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Unmet needs in the treatment of ankylosing spondylitis: a long-term observational study from a single university center

Eleftherios Pelechas[1] · Evripidis Kaltsonoudis[1] · Paraskevi V. Voulgari[1] · Alexandros A. Drosos[1]

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Abstract

Despite the progress in the treatment of ankylosing spondylitis (AS), a significant number of patients do not achieve low disease activity (LDA). The aim of the study is to estimate the size of unmet needs in the treatment of AS in a long-term observational study. Between January 2003 and December 2017, 220 patients with radiographic SpA were evaluated fulfilling the ASAS criteria. They were followed up at predefined times and were naive to biological treatment with anti-tumor necrosis factor agents (anti-TNFs) and the interleukin (IL)-17 inhibitor. NSAIDs, all anti-TNFs and the IL-17 inhibitor secukinumab were used according to the European, United States and Canadian guidelines for AS. During follow-up, several clinical parameters including disease activity scores were recorded. All 220 patients had an active disease and received at least two NSAIDs for 3 months. The anti-TNF of first choice was infliximab—51%, followed by adalimumab—27% and etanercept—22%. During follow-up, 22 patients were excluded from the study (18 lost, 4 never received anti-TNF due to comorbidities). From the rest (198), 12 did not receive anti-TNFs (8 due to sustained LDA on NSAIDs solely and 4 due to treatment denial). Finally, 186 (94%) were treated with anti-TNFs demonstrating sustained long-term LDA. However, 16 patients never achieved LDA despite they received two or three anti-TNFs or the IL-17 inhibitor. Thus, a total of 20 (10.1%) patients never achieved LDA. This is the first study aiming to estimate the gap and the size of unmet needs in AS patients using the international guidelines and recommendations for AS treatment, which is 10.1%.

Keywords Unmet needs · Ankylosing spondylitis · Anti-TNF · NSAIDs · IL-17 inhibitors

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting mainly the axial skeleton, leading to vertebral damage and functional disability [1]. The estimated prevalence of AS is 0.9–1.4% of adult population [2–4]. If the disease remains untreated, it can cause significant disability, and poor quality of life with high morbidity and mortality [1, 5]. Treatment goals for AS target in reducing symptoms, improving and maintaining spinal flexibility, reducing functional limitation, maintaining the ability to work and decreasing disease complications [1]. As such, early diagnosis and treatment are an imperative. The 2009 Assessment of the Spondyloarthritis International Society (ASAS) classification criteria helped physicians to have a better understanding of radiographic and non-radiographic SpA [6, 7]. Regarding the treatment options, during the last 2 decades a great progress has been made. With the introduction of the biologic disease-modifying anti-rheumatic drugs (bDMARDs) targeting cytokines such as the tumor necrosis factor (TNF) [8–11] or the interleukin 17 (IL-17) [12–14], the management of SpA has been revolutionized, especially for radiographic SpA. The bDMARDs are more effective than non-steroidal anti-inflammatory drugs (NSAIDs) with a better safety profile for AS patients [15, 16]. In addition, as new guidelines and recommendations for the management of AS have been issued by expert panels in Europe,

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✉ Alexandros A. Drosos
adrosos@cc.uoi.gr

[1] Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

US and Canada, the implementation of these guidelines has improved significantly the clinical outcomes of patients with AS [17–20].

On the other hand, not all patients have an adequate and sustained response to these agents reinforcing the unmet need for better AS treatment strategies. Reports from registries of different countries as well as by expert opinion panels agree that a considerable number of patients do not achieve remission or low disease activity (LDA). Thus, the size of unmet needs for AS management is not well known. The aim of this study was to estimate the size of unmet needs, which means failure to achieve LDA, using NSAIDs and/or anti-cytokine therapy following the international guidelines and recommendation for the treatment of AS.

Materials and methods

From January 2003 to December 2017, in a long-term observational study, 220 patients with AS were diagnosed and followed up in a tertiary outpatient rheumatology clinic. Inclusion criteria were patients who fulfilled the 2009 ASAS criteria for radiographic SpA. Patients with non-radiographic SpA or evidence of psoriasis, reactive arthritis or inflammatory bowel disease were all excluded. All patients were followed up at predefined times, initially every month for the first 3 months and every 2–3 months thereafter. At every visit, demographic, clinical and laboratory data, as well as the treatment decisions and strategies were all recorded. More specifically, the following parameters were recorded: complete blood count with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine analysis, as well as liver and kidney function tests. Before entering to treatment with anti-cytokine therapy, all patients were screened appropriately for latent tuberculosis and hepatitis B and C viruses. In addition, adverse drug reactions (ADR), the reason of termination or changing treatment strategies, disease complication and comorbidities were also recorded. Patients were treated according to the European, US and Canadian guidelines for AS [17–20]. More specifically, NSAIDs, including selective inhibitors of cyclooxygenase-2, were introduced in all patients. For peripheral arthritis, methotrexate (MTX) 0.3 mg/kgr/week per os (po) along with 5 mg of folic acid once a week or sulfasalazine (SSZ) 2–3 gr/day po were used. In addition, intra-articular steroids were used when indicated. The following anti-TNFs were used: adalimumab (ADA) 40 mg every 2 weeks subcutaneously (sc), certolizumab (CTZ) 400 mg sc at 0–2–4 weeks and 200 mg every 2 weeks thereafter, etanercept (ETN) 50 mg sc/week, golimumab (GOL) 50 mg sc every month or 100 mg if the patient's body weight was over 100 kgr, infliximab (INF) 5 mg/kgr at 0–2–6 weeks intravenously and every 8 weeks thereafter. We also used secukinumab 150 mg sc at weeks 1–4 and every 4 weeks thereafter. All patients entering to our study were naive to anti-TNF treatment. Disease activity was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [21] and the Ankylosing Spondylitis Disease Activity Score (ASDAS) using the C-RP (mg/l) [22, 23]. LDA was defined as BASDAI ≤ 4 and ASDAS < 2.1. Statistical analysis was performed using SPSS Statistics, version 20.0. We used the paired samples t-test for variables with normal distribution and Wilcoxon signed-rank test for variables which were not normally distributed. An informed consent form has been obtained by all patients and the study has been approved by the hospital's ethics committee (number 511/13-03-2012).

Results

A total number of 220 patients were included. During follow-up, 18 patients were lost and 4 never received anti-TNF therapy. The reasons not being able to be treated with anti-TNFs were: one had past medical history of pulmonary tuberculosis, another had an active hepatitis C virus infection, one had chronic pulmonary lung disease and one diabetes mellitus with peripheral polyneuropathy. Thus, the final results are referred to 198 patients. There were 160 males and 38 females with a mean age of 35.5 ± 6.2 years, mean disease duration 6.8 ± 3.2 years and a mean follow-up period of 12.8 ± 5.1 years. All patients had an active disease according to high BASDAI and ASDAS, as well as high acute-phase reactants. All had axial disease, while 13% had also peripheral arthritis (Table 1). All patients received at least two NSAIDs for 3 months while 12 (6%) continued receiving NSAIDs with significant clinical improvement and sustained LDA for a long period of time. However, four patients from this group never achieved LDA nor received anti-TNF therapy because they refused such treatment (Fig. 1). On the other hand, 186 (94%) were treated with anti-TNF agents. The majority of them demonstrated sustained LDA for a long period of time with an improvement of the global disease assessment, reduction of BASDAI, ASDAS and acute-phase reactants (Table 2). The mean period of achieving LDA was 8.2 months. However, from this group, 16 patients never achieved LDA despite they received two to three anti-TNFs or the IL-17 inhibitor, secukinumab (Fig. 1). Thus a total of 20 patients (10.1%) never achieved LDA.

The first anti-TNF was INF (51% of patients), followed by ADA (27%) and ETN (22%). During follow-up, ten patients receiving INF, three receiving ADA and three treated with ETN never achieved LDA despite they were switched to a second or third anti-TNF agent or the IL-17 inhibitor. In Fig. 2, the flow chart of AS patients treated with anti-TNFs is shown. Twelve patients discontinued anti-TNFs due to

Table 1 Characteristics of patients with ankylosing spondylitis treated with NSAIDs or/and TNF blockers

Parameters	Values
Number of patients	198
Male/female	160/38
Mean age (± years)	35.5 (6.2)
Mean disease duration (± years)	6.8 (3.2)
Mean follow-up (± years)	12.8 (5.1)
HLA B_{27} positivity *n* (%)	175 (88)
BMI (kg/m^2) > 25 *n* (%)	30 (15)
Current smokers *n* (%)	45 (23)
Ex-smokers *n* (%)	50 (25)
Peripheral arthritis *n* (%)	26 (13)
Enthesitis *n* (%)	20 (10)
Uveitis *n* (%)	20 (10)
NSAID intake *n* (%)	198 (100)
MTX intake *n* (%)	16 (8)
SSZ intake *n* (%)	10 (5)
Anti-TNF first choice *n* (%)	
INF *n* (%)	98 (51)
ADA *n* (%)	51 (27)
ETN *n* (%)	41 (22)

NSAIDs non-steroidal anti-inflammatory drugs, *HLA* human leukocyte antigen, *BMI* Body Mass Index, *MTX* methotrexate, *SSZ* sulfasalazine, *TNF* tumor necrosis factor, *INF* infliximab, *ADA* adalimumab, *ETN* etanercept

ADRs, while four due to inadequate response. No other significant side effects were noted during the treatment period of all patients requiring discontinuation of the treatment. Table 3 shows the most frequently reported adverse events occurring in our patients during the study period.

Discussion

Recently, we have reported an observational study in early rheumatoid arthritis (RA) with a pool of patients that have been followed up for 12 years and we found that the gap of unmet needs for RA treatment was approximately 20% [24]. The present study is a similar observational study following specific guidelines and strategies for AS treatment. In this report, we estimated the gap of the unmet needs in the treatment of AS, in a large AS population, followed up for a long period of time, using NSAIDs or/and cytokine inhibitors according to guidelines and recommendation for AS management issued by expert panels in Europe, United States and Canada [16–20]. We found that 10.1% of our patients did not achieve LDA despite the fact that they received all the above-mentioned treatment strategies. More specifically, all of our patients received NSAIDs for at least 3 months; however, only 6% continued receiving NSAIDs for a long period of time with sustained clinical response. Also, four patients did not achieve LDA nor received anti-cytokine therapy because they refused such treatment. It is well known that NSAIDs are effective in relieving the signs

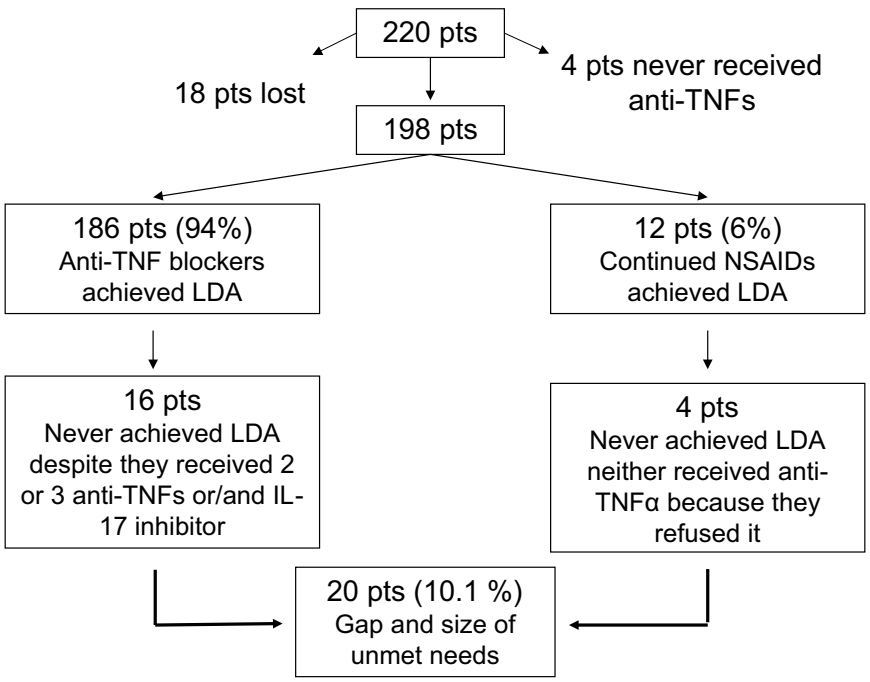

Fig. 1 Treatment flow chart of AS patients

NSAIDs: non-steroidal anti-inflammatory drugs; anti-TNF: tumor necrosis factor; LDA: low disease activity

Table 2 Assessment of response for clinical and laboratory parameters in AS patients treated with anti-cytokines therapy

Parameters*	Baseline	End of the study
Global disease assessment		
Patient (0–10 cm)	7.6 (1.3)	2.3 (0.9)
Physician (0–10 cm)	7.5 (1.2)	2.4 (0.8)
BASDAI	6.5 (1.1)	2.0 (1.0)
ASDAS	3.6 (1.1)	0.9 (0.5)
CRP (mg/l)	25.4 (10.5)	5.8 (4.5)
ESR (mm/h)	38.5 (11.7)	12.6 (5.7)

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

*Are expressed as mean (SD), *P* value < 0.01 at the end of the study versus baseline for all comparisons

and symptoms of AS, but many patients experience inadequate response, drug intolerance, or even relapse of the disease symptomatology. We found that the frequency of response to NSAID treatment in this study was much lower than reported in other studies. This can be explained that our hospital is a tertiary centre with more severe cases already referred by other physicians. Moreover, on the grounds of safety concerns a large proportion of the patients choose to discontinue their long-term treatment with NSAIDs [25]. For these patients, the use of anti-TNFs is strongly recommended. Thus, in our study, 94% of AS patients were treated with anti-TNFs. There are currently five anti-TNF-targeting therapies approved for AS treatment: ADA, CTZ, ETN, GOL and INF. With the appropriate screening, close follow-up and monitoring, many randomized controlled trials and many open-label studies have achieved rapid, profound and sustained clinical improvement with high drug survival, using anti-TNFs [26–33].

Despite the considerable progress in the management of AS, a significant number of patients do not meet the criteria for LDA. As a result, the unmet needs remain high. In addition, there are no studies measuring the therapeutic gap in AS even though there are several reports in the field of the unmet needs in rheumatology, including AS. The majority of these reports are coming from experts in international meetings. Specific groups of experts were asked to identify the unmet needs, if any, in three categorical areas (basic research, clinical and therapeutic sciences) as well as in different types of rheumatic diseases (inflammatory arthropathies and systemic autoimmune diseases). The results of the above publications were based mainly on literature review and expert opinions. In this way, a large gap of unmet needs

Table 3 Adverse events occurring during the study period of AS patients treated with TNF blockers

Most frequently reported events ≥ 5%	End of the study *n* (%)
Upper respiratory tract infections	101 (51)
Urinary infections	53 (27)
Increased liver enzymes	26 (13)
Diarrhea	20 (10)
Viral infections	20 (10)
Psoriatic skin lesions	16 (8)
Headache	10 (5)
Vertigo	10 (5)
Patients reported at least one adverse event	158 (80)

AS ankylosing spondylitis, *TNF* tumor necrosis factor

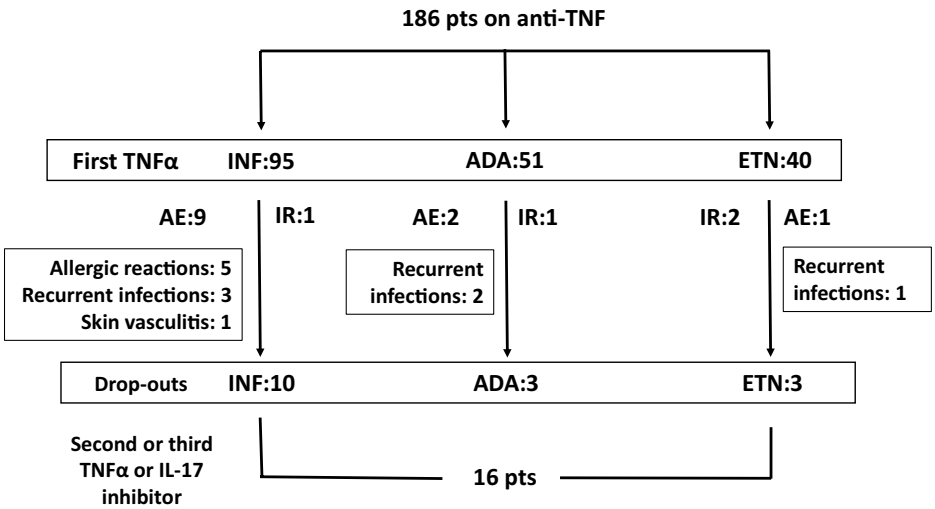

Fig. 2 Flow chart of AS patients treated with TNF α blockers

INF: infliximab; ETN: etanercept; ADA: adalimumab; TNFα: tumor necrosis factor alpha; AE: adverse events; IR: inadequate response

in disease pathogenesis, a substantial gap in diagnosis and a huge gap in the treatment of inflammatory arthropathies and systemic autoimmune diseases was identified [34–37]. Thus, our study is the first report in the literature aiming to cover this gap and is the longest prospective study following AS patients for more than 1 decade.

Although anti-TNFs have revolutionized the treatment of AS, a substantial minority of patients do not respond to these medications. Thus, other biologics with different mode of action (MOA) are used. Biologics other than anti-TNFs with different MOA currently in use for AS is secukinumab, an IL-17 inhibitor [12–14]. In a recent phase III trial that included patients in whom previous therapy with anti-TNF agents had produced an inadequate response or unacceptable side effects, secukinumab showed dramatic efficacy, similar to that seen in the original trials of treatment with the anti-TNFs [38]. From the group of patients receiving an anti-TNF agent and then switched to a second or third anti-TNF or secukinumab, 16 patients never achieved LDA despite that they received all the therapeutic options. The majority of them (12 patients) experienced ADRs while four had an inadequate response. No other severe side effects were noted during the study period requiring drug discontinuation. Our limitation is that we do not have a control group. However, our study is the longest study following AS patients for more than a decade with a quite large sample of patients treated with bDMARDs.

In summary, in the present study, AS patients were treated according to the international guidelines and recommendations for AS management. With this approach, we were able to treat the majority of patients with the use of NSAIDs and anti-TNF therapy. This is the first study aiming to estimate the gap and the size of unmet needs for AS treatment in a large patient population followed up in a tertiary university center showing that the size of unmet needs in the treatment of AS is not so large.

Author contributions EP and EK acquisition and analysis of the data. Manuscript drafting. PVV acquisition, analysis and interpretation of the data. AAD review of the manuscript and final approval.

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Compliance with ethical standards

Conflict of interest E. Pelechas declares no conflict of interest; Evripidis Kaltsonoudis declares no conflict of interest; Paraskevi V. Voulgari declares no conflict of interest; Alexandros A. Drosos declares no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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