczenia, narastającą do 6. miesiąca. Lek biologiczny odstawiono z powodu remisji (wg BASDAI) u 20/48 pacjentów przyjmujących etanercept oraz u 19/36 pacjentów przyjmujących adalimumab. Okres obserwacji po odstawieniu leku dla obu grup był zbliżony i wynosił około 7 miesięcy. Czas trwania remisji (wg BASDAI) bez leczenia był krótki i w przypadku etanerceptu wyniósł 3,55 ± 2,28 miesiąca *vs* 5,21 ± 2,53 miesiąca w przypadku adalimumabu (p = 0,038). **Wnioski:** Włączenie inhibitora TNF-α u chorych z niezadowalającą odpowiedzią na leczenie niesteroidowymi lekami przeciwzapalnymi skutkowało znacznym zmniejszeniem aktywności choroby. Nie wykazano

istotnej statystycznie różnicy w skuteczności leczenia pomiędzy poszczególnymi inhibitorami TNF-α, tj. etanerceptem, adalimumabem i golimumabem. W grupie chorych leczonych adalimumabem zaobserwowano trend w kierunku dłuższego utrzymywania się remisji po odstawieniu leku, ale trwała ona krótko i konieczny okazał się powrót do leczenia.

Słowa kluczowe: zesztywniające zapalenie stawów kręgosłupa, ZZSK, inhibitory TNF-α, spondyloartropatia

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, progressive inflammatory disease of the joints that belongs – together with psoriatic arthritis, reactive arthritis, and arthritis accompanying intestinal inflammation – to the group of seronegative spondyloarthropathies[1]. The prevalence of AS is estimated at around 0.3–0.5% in Europe and 0.3–1.5% in the world[2]. The prevalence in the Polish population for 2008–2017 was approximately 0.1%[3]. The disease mainly affects young people and is more common in males. In Poland, the average male/female ratio for the incidence of AS in 2008–2017 was 1.33[3].

AS aetiology is multifactorial and has not been yet completely recognised. In aetiopathogenesis, apart from the undoubted influence of genetic factors (especially the human leukocyte antigen B27, HLA-B27), an important role seems to be played by environmental factors, including infectious ones. Tumour necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine which is of fundamental importance in the pathogenesis of AS. Its increased concentration has been noted in joint plasma and synovial fluid. The clinical image of AS is dominated by symptoms of spinal arthritis, manifested in the so-called inflammatory back pain. Moreover, the course of the disease may involve inflammation of the peripheral joints (arthritis), tendinous attachments, and extra-articular manifestations. AS progresses with periods of exacerbation and remission; if left untreated, it leads to disability and increased mortality[4].

Treatment of AS includes a non-pharmacological and pharmacological component. Non-pharmacological management includes: patient education, promotion of a healthy lifestyle, including physical activity and smoking cessation, rehabilitation, and surgery. First-line pharmacological treatment involves non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, topical glucocorticosteroids (GCs) (e.g. intra-articular or tendon injection). It is not recommended to use systemic GCs or conventional disease-modifying antirheumatic drugs, with the exception of sulfasalazine, in peripheral joint involvement; there is insufficient evidence for the effectiveness of methotrexate[5]. If NSAIDs are ineffective and there is persistent high disease activity, biological disease-modifying antirheumatic drugs (bDMARDs) are recommended. The first line of recommendations involves tumour necrosis factor α inhibitors (iTNF-α): infliximab (INF), golimumab (GLM), adalimumab (ADA), etanercept (ETA) or certolizumab pegol (CZP), and in the event of their ineffectiveness or contraindications – interleukin-17 (IL-17) inhibitors, e.g. secukinumab[5–8]. Analysis of the existing data revealed no advantage of one iTNF-α over another, and the decision regarding the choice of a drug from this group should be made jointly with the patient, taking into account the coexisting extra-articular changes and systemic complications[5,6]. According to the recommendations of ASAS/EULAR experts (The Assessment of SpondyloArthritis International Society/The European Alliance of Associations for Rheumatology), treatment is aimed at achieving remission or low disease activity within 6 months of therapy and at maintaining this state throughout the illness. An early condition for continuing treatment is a significant improvement after just 3 months. In patients with permanent remission, a dose reduction may be considered. Everyday medical practice involves the use of complex indicators based on the patient's assessment of symptoms to assess the activity of AS (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI) or more preferably – combined with the assessment of C-reactive protein (CRP) concentration (Ankylosing Spondylitis Disease Activity Score CRP, ASDAS-CRP) or the erythrocyte sedimentation rate (ESR) (ASDAS-ESR)[5,6].

The effectiveness of iTNF-α treatment has been confirmed in many clinical trials, in which patient enrolment was subject to a number of limitations. This study aimed to evaluate the effectiveness of this therapy in the daily medical practice at one of the centres. We also compared the effectiveness of various iTNF-α preparations.

MATERIALS AND METHODS

We conducted a retrospective study of the medical records of 106 patients with AS treated in 2012–2019 in the Rheumatology Clinic of the Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine under the drug program of the National Health Fund (NHF) according to Annex B.36[9]. The inclusion criteria were: age ≥18, diagnosis of AS according to modified New York criteria for AS[10], active and severe disease, defined by meeting all of the following criteria: a) BASDAI value ≥4 or ASDAS value ≥2.1 from duplicate measurements at an interval of at least 4 weeks; b) back pain score ≥4 on a visual scale from 0 to 10 cm,

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from duplicate measurements at an interval of at least 4 weeks; c) overall disease status >5 cm on a 0 to 10 cm scale; d) unsatisfactory response to at least 2 NSAIDs, each of which was used for a minimum of 4 weeks as monotherapy[9]. Follow-up visits were performed at 12-week intervals. The analysed laboratory parameters included ESR and CRP concentrations. Disease activity was assessed using the BASDAI, ASDAS-ESR, and ASDAS-CRP scales[4,10,11]. Data from the initiation visit (visit 1) and from visits conducted after 3 (visit 2) and 6 months (visit 3) following the inclusion of iTNF-α were analysed. The patients were divided into 3 groups depending on the iTNF-α received: group 1 – etanercept (ETA), group 2 – adalimumab (ADA) group 3 – golimumab (GLM). The therapeutic objective was adopted in accordance with the program provisions and the ASAS/EULAR recommendations[5,6,9]: after 3 months, a ≥50% reduction in BASDAI or a ≥2 unit drop or a 50% reduction in ASDAS or a ≥1.1 unit drop from the pretreatment value; after 6 months of treatment, low disease activity defined by BASDAI <3 or ASDAS <1.3. In accordance with the provisions of the NHF program in force from March 1, 2017 to January 1, 2021, treatment was discontinued in patients with disease remission, expressed as BASDAI <3 or ASDAS <1.3, persisting for 12–15 months[9]. However, in patients qualified for biological treatment prior to March 1, 2017, the therapy was discontinued when low disease activity, expressed as BASDAI <3, persisted for 6 months. In the event of an exacerbation, biological treatment could be reintroduced. In the present study, patients who had no significant improvement after 3 months of treatment or who were discontinued due to an adverse event, were excluded from further follow-up because they were administered a biological medicine of another choice.

Characteristics of the study group, *n* = 106		
Parameter	**Average (SD)/ *n* (%)**	**Range**
Age [years]	37.34 (±11.85)	18–74 years
Male sex [%]	80 (75.47%)	
BMI (*n* = 81)	25.35 (±3.85)	18.07–36.58
Number of patients with uveitis	20 (18.86%)	
Number of patients with arthritis	39 (36.79%)	
Number of patients receiving MTX	32 (30.19%)	
Number of patients receiving SSA	8 (7.55%)	
Number of patients receiving CsA	5 (4.72%)	
Number of patients receiving GCs	14 (13.21%)	
SD – standard deviation; **BMI –** body mass index; **MTX** – methotrexate; **SSA** – sulfasalazine; **CsA** – cyclosporine; **GCs** – glucocorticosteroids.		

Tab. 1. Characteristics of the study group during visit 1

Statistical analysis

Statistical analyses were performed by means of the Statistica 12 package (StatSoft Inc.). The results are indicated as the mean with standard deviation (*SD*) for continuous variables, a number (*n*), and a percentage (%) for categorical variables. Continuous variables were compared by means of Student's *t*-test or Mann–Whitney *U* test (depending on the distribution), and qualitative variables were analysed by chi-square test or Fisher's exact test. The level of statistical significance was assumed at $p < 0.05$.

RESULTS

The analysis covered data from 106 patients. At treatment week 12, 7 patients with no significant improvement in BASDAI disease activity and 2 patients with treatment-related adverse events received another iTNF-α. These patients were excluded from further statistical analysis. The

Parameter	Etanercept *n* = 50	Adalimumab *n* = 39	Golimumab *n* = 17	*p*
	Average (SD)/*n* (%)			
Age [years]	36.35 (±10.28)	37.85 (±12.55)	39.06 (±14.67)	0.68
Male sex [%]	37 (74%)	31 (79.49%)	12 (70.59%)	0.73
ESR [mm/h]	32.55 (±21.90)	28.63 (±21.67)	22.18 (±17.29)	0.21
CRP [mg/dL]	1.93 (±1.89)	1.99 (±4.14)	2.25 (±2.43)	0.92
BASDAI	7.92 (±1.27)	7.24 (±1.19)	7.22 (±1.17)	0.018
ASDAS-ESR	4.17 (±0.76)	3.98 (±0.73)	3.82 (±0.77)	0.27
ASDAS-CRP	4.33 (±0.70)	3.97 (±0.62)	4.12 (±0.76)	0.096
Number of patients with uveitis [%]	9 (18%)	8 (20.51%)	3 (17.65%)	0.96
Number of patients with arthritis [%]	20 (40%)	14 (35.90%)	5 (29.41%)	0.64
Number of patients receiving MTX [%]	16 (32%)	12 (30.77%)	4 (23.53%)	0.80
Number of patients receiving SSA [%]	5 (10%)	2 (5.13%)	1 (5.88%)	0.66
Number of patients receiving CsA [%]	2 (4%)	2 (5.13%)	1 (5.88%)	0.94
Number of patients receiving GCs [%]	8 (16%)	5 (12.82%)	1 (5.88%)	0.57
SD – standard deviation; **ESR** – erythrocyte sedimentation rate; **CRP** – C-reactive protein; **BASDAI** – Bath Ankylosing Spondylitis Disease Activity Index; **ASDAS** – Ankylosing Spondylitis Disease Activity Score; **MTX** – methotrexate; **SSA** – sulfasalazine; **CsA** – cyclosporine; **GCs** – glucocorticosteroids.				

Tab. 2. Characteristics of subgroups receiving particular biological disease-modifying drugs

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Etanercept					
Parameter	**Visit 1**	**Visit 2**	**Visit 3**	***p***	**Post hoc**
ESR [mm/h] *n* = 46	32.46 (±22.32)	11.64 (±14.81)	11.37 (±14.79)	<0.00001	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.87$
CRP [mg/dL] *n* = 47	1.93 (±1.93)	0.62 (±1.58)	0.68 (±1.23)	<0.00001	1 vs. 2 $p = 0.00052$ 1 vs. 3 $p = 0.00026$ 2 vs. 3 $p = 0.85$
BASDAI *n* = 47	7.90 (±1.28)	3.59 (±1.91)	2.64 (±1.43)	<0.00001	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.007$
ASDAS-ESR *n* = 31	4.17 (±0.79)	2.02 (±0.94)	1.66 (±0.86)	<0.00001	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.08$
ASDAS-CRP *n* = 31	4.37 (±0.72)	2.09 (±0.91)	1.67 (±0.73)	<0.00001	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.056$
ESR – erythrocyte sedimentation rate; **CRP** – C-reactive protein; **BASDAI** – Bath Ankylosing Spondylitis Disease Activity Index; **ASDAS** – Ankylosing Spondylitis Disease Activity Score; ***n*** – number of patients with available data at all visits.					

Tab. 3. Inflammation markers and disease activity in the subgroup of patients treated with etanercept

Adalimumab					
Parameter	**Visit 1**	**Visit 2**	**Visit 3**	***p***	**Post hoc**
ESR [mm/h] *n* = 34	29.94 (±21.58)	11.00 (±12.74)	14.44 (±20.69)	<0.00001	1 vs. 2 $p = 0.000057$ 1 vs. 3 $p = 0.0035$ 2 vs. 3 $p = 0.44$
CRP [mg/dL] *n* = 34	2.16 (±4.35)	0.44 (±0.58)	0.84 (±1.62)	0.00005	1 vs. 2 $p = 0.028$ 1 vs. 3 $p = 0.10$ 2 vs. 3 $p = 0.19$
BASDAI *n* = 36	7.30 (±1.18)	3.14 (±1.39)	2.52 (±1.23)	<0.00001	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.048$
ASDAS-ESR *n* = 27	4.00 (±0.68)	1.90 (±0.71)	1.75 (±0.73)	<0.00001	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.53$
ASDAS-CRP *n* = 27	4.03 (±0.61)	1.90 (±0.67)	1.71 (±0.77)	<0.00001	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.4$
ESR – erythrocyte sedimentation rate; **CRP** – C-reactive protein; **BASDAI** – Bath Ankylosing Spondylitis Disease Activity Index; **ASDAS** – Ankylosing Spondylitis Disease Activity Score; ***n*** – number of patients with available data at all visits.					

Tab. 4. Inflammation markers and disease activity in the subgroup of patients treated with adalimumab

Golimumab					
Parameter	**Visit 1**	**Visit 2**	**Visit 3**	***p***	**Post hoc**
ESR [mm/h] *n* = 13	22.38 (±11.96)	5.54 (±4.75)	6.69 (±4.44)	0.00002	1 vs. 2 $p = 0.000084$ 1 vs. 3 $p = 0.00017$ 2 vs. 3 $p = 0.53$
CRP [mg/dL] *n* = 13	2.29 (±2.12)	0.32 (±0.51)	0.33 (±0.40)	0.00037	1 vs. 2 $p = 0.003$ 1 vs. 3 $p = 0.003$ 2 vs. 3 $p = 0.93$
BASDAI *n* = 13	7.07 (±1.10)	3.07 (±1.50)	2.08 (±0.86)	<0.00001	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.051$
ASDAS-ESR *n* = 12	3.78 (±0.58)	1.71 (±0.62)	1.50 (±0.43)	0.00011	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.33$
ASDAS-CRP *n* = 12	4.10 (±0.56)	1.73 (±0.74)	1.50 (±0.49)	0.00008	1 vs. 2 $p < 0.000001$ 1 vs. 3 $p < 0.000001$ 2 vs. 3 $p = 0.42$
ESR – erythrocyte sedimentation rate; **CRP** – C-reactive protein; **BASDAI** – Bath Ankylosing Spondylitis Disease Activity Index; **ASDAS** – Ankylosing Spondylitis Disease Activity Score; ***n*** – number of patients with available data at all visits.					

Tab. 5. Inflammation markers and disease activity in the subgroup of patients treated with golimumab

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Visit no. 3 after 6 months	Overall	ETA	ADA	GLM	*p*	Post hoc
BASDAI – objective	64.95% *n* = 97	58,70% *n* = 46	64,86% *n* = 37	85,71% *n* = 14	0,18	1 vs. 2 *p* = 0,57 1 vs. 3 *p* = 0,06 2 vs. 3 *p* = 0,15
ASDAS-CRP – objective	72.37% *n* = 76	75% *n* = 32	60% *n* = 30	85,71% *n* = 14	0,175	1 vs. 2 *p* = 0,21 1 vs. 3 *p* = 0,42 2 vs. 3 *p* = 0,09
ASDAS-CRP – remission	27.63% *n* = 76	21.88% *n* = 32	26,67% *n* = 30	42,86% *n* = 14	0,338	1 vs. 2 *p* = 0,66 1 vs. 3 *p* = 0,15 2 vs. 3 *p* = 0,28

ETA – etanercept; **ADA** – adalimumab; **GLM** – golimumab; **BASDAI** – Bath Ankylosing Spondylitis Disease Activity Index; **CRP** – C-reactive protein; **ASDAS** – Ankylosing Spondylitis Disease Activity Score.

Tab. 6. Disease activity after 6 months of therapy for individual disease-modifying biological drugs

study group characteristics are presented in Tab. 1. Some patients with coexisting arthritis or uveitis received biological drugs in combination with synthetic disease-modifying antirheumatic drugs (methotrexate, sulfasalazine or cyclosporine) and/or GCs. The doses remained unchanged throughout the observation period. The choice of the iTNF-α drug was based on a joint decision of the rheumatologist and the patient.

The characteristics of patient subgroups distinguished on the basis of the received biological drug are presented in Tab. 2. Apart from a slightly higher baseline BASDAI value for ETA (7.92 for ETA vs. 7.24 for ADA and 7.22 for GLM, $p = 0.018$), there were no other significant differences between the subgroups.

The behaviour of laboratory and clinical indicators of disease activity during individual visits is presented separately for etanercept (Tab. 3), adalimumab (Tab. 4), and golimumab (Tab. 5). As shown in Tab. 3, patients treated with etanercept had statistically significantly decreased values of all indices at visit 2 compared to the baseline visit; further, but not significant, improvement compared to visit 2 was observed at visit 3. A significant reduction from visit 2 was observed for the BASDAI and ASDAS-CRP scales.

As shown in Tab. 4, patients treated with adalimumab had statistically significantly decreased values of all indices compared to the baseline visit. There was a major improvement in the data from visit 2. At visit 3, apart from the CRP concentration, all indices decreased significantly compared to the baseline visit, while compared to visit 2, only the BASDAI value decreased significantly; for the remaining clinical and laboratory values, this change was not significant.

Patients treated with golimumab (Tab. 5) had a very large improvement in all indicators during visit 2, which was also maintained during visit 3 without significant changes.

During the follow-up period, the biological drug was discontinued due to remission (assessed as a BASDAI score <3) in 41.67% of patients receiving ETA (n = 20/48) and in 52.78% of patients receiving ADA (n = 19/36). During the follow-up after treatment discontinuation, which was 7.50 ± 2.21 months vs. 7.95 ± 1.43 months for both groups, respectively, remission measured by BASDAI index was maintained until the end of the follow-up period in 2/20 patients treated with ETA and in 5/19 patients treated with ADA (difference not statistically significant, $p = 0.37$), measured by ASDAS index – in 5/13 patients treated with ETA and in 4/13 patients treated with ADA (difference not statistically significant, $p = 0.68$). The no-treatment period of remission (as measured by the BASDAI index) was significantly shorter for ETA than for ADA: 3.55 ± 2.28 months vs. 5.21 ± 2.53 months ($p = 0.038$) – the analysis also involved patients in remission until the end of the follow-up period. The mean time from discontinuation of the biological drug to exacerbation (after excluding patients who were in remission by the end of the follow-up period from the analysis) was slightly longer for ADA (4.28 ± 2.13 months vs. 3.39 ± 1.91 months), whereby the difference was not statistically significant ($p = 0.22$). The analysis did not include patients treated with golimumab, because most patients from this group were qualified for therapy after March 1, 2017, when the criteria of the drug program had changed (continuation of treatment – if an adequate response to therapy is obtained – for 12–15 months).

DISCUSSION

Over the years, AS has been treated mainly with NSAIDs and physiotherapy. Contrary to rheumatoid arthritis or peripheral forms of spondyloarthritis, synthetic disease-modifying antirheumatic drugs in the form of axial spondyloarthritis are ineffective. In fact, it was only the introduction of iTNF-α to therapy that radically changed the prognosis in this group of patients[12]. In Poland, the treatment of iTNF-α is reimbursed under the NHF drug program. This paper presents data on patients treated with etanercept, adalimumab, and golimumab. The latter two are fully human monoclonal antibodies from the IgG1 class, genetically engineered in Chinese hamster ovary (ADA) cells and from the mouse hybridoma cell line (GLM). By binding specifically to TNF-α, with both soluble and membrane-bound forms, they block the binding of the TNF-α molecule to its receptors located on the cell

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membrane. This leads to, among others, a decrease in inflammatory markers, a decrease in plasma concentration and pro-inflammatory cytokines such as IL-6, IL-8, and a reduction in the concentration of matrix metalloproteinases responsible for the degradation of articular cartilage. In turn, ETA is a fusion protein consisting of the Fc fragment of human IgG1 and 2 TNF-α receptor molecules, obtained by genetic engineering from Chinese hamster ovary cells. Unlike ADA and GLM, it is a soluble receptor that competitively inhibits the binding of the soluble form of TNF-α to its specific receptors, without affecting its transmembrane form[2].

Therapeutic decisions concerning the patients included in this study were made solely on the basis of the BASDAI index. Its disadvantage is a subjective nature – it is based only on the assessment made by the patient. The ASDAS index seems to be a more objective parameter for assessing treatment activity and effectiveness of treatment, which includes, in addition to the parameters assessed by the patient, the inflammatory index – the concentration of CRP or ESR. The authors of the 2017 recommendation, Smolen et al., prefer to use CRP, the concentration of which correlates with disease activity, radiographic changes, and rapid disease progression[6]. In addition, unlike BASDAI, ASDAS has validated cut-offs for disease activity states, i.e. <1.3 – inactivity, from 1.3 to <2.1 – low activity, from 2.1 to ≤3.5 – high activity, >3.5 – very high activity. The BASDAI cut-off values were chosen arbitrarily[13,14]. Since BASDAI and ASDAS-CRP indices have a different structure, in theory there can occur differences in the assessment of the therapeutic objective with both parameters, but in fact no significant differences were observed in the presented analysis – both in the entire study group and in individual subgroups, the percentages of patients achieving the therapeutic objective were similar regardless of the type of indicator used. On the other hand, it is worth noting the relatively low remission rate (according to ASDAS-CRP) after 6 months from the initiation of treatment – while the percentage of patients achieving the therapeutic objective oscillated between 60–70%, the percentage achieving remission did not exceed 30%.

Significant clinical and laboratory improvement was observed in all subgroups during the first 6 months of therapy. Comparing individual visits, the greatest improvement was observed at visit 2 for all TNF-α after 3 months of treatment; a further, but not statistically significant, improvement was also noted during visit 3 after 6 months of therapy.

The results of the described study confirm previous reports on the effectiveness of ETA, ADA, GLM in the treatment of AS. A multicentre, placebo-controlled, randomised trial included 315 patients with active disease as measured by the BASDAI index (ADA: $n = 208$; placebo: $n = 107$). The duration of treatment was 24 weeks. At week 12, 45.2% (94/208) of ADA patients achieved a BASDAI improvement of at least 50%, significantly greater than placebo – 15.9% (17/107) ($p < 0.001$). Significant improvement was maintained through treatment week 24 in 42.3% (88/208) of patients in the ADA group vs. 15.0% (16/107) from the placebo group ($p < 0.001$). Partial remission according to ASAS was achieved by 22.1% of patients in the ADA group vs. 5.6% of patients in the placebo group ($p < 0.001$)[15]. In another multicentre study, Davis et al. demonstrated the efficacy and safety of ETA in the treatment of AS. The double-blind study included 277 patients with active AS. Patients were randomly assigned to the ETA group ($n = 138$) at a dose of 25 mg s.c. twice weekly and the placebo group ($n = 139$). The observation period was 24 weeks. The primary efficacy endpoint of 20% improvement (as measured by the ASAS20 index) after 12 weeks of treatment was achieved by 59% (82/138) of patients in the ETA group and 28% (39/139) in the placebo group ($p < 0.0001$). Similar results were recorded at the 24th week of therapy, with an improvement in ASAS20 in 57% (78/136) and 22% (31/139) of patients, respectively ($p < 0.0001$). A statistically significant difference was also observed between the groups with regard to partial remission (according to ASAS): 17% of patients in the ETA group vs. 4% in the placebo group at week 24 of therapy[16]. In turn, the authors of the GO-RAISE study proved the effectiveness of golimumab. Patients were randomized into 3 groups receiving every 4 weeks GLM 50 mg/week, GLM 100 mg/week, and placebo. After 14 weeks, the ASAS20 response was achieved by 59.40%, 60.0%, and 21.8% of patients, respectively ($p < 0.001$). The percentage of patients achieving at least a 50% improvement on BASDAI at week 24 of therapy was significantly higher in the GLM group compared to the placebo group[17].

This study found no statistically significant difference in the treatment efficacy between individual iTNF-α – the percentage of patients achieving the therapeutic objective and remission was similar in all subgroups. These results are in line with the current guidelines, which emphasize the comparable efficacy of iTNF-α drugs[5,18].

At the same time, it should be emphasised that most of the available studies comparing the effectiveness of iTNF-α are indirect comparisons (not head-to-head studies). A direct comparison of the effectiveness of ETA with ADA was carried out, among others, by Wei et al. in a group of 19 patients with AS. The patients were randomized into 2 groups. The first group received ETA at a dose of 25 mg s.c. twice a week, which was converted to ADA of 40 mg s.c. after week 8 of therapy every 2 weeks for the next 8 weeks. In contrast, the control group received ADA in a dose of 40 mg s.c. every 2 weeks, which was switched to ETA of 25 mg s.c. after 8 weeks of therapy every 2 weeks for the next 8 weeks. Disease activity was assessed at baseline and at weeks 4, 8, 12, and 16. Both groups demonstrated a significant

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improvement in clinical and laboratory indicators of disease activity, but there was no significant difference in the change in the BASDAI and ASDAS-CRP values between ETA and ADA[19]. Similarly, in another head-to-head study Giardina et al. showed no statistically significant difference in efficacy between interferon (INF) and ETA. It was an open-label, 2-year study of 50 patients with active AS[20]. On the other hand, Ungprasert et al. conducted a systematic review in which they observed no significant difference in effectiveness between CZP and ETA, ADA and INF[21]. In another systematic review and meta-analysis, Baji et al. demonstrated no significant differences between the effectiveness of biosimilar INF and the effectiveness of INF, ETA, ADA, and GLM[22]. Differences in the effectiveness of individual TNF-α inhibitors were observed in relation to some extra-articular symptoms, e.g. recurrent uveitis or concomitant inflammatory bowel disease – monoclonal antibodies INF, ADA, CZP, GLM are more effective than ETA in treating inflammatory bowel disease and preventing recurrent uveitis[5].

In the present study, in some patients treated with ADA and ETA the therapy was discontinued due to persistent remission. Despite the relatively short – several months' long – follow-up period, after treatment discontinuation, most patients experienced relapse. There were no significant differences between ADA and ETA-treated patients in the percentage of patients remaining in remission, but there was a trend towards longer-lasting remission in patients treated with ADA. However, this is not surprising given that the half-life of T½ is significantly longer for ADA: T½ for ETA is 7–300 hours while for ADA it is 10–20 days[23,24].

The study has numerous limitations. First, the study group was relatively small. Nevertheless, the results do not differ significantly from the outcomes of previous studies. Secondly, the follow-up period was relatively short; therefore, it was impossible to accurately assess the differences in remission duration between drugs. Third, the inclusion criteria for biological treatment, the duration of bDMARD therapy, and the assessment of disease activity were dictated by the drug program.

CONCLUSIONS

The study confirmed previous reports on the efficacy of iTNF-α in the treatment of AS. The efficacy of etanercept, adalimumab and golimumab in the treatment of AS has been shown to be comparable. However, the results indicate possible differences in remission time after treatment discontinuation. So far, no head-to-head study comparing the remission time between individual iTNF-α has been conducted.

Conflict of interest

The authors report no financial or personal connections with other persons or organisations that could adversely affect the content of the publication and claim the right to this publication.

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