Treatment with Tumor Necrosis Factor Inhibitors in Axial Spondyloarthritis: Comparison Between Private Rheumatology Practices and Academic Centers in a Large Observational Cohort

Adrian Ciurea, Ulrich Weber, Daniel Stekhoven, Almut Scherer, Giorgio Tamborrini, Jürg Bernhard, Martin Toniolo, Peter M. Villiger, Pascal Zufferey, Rudolf O. Kissling, Beat A. Michel, and Pascale Exer, on behalf of the Rheumatologists of Swiss Clinical Quality Management

ABSTRACT. ***Objective.*** To evaluate the initiation of and response to tumor necrosis factor (TNF) inhibitors for axial spondyloarthritis (axSpA) in private rheumatology practices versus academic centers.

Methods. We compared newly initiated TNF inhibition for axSpA in 363 patients enrolled in private practices with 100 patients recruited in 6 university hospitals within the Swiss Clinical Quality Management (SCQM) cohort.

Results. All patients had been treated with ≥ 1 nonsteroidal antiinflammatory drug and > 70% of patients had a baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 before anti-TNF agent initiation. The proportion of patients with nonradiographic axSpA (nr-axSpA) treated with TNF inhibitors was higher in hospitals versus private practices (30.4% vs 18.7%, p = 0.02). The burden of disease as assessed by patient-reported outcomes at baseline was slightly higher in the hospital setting. Mean levels (± SD) of the Ankylosing Spondylitis Disease Activity Score were, however, virtually identical in private practices and academic centers (3.4 ± 1.0 vs 3.4 ± 0.9, p = 0.68). An Assessment of SpondyloArthritis international Society (ASAS40) response at 1 year was reached for ankylosing spondylitis in 51.7% in private practices and 52.9% in university hospitals (p = 1.0) and for nr-axSpA in 27.5% versus 25.0%, respectively (p = 1.0).

Conclusion. With the exception of a lower proportion of patients with nr-axSpA newly treated with anti-TNF agents in private practices in comparison to academic centers, adherence to ASAS treatment recommendations for TNF inhibition was equally high, and similar response rates to TNF blockers were achieved in both clinical settings. (First Release Nov 1 2014; J Rheumatol 2015; 42:101–5; doi:10.3899/jrheum.140229)

Key Indexing Terms:
AXIAL SPONDYLOARTHRITIS TREATMENT RESPONSE
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The Assessment in SpondyloArthritis international Society (ASAS) has recommended that patients with highly active axial spondyloarthritis (axSpA) that is not sufficiently responding to nonsteroidal antiinflammatory drugs (NSAID) may be considered for treatment with anti-tumor necrosis factor (TNF) agents, regardless of the presence or

From the Department of Rheumatology, University Hospital; Department of Rheumatology, Uniklinik Balgrist; Swiss Clinical Quality Management Foundation, Zurich; Department of Rheumatology, Bethesda Hospital, Basel; Department of Rheumatology and Rehabilitation, Bürgerspital, Solothurn; Department of Rheumatology and Clinical Immunology, University Hospital, Bern; Department of Rheumatology, Centre Hospitalier Universitaire Vaudois, Lausanne; Praxis Rheuma-Basel, Basel, Switzerland.

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A. Ciurea, MD; M. Toniolo, MD; B.A. Michel, MD, Department of Rheumatology, University Hospital Zurich; U. Weber, MD, King Christian 10th Hospital for Rheumatic Diseases, Gråsten, Denmark; R.O. Kissling, MD, Uniklinik Balgrist; D. Stekhoven, PhD; A. Scherer, PhD, SCQM Foundation; G. Tamborrini, MD, Bethesda Hospital; J. Bernhard, Department of Rheumatology and Rehabilitation, Bürgerspital Solothurn; P.M. Villiger, MD, Department of Rheumatology and Clinical Immunology, University Hospital Bern; P. Zufferey, MD, Department of Rheumatology, Centre Hospitalier Universitaire Vaudois; P. Exer, MD, Praxis Rheuma-Basel.

Address correspondence to Dr. A. Ciurea, Department of Rheumatology, University Hospital Zurich, Gloriastrasse 25, CH-8091 Zurich, Switzerland. E-mail: adrian.ciurea@usz.ch

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absence of definite structural sacroiliac joint lesions[1]. This recommendation paved the way for the treatment of non-radiographic axSpA (nr-axSpA) with TNF blockers. The requirements for the initiation of anti-TNF treatment include the previous failure of conventional treatment with persistently high disease activity for at least 4 weeks [defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of ≥ 4 and the positive expert opinion of the treating rheumatologist]. A worldwide comparison of 23 national recommendations for the use of TNF inhibitors in ankylosing spondylitis (AS) revealed that the majority were similar to the ASAS recommendations with regard to the diagnosis of AS, the assessment of disease, and the treatment response[2]. However, additional objective measures of disease activity, such as elevated acute-phase reactants and/or inflammation on magnetic resonance imaging, were required in 8 countries.

There is limited evidence of how widely the new concept of axSpA and the recommendations to initiate biological treatment have been adopted in clinical practice. An ASAS-initiated project evaluated the dissemination of the ASAS/European League Against Rheumatism recommendations for the management of AS involving 1507 rheumatologists in 10 countries in 2006[3]. It demonstrated a high conceptual agreement with the recommendations[4], but also highlighted inequalities in access to healthcare for patients with AS in different countries. Dissemination of treatment recommendations may differ between the 2 clinical settings of private rheumatology practices and academic centers.

The aims of our study in a nationwide observational cohort were to compare baseline characteristics of patients with axSpA newly treated with TNF antagonists by rheumatologists in private practice versus university hospitals; to evaluate whether routine practice of initiation of anti-TNF agents in community and in academic settings is consistent with current international recommendations; and to compare response to TNF inhibition in both clinical settings.

MATERIALS AND METHODS

Study population. Recruitment criteria for the nationwide, ongoing observational Swiss Clinical Quality Management Cohort for patients with axSpA (SCQM-axSpA) encompassed all patients with AS or other forms of SpA with predominantly axial disease according to the opinion of the treating rheumatologist[5]. Ethics approval for the collection of patient data was given by the regional review boards. Informed consent was obtained from all patients before inclusion in the cohort. Clinical assessments were performed at baseline as well as annually thereafter and included a physical examination (presence of peripheral arthritis, dactylitis, and enthesitis, spinal mobility according to the Bath Ankylosing Spondylitis Metrology Index[6], measurement of height, weight, chest expansion, and finger-to-floor distance), laboratory tests [erythrocyte sedimentation rate, C-reactive protein (CRP) level, hemoglobin level], data on treatment with conventional and biological drugs with exact dosage as well as start and stop dates, and data on NSAID as yes/no. Patient questionnaires included the BASDAI[7], the Bath Ankylosing Spondylitis Functional Index (BASFI)[8], the Medical Outcomes Study Short Form-36 (SF-36) health survey[9], and the EuroQol 5-domain questionnaire for the assessment of health-related quality of life[10].

Inclusion criteria for the current study. Patients were eligible for the current study if they were recruited in a private rheumatology practice or in one of 6 academic centers (comparator group) before April 2014 and if they fulfilled the ASAS 2009 classification criteria for axSpA[11] with minor modifications because the cohort was initiated in 2005, before the publication of these criteria. First, the criterion "inflammatory back pain" was defined as low back pain and morning stiffness for > 3 months, improving with exercise but not relieved by rest, as well as age at onset < 45 years. Second, the criterion "good response to NSAID" was added to the online questionnaire in 2009, and this information was not available for all patients.

Treatment with TNF inhibitors. Response to a first anti-TNF agent was assessed at 1 year (± 3 mos). The last observation carried forward (LOCF) technique was used to replace missing values for each patient from 2 months after TNF inhibitor initiation to this timepoint. The following efficacy variables were assessed: the ASAS criteria for 40% improvement (ASAS40), defined as improvement ≥ 40% or absolute improvement from baseline of ≥ 2 units (range 1–10) in ≥ 3 of the following 4 domains [patient's global assessment, total back pain, BASFI, and inflammation/morning stiffness (mean score for items 5 and 6 of the BASDAI) without any worsening in the remaining domains][12]; the clinically important improvement in the AS Disease Activity Score (ASDAS; change of ≥ 1.1 between baseline and followup); the major improvement in the ASDAS (change of ≥ 2.0 between baseline and followup); and the ASDAS inactive disease status as defined by an ASDAS < 1.3[13].

Because physical exercise as a co-intervention might affect the evolution of disease activity over time, and encouragement for increased physical activity and stretching might differ between recruitment centers, weekly exercise frequency was assessed at baseline and followup (home-based or group exercise sessions, supervised physiotherapy, fitness studio training).

Statistical analysis. To compare baseline characteristics at TNF blocker initiation in patients enrolled by rheumatologists in private practice versus a hospital setting, the mean and SD in each group were provided for continuous variables. We used Fisher's exact test for comparing distributions between the 2 groups for nominal variables and the Mann-Whitney U test for continuous variables. To assess the significance of differences in response rates after 1 year of treatment with a first anti-TNF agent, Fisher's exact test was used, and the OR and 95% CI are reported. R version 3.11.0 software (www.r-project.org) was used for the analyses.

RESULTS

A total of 2103 out of 3046 patients enrolled in SCQM-axSpA fulfilled the ASAS classification criteria by the end of March 2014. Out of these, 1073 patients were recruited by 177 private practice rheumatologists and 383 patients were enrolled in the rheumatology departments of 6 university hospitals. The proportion of patients already treated with anti-TNF agents at inclusion into SCQM was similar in both settings (30.3% vs 32.9%, p = 0.37). In the remaining patients, treatment with a first TNF inhibitor was initiated by office rheumatologists in 32.7% (n = 363) and by physicians in university hospitals in 28% (n = 100; p = 0.10). Only 8 patients changed affiliation between the practice and academic sector during the observation period relevant for the response analysis. Patient characteristics at the visit before treatment initiation are summarized in Table 1.

Pelvic radiographs for further classification of these

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Table 1. Characteristics of and disease activity in patients with axSpA at the time of tumor necrosis factor (TNF) initiation. Except where indicated otherwise, values are mean (SD).

Characteristic	n	Private Practices, n = 363	Academic Centers, n = 100	p
Male sex, %	463	62.3	62.0	1.00
Age, yrs	463	40.7 ± 12.1	39.4 ± 11.1	0.34
Disease duration, yrs	456	12.7 ± 10.0	13.7 ± 12.0	0.82
Nr-axSpA, %	397	18.7	30.4	0.02
HLA-B27+, %	408	80.5	72.5	0.13
BASDAI	463	5.3 ± 2.1	5.9 ± 2.0	0.01
BASDAI ≥ 4, %	463	73.8	77.0	0.60
ASDAS-CRP	433	3.4 ± 1.0	3.4 ± 0.9	0.68
ASDAS ≥ 2.1, %	433	89.6	92.8	0.44
BASFI	464	3.9 ± 2.4	4.5 ± 2.5	0.03
BASMI	406	2.4 ± 2.1	1.8 ± 1.9	0.01
Sacroiliitis on MRI, %	463	34.4	56.0	< 0.001
Ever peripheral arthritis, %	455	34.3	40.4	0.29
Elevated CRP, %	434	53.7	51.5	0.73
CRP, mg/l	436	17.2 ± 21.7	13.1 ± 16.5	0.01
ESR, mm/h	439	22.2 ± 20.4	18.6 ± 19.2	0.10
SF-36 MCS	386	43.6 ± 11.7	39.8 ± 9.8	0.004
SF-36 PCS	386	34.7 ± 9.7	33.2 ± 8.5	0.16
EQ-5D	452	54.9 ± 22.2	52.4 ± 22.4	0.27
No. exercise sessions/week	415	2.0 ± 2.0	2.0 ± 2.5	0.26
Smoker, %	460	60.6	64.0	0.56
Ever NSAID, %	463	100	100	—
Ever DMARD, %	463	40.8	48.0	0.21
Anti-TNF type, IV/SC, %	463	23.4/76.6	30.0/70.0	0.19

AxSpA: axial spondyloarthritis; nr-axSpA: nonradiographic axSpA; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein (CRP) levels; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; sacroiliitis on MRI: inflammation of the sacroiliac joint appearing on magnetic resonance imaging; ESR: erythrocyte sedimentation rate; SF-36: Medical Outcomes Study Short Form-36 health survey; PCS: physical component score; MCS: mental component score; EQ-5D: EuroQol 5-domain; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug; IV: intravenous; SC: subcutaneous.

patients with axSpA were available in a similar percentage of patients in both clinical settings. TNF inhibition was initiated in a higher proportion of patients with nr-axSpA in university hospitals (30.4% vs 18.1% in private practices, p = 0.02). All patients had already been treated with at least 1 NSAID. Self-reported disease activity and functional impairment were more severe in academic centers, while slightly higher mean CRP levels (± SD) were detected in community practices (17.2 ± 21.7 mg/l vs 13.1 ± 16.5 mg/l, p = 0.01). Mean ASDAS-CRP levels (± SD) were virtually identical in the 2 settings (3.4 ± 1.0 vs 3.4 ± 0.9, p = 0.68). The percentages of patients having a baseline BASDAI ≥ 4 and a baseline ASDAS ≥ 2.1 were similar in both groups (73.8% vs 77.0%, p = 0.6 and 89.6% vs 92.8%, p = 0.44, in private practices vs academic centers, respectively). With regard to the type of initiated TNF inhibitor, office rheumatologists prescribed anti-TNF agents with intravenous administration in a similar percentage of patients as physicians in academic centers (23.4% vs 30.0%, p = 0.19; Table 1).

Followup information with complete datasets for the evaluation of response rates at 1 year was available in 73.3% and 74.0% of patients treated in the academic and community settings, respectively (p = 1.0). The baseline characteristics of patients with incomplete followup were similar to those included in the analysis (data not shown). For the axSpA patients with complete data, the mean BASDAI (± SD) decreased from 6.1 ± 1.8 to 4.1 ± 2.6 in university hospitals and from 5.5 ± 2.0 to 3.3 ± 2.2 in private practices (p = 0.3). The mean number of exercise sessions per week was similar at initiation of TNF inhibition (2.0 ± 2.1 vs 1.8 ± 2.0, p = 0.23) as well as at 1 year of treatment (2.2 ± 2.0 vs 2.5 ± 2.3, p = 0.73) in private practices and academic centers, respectively. When analyzing the whole group of patients with axSpA, a numerically slightly higher ASAS40 response was found in patients recruited by office rheumatologists (48.5% vs 43.4% in hospitals); it did not reach statistical significance (p = 0.51; Table 2). To assess whether the slightly lower response rates in the hospital setting might be due to the higher proportion of patients with nr-axSpA, response rates were analyzed in patients with available pelvis radiographs, stratified by classification as definite AS and nr-axSpA. Remarkably similar ASAS40

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Table 2. Response rates after 1 year of treatment with anti-TNF agents. Except where indicated otherwise, values are percentages.

	n	Private Practices	Academic Centers	OR (95% CI)	p
All Patients with Axial SpA					
ASAS40	336	48.5	43.4	1.22 (0.71–2.13)	0.51
ASDAS clinically important improvement	296	59.7	60.0	0.99 (0.55–1.77)	1.00
ASDAS major improvement	296	35.8	32.9	1.14 (0.63–2.12)	0.67
ASDAS inactive disease	296	16.9	20.0	0.81 (0.40–1.74)	0.59
Patients with AS					
ASAS40	231	51.7	52.9	0.95 (0.48–1.86)	1.00
Patients with Nonradiographic Axial SpA					
ASAS40	60	27.5	25.0	1.14 (0.29–4.97)	1.00

Anti-TNF: anti-tumor necrosis factor; SpA: spondyloarthritis; ASAS: Assessment of SpondyloArthritis international Society; ASAS40: ≥ 40% improvement according to ASAS; ASDAS: Ankylosing Spondylitis Disease Activity Score.

responses were reached in these subgroups (51.7% vs 52.9%, p = 1.0, for AS and 27.5% vs 25.0%, p = 1.0, for nr-axSpA, in the community and hospital settings, respectively; Table 2). Similar results were found when a complete case analysis was performed at 1 year, omitting LOCF data (data not shown). Moreover, no significant differences were found for ASDAS improvement rates between community and hospital patients for the whole group of patients with axSpA (Table 2).

DISCUSSION

Our study demonstrates that patients with axSpA treated with TNF inhibitors in private practices have a slightly lower burden of disease compared with patients cared for in academic centers. Adherence to the ASAS recommendations for the use of anti-TNF agents was similar in both recruitment settings. Before initiation of a first TNF blocker, all patients had been treated with NSAID. Moreover, 74% and 77% of the patients in the 2 clinical settings had a BASDAI level ≥ 4, even though this criterion was not a prerequisite for drug reimbursement in Switzerland. Importantly, a comparably good response to TNF inhibition was reached in the practice and academic sector, with an ASAS40 response of 52% for AS and around 25% for nr-axSpA. A major limitation of the longitudinal analysis, inherent to the observational character of the cohort, is missing followup data. This might have led to an overestimation of the treatment effect, because responses could be analyzed only in patients with complete followup data. However, omitting the LOCF imputation method did not alter the results of the comparison between the 2 clinical settings. Because ASDAS incorporates CRP levels, which were missing in an additional number of patients, ASDAS improvement rates could be assessed only within the whole axSpA population.

Our findings have to be interpreted in the context of the Swiss healthcare system. A total of 460 board-certified rheumatologists was practicing in Switzerland in 2013 for a population of 8.1 million. The access to TNF inhibitor use in Switzerland does not differ between board-certified rheumatologists in private practice and in academic settings. Of 310 rheumatologists working in private practices, 177 (57%) have contributed to the SCQM-axSpA cohort. According to our study design, only patients recruited in university rheumatology settings and not from nonacademic hospitals were included as a comparator group. The conditions set by Swiss healthcare authorities for reimbursement of anti-TNF treatment are a clinical diagnosis of "Bechterew's disease" and an inadequate response to conventional therapy. Because the fulfillment of the modified New York classification criteria was not required for TNF blocker reimbursement, rheumatologists have also treated patients with nr-axSpA, although at a significantly lower rate in private practices than in academic centers (18.7% vs 30.4%). We speculate that community rheumatologists might have referred some patients with nr-axSpA eligible for TNF inhibition to tertiary centers to obtain a second opinion before initiating treatment, because the option to treat patients with nr-axSpA was only introduced at the time of the 2010 update of the ASAS recommendations[1].

Interestingly, the proportion of patients treated with intravenously administered anti-TNF agents was not lower in private practices than in hospitals, suggesting that the infrastructure for parenteral therapy is available in most private practices in Switzerland. Although this type of administration requires more private-practice resources, some patients might prefer the longer application intervals. Moreover, it allows the rheumatologists to evaluate disease activity and/or side effects at regular intervals, which might be more challenging in the long term for patients who prefer subcutaneous self-administering of TNF inhibitors.

To the best of our knowledge, this is the first report

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comparing management of patients with axSpA in private practices and academic centers. It remains to be shown whether our results can be confirmed in other countries with a comparably high proportion of community rheumatologists.

Our study demonstrates a similarly high adherence to ASAS recommendations for initiating biological treatment in patients with axSpA and a comparably good response to TNF inhibition in both private practice and academic rheumatology setting.

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