Should over-treatment of axial spondyloarthritis with biologics remain a concern after the issue of the new ASAS criteria? Data from REGISPONSERBIO (Spanish Register of Biological Therapy in Spondyloarthritides)

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Abstract

Objective

To study whether disease status at treatment initiation has changed after the issue of the ASAS classification criteria.

Methods

REGISPONSERBIO registers patients with axial spondyloarthritis (axSpA) on biological treatment since 2013. It includes patients starting biological treatment (incident) or already on biological therapies (prevalent). Patients in both groups were compared in terms of: age at disease onset and at treatment start, disease duration, gender, HLA-B27, body mass index (BMI), BASDAI, BASFI, C-reactive protein, ESR, metrological data, ASQoL, WAPAI, extra-articular manifestations, comorbidities, radiological study, type of biological treatment and concomitant treatments.

Results

256 patients were included, of whom 174 (65%) were already on biologic therapy. Compared to incident patients, prevalent patients started treatment with longer disease duration (15 vs. 8.6 years; p<0.001), a higher proportion of them were men (83% vs. 67%; p=0.01), a smaller proportion of them showed non-radiographic axial spondylarthritis (nr-axSpA)(17% vs. 32%; p<0.01), and a higher proportion had HLAB27 (85% vs. 73%; p=0.02). There were no statistically significant differences in terms of disease activity, degree of disability, quality of life, or prevalence of extra-articular manifestations.

Conclusions

Data suggest that, after the issue of the new classification criteria for SpA, biological therapy is being administered earlier than previously in SpA patients and in a higher proportion of patients with nr-axSpA. However, this change in prescribing profile, apparently, has not caused an over-treatment, as patients do not seem to have a lower disease burden than prior to the issue of the criteria.

Key words

biologics, registers, health services research, disease activity

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Introduction

Spondyloarthritides (SpA) are a group of inflammatory diseases that share common characteristics in clinical, pathogenesis, radiology, epidemiology and immunogenetics. However, they show great variability in clinical manifestations at the musculoskeletal system and others, such as psoriasis, uveitis or inflammatory bowel disease; it is thus understandable, that different disease phenotypes may require specific approaches and treatment (1, 2).

One of the most important advances in SpA has been the introduction of TNF inhibitors (TNFi), all of which have shown reductions in signs and symptoms of ankylosing spondylitis (AS) and of non-radiographic axial spondyloarthritis (nr-axSpA) (3). However, these are chronic treatments with high economic impact and safety concerns in the medium- and long-term, especially in fragile patients. When the Assessment of SpondyloArthritis international Society (ASAS) issued the new classification criteria in 2011 that included as SpA patients without radiographic changes (4), the inevitable response of health managers was concern about over-treatment.

Health managers need reliable data to distribute and allocate health and social resources objectively and fairly. Sources of data should be flexible to incorporate changes that occur in clinical practice and scientific knowledge. Registers are useful tools to study populations of heterogeneous patients, as is the case of patients with SpA. In general, registries collect pre-established information prospectively and have pre-established objectives supervised by a scientific committee, resembling longitudinal studies (5).

In recent years a large number of registers have appeared in the field of SpA. One of the first that emerged was the Spanish REGISPONSER (6), a register specifically focused on SpA from which other registers such as RESPONDIA (Ibero-American registry) evolved (7), REGISPONSER allowed us to acquire experience in the use of registries in both information collection and evaluation and to apply the results obtained to improve the management and treatment of patients with SpA (8, 9). In addition, our group also launched a prospective register of patients with axSpA on biological therapy (REGISPONSERBIO) with the objective of evaluating the clinical influence, safety and social impact of biological therapies in patients with axSpA.

By comparing disease status of patients who started treatment prior to the issue, and subsequently uptake, of the new ASAS classification of SpA (4), it should be possible to determine whether these new criteria have brought up an overtreatment. The research question would be whether patients with axSpA starting biologic treatment after 2011 have less severe characteristics than previously treated patients.

Patients and methods

This study analyses cross-sectionally data from REGISPONSERBIO, a prospective multicentre register of patients with axSpA who are receiving treatment with TNFi in the participating centres. For this analysis we included patients registered between September 2013 and December 2014. Patients in the register are followed-up for 3 years with clinical and laboratory controls every 6 months. The register and subsidiary efficacy and safety analyses were approved by the Ethical Review Boards of all participating hospitals and patients needed to sign an informed consent form to be included.

REGISPONSERBIO includes patients who were already on TNFi treatment (*prevalent patients*) as of register launch, and those who were started on TNFi therapy according to the clinician's judgment after launch (*incident patients*). All patients included in the register meet the ASAS criteria for axSpA and have been prescribed TNFi therapy criteria according to the recommendations of the Spanish Society of Rheumatology (10). Patients with predominant peripheral SpA, or with rheumatic diseases that could confound the evaluation of the disease (*e.g.* fibromyalgia) and prevalent patients without sufficient data to evaluate study objectives at the beginning of the treatment with TNFi were excluded.

Variables

All the patients' had their sociodemographic, clinical and laboratory variables collected: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), visual analogue scale (VAS) of global medical assessment, VAS of global patient assessment, VAS of nocturnal back pain, HLAB27, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), Work Productivity And Activity Impairment Questionnaire (WAPAI), Ankylosing Spondylitis Quality Of Life questionnaire (ASQoL), extra-skeletal features (uveitis, inflammatory bowel disease), radiographic evaluation, comorbidities, treatments, adverse events, demographic variables and type of spondyloarthritis and duration of illness. Prevalent patients to be included in the register should have a minimum of demographic, clinical and therapeutic variables, namely BASDAI, VAS of global medical and patient assessments, CRP, ESR, HLAB27, radiographic evaluation and treatments. The new ASAS criteria were applied retrospectively based on patient characteristics at treatment start (4).

All the data collected were anonymised. Recording and storage was done in electronic format. For this purpose, a web platform was designed (http://www.regisbiogresser.com/). An administrator and a virtual monitor were appointed. A pilot test of the electronic case report form and web platform was performed to detect possible problems. A user manual was written to describe and standardise the study processes, as well as to resolve doubts regarding electronic forms.

Statistical analysis

We used descriptive statistics and classical hypothesis testing to answer the research question. For continuous variables, the results are summarised and presented in the form of "n", mean, standard deviation or median and range depending on the distribution of variables. In categorical variables, the number and relative percentage of subjects were used. For the comparison between groups, Chi square test was used for qualitative variables and Student's *t*-test for quantitative variables. The differences were considered statistically significant if the *p*-value was less than or equal to 0.05.

Results

Two hundred and fifty-six patients were recruited from 17 Spanish centres, of which 174 (68%) were prevalent and 82 (32%) incident users.

Demographic characteristics, disease activity and treatments of the patients included in the register are shown in Table I. Variables are presented globally and stratified by prevalent and incident users of biological therapies.

Mean age was 48 years and the majority of patients were men, with 13 years of mean disease duration and a mean BASDAI at treatment start of 5.5. Compared to incident patients, prevalent users started treatment with longer disease duration (15 *vs*. 8.6 years; $p<0.001$), a higher proportion of them were men (83% *vs*. 67%; $p=0.01$), a smaller proportion of them showed non-radiographic axial spondylarthritis (nr-axSpA)(17% *vs*. 32%; $p<0.01$), and a higher proportion had HLAB27 (85% *vs*. 73%; $p=0.02$). There were no statistically significant differences in terms of disease activity, degree of disability, quality of life, or prevalence of extra-articular manifestations. Finally, there were significant differences in the type of TNFi used, with a lower proportion of infliximab and a higher frequency of other subcutaneous TNFi among the incident users compared to the prevalent ones.

Discussion

We observed, using data from a multicen SpA register, that the indication of biological therapy is made at earlier stage in recent times than before the issue of the new ASAS criteria; also, we observed that it is increasingly common to indicate biological treatment to patients with nr-axSpA. However, the burden of disease at the start of treatment does not seem to have varied significantly over time.

The observation that biological therapy is currently started earlier in SpA patients is in line with those observed in other studies (11, 12). An early start of TNFi therapy is consistent with recently published data suggesting that early initiation of this therapy improves outcomes (13); and it is also in line with the main recommendations and guidelines for the treatment of patients with axSpA (3, 10).

The proportion of nr-axSpA in treatment with biological therapy varies greatly depending on the different series, and it is in direct relation with age and disease duration of the participants (14). In our series, 22% of the patients presented nr-axSpA, which is consistent with what has been observed in other registers and series including patients with similar characteristics (15). However, it is interesting to note that the proportion of patients with nr-axSpA has increased significantly in recent years (32% of incident users *vs*. 17% of prevalent users). The early introduction of treatment with a good response is a factor that undoubtedly contributes to these results. However, it is clear that the main factor has been the definition and assimilation of the concept of nr-axSpA developed by the ASAS group (4). Different studies comparing populations of patients with nr-axSpA and with established AS have shown a shorter disease duration and a higher proportion of women in the population of patients with nr-axSpA, similar to what has been observed in our study (12, 16). In line with recently published clinical data, disease burden (activity, disability, and quality of life) of patients with nr-axSpA who are indicated TNFi therapy was not different from that of patients with AS (12, 17). These data is especially relevant because they show that, in real clinical practice conditions, the acceptance of the indication of biological therapy in patients with nr-axSpA has not led to a treatment indication bias towards overtreatment of less severe patients.

SpA classically affects young working-age males and is related to HLA-B27 positivity. In this sense, our register shows a male predominance (78%) similar to that shown in other registries with an 81% HLA-B27 positivity also in agreement with the results presented

Table I. Description of the patients included in REGISPONSERBIO as of biological treatment start before (*prevalent user*) or after (*incident user*) the launch of the register in 2013. All data refer to the starting date of therapy.

Variable	-n†	All n=256	Prevalent n=174 (68%)	Incident n=82 (32%)	
Age (years) , m ± SD	1	48 ± 12	48 ± 11	48 ± 13	
Gender (men), n (%)	0	199 (78)	144 (83)	55 (67)	**
Disease duration (years), m ± SD	6	13 ± 11	15 ± 11	8.6 ± 10	***
Disease duration at first TNFi therapy (years), m ± SD	6	9.5 ± 9.9	10.0 ± 9.7	8.3 ± 10.4	
Body mass index, m ± SD	23	27 ± 11	28 ± 4	26 ± 4	
Tobacco use, n (%)	1				
Never-smoker		104 (41)	73 (42)	31 (38)	
Ex-smoker		72 (28)	49 (28)	23 (28)	
Current smoker		79 (31)	51 (30)	28 (34)	
Work disability, n (%)	12	43 (18)	26 (15)	17 (23)	
Type of spondyloarthritis, n (%)	0				
Ankylosing spondylitis		201 (79)	145 (83)	56 (68)	**
Non-radiographic axial spondyloarthritis		55 (22)	29 (17)	26 (32)	**
HLA-B27 positive, n (%)	5	204 (81)	146 (85)	58 (73)	*
Extra-skeletal features, n (%)					
Uveitis	1	67 (26)	47 (27)	20 (24)	
Psoriasis	3	20 (8)	15 (9)	5 (6)	
Inflammatory bowel disease	4	24 (9)	15 (9)	9 (11)	
Current TNFi, n (%)	2				***
Adalimumab		90 (35)	65 (38)	25 (31)	
Etanercept		82 (32)	60 (35)	22 (27)	
Infliximab		35 (14)	29 (17)	6 (7)	*
Golimumab		41 (16)	17 (10)	24 (29)	***
Certolizumab pegol		6 (2)	1 (0.6)	5 (6)	**
First TNFi, n (%)	2				***
Adalimumab		95 (37)	70 (41)	25 (31)	
Etanercept		65 (26)	43 (25)	22 (27)	
Infliximab		55 (22)	49 (29)	6 (7)	***
Golimumab		34 (13)	10 (6)	24 (29)	***
Certolizumab		5 (2)	-	5 (6)	**
Concomitant NSAID	1	155 (61)	92 (53)	63 (77)	***
Concomitant DMARD	1	57 (22)	39 (23)	18 (22)	
Erythrocyte sedimentation rate (mm/h), m ± SD	8	25 ± 21	26 ± 22	22 ± 19	
C-reactive protein (mg/L), m ± SD	5	17 ± 19	19 ± 20	13 ± 15	*
BASDAI (0-10), m ± SD	1	5.5 ± 2.0	5.4 ± 1.9	5.7± 2.3	
Patient Global Assessment VAS (0-10), m ± SD	5	6.3 ± 2.2	6.2 ± 2.0	6.4 ± 2.5	
Nocturnal back pain (VAS scale 0-10), m ± SD	36	5.8 ± 2.6	5.7 ± 2.5	6.2 ± 2.6	
BASFI, m ± SD	9	5.1 ± 2.4	4.9 ± 2.3	5.4 ± 2.5	

*p<0.05; **p<0.01, ***p<0.001 between prevalent and incident. †number of missing values.
BASDAI: Bath ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis functional Index; ASQoL: Ankylosing Spondylitis Quality of Life; WAPAI: Work Productivity and Activity Impairment Questionnaire; PsA: psoriatic arthritis; NSAID: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying anti-rheumatic drugs; TNFi: tumour necrosis factor inhibitors.

in previous registers (6, 18, 19). Our study also showed a decrease in the prescription of infliximab and an increase of the subcutaneous TNFi, probably due to patient or doctor preferences in the route of administration and the immunogenic characteristics of the drug.

The rate of disability in our study was 18%, which is within the low range of the figures described in other European registers with figures from 15 to 45% (17, 20), and well below that observed in the Biologic Treatment Registry Across Canada (BioTRAC) (18). Finally, extra-articular manifestations such as uveitis (26%), psoriasis (8%) and inflammatory bowel disease (9%) appeared in a similar percentage of existing registries (12, 18, 19).

One of the major strengths of our register is that baseline data included patients who initiated treatment at that time along with others with established treatment. The mixture of incident and prevalent users allowed us to easily compare and detect trends in the use of biological therapy in routine clinical practice. Others have criticised comparative effectiveness research between incident and prevalent users, arguing that prevalent users are subject to immortal bias, among others (21). Our research question was not related to the outcome, but to treatment start, and in REGISPONSERBIO, all patients with SpA ever exposed to biological therapies in the participating centres are included. Therefore, we are less concerned about potential biases, although these are impossible to rule out.

In summary, our study has demonstrated the increasing inclusion of patients with nr-axSpA in TNFi therapy, as well as a progressive tendency to start TNFi treatment earlier; however, this change in the prescription of TNFi therapy has not been accompanied by over-treatment of patients with low disease burden.

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