Aus der Klinik für Gastroenterologie, Infektiologie und Rheumatologie
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DISSERTATION

Progression of structural damage in the sacroiliac joints in patients with early axial spondyloarthritis during long-term anti-tumor necrosis factor treatment

Progression der Strukturschäden in den Iliosakralgelenken bei Patienten mit früher axialer Spondyloarthritis bei langfristiger Anti-Tumornekrosefaktor-Therapie

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LIST OF ABBREVIATIONS

AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
COX-2	cyclo-oxygenase-2
CRP	C-reactive protein
EULAR	European League Against Rheumatism
mNY	modified New York
mSASSS	modified Stoke Ankylosing Spondylitis Spine Score
MRI	magnetic resonance imaging
nr-axSpA	non-radiographic axSpA
NSAID	non-steroidal anti-inflammatory drug
r-axSpA	radiographic axSpA
SI joints	sacroiliac joints
SpA	spondyloarthritis
STIR	short tau inversion recovery
TNF	tumor necrosis factor

ABSTRACT

(English)

Background: Several observational studies have addressed the question of the natural structural damage progression in the sacroiliac joints in patients with axial spondyloarthritis (axSpA) over 2 to 5 years. Few predictors of progressions, such as elevated C-reactive protein (CRP) and active inflammation on magnetic resonance imaging (MRI), have been identified mostly in patients not treated with TNF inhibitors. To date, it is not clear whether these predictors also work in patients treated with anti-TNF agents and whether anti-TNF therapy is able to retard such a progression.

Objective: To assess the radiographic progression in the sacroiliac joints and to identify possible predictor factors in patients with early axSpA treated up to six years with TNF inhibitor etanercept.

Methods: Patients with early axSpA treated with etanercept for up to 6 years were selected from the Etanercept versus Sulfasalazine in Early Axial Spondyloarthritis (ESTHER) trial based on the availability of radiographs of the sacroiliac joints. Two readers, who were blinded for all clinical and timepoint data, score independently the sacroiliac radiographs, according to the grading system of the modified New York criteria (range 0-4 per SI joint). Patients were classified as having a radiographic axSpA (r-axSpA) if both readers recorded the presence of definite radiographic sacroiliitis of at least grade 2 bilaterally or at least grade 3 unilaterally. Otherwise patients were classified as non-radiographic (nr-) axSpA. The sacroiliitis sum score was calculated as the mean of both readers scores and had a total range from 0 to 8. Magnetic resonance imaging (MRI) of the sacroiliac joints were performed at baseline, year 2 and year 4 to assess active and chronic inflammatory changes in the sacroiliac joints according to the Berlin MRI scoring system. A longitudinal mixed model analysis was performed to identify possible predictors on the sacroiliac progression.

Results: From the 76 patients originally included in the ESTHER trial, 42 had radiographs with visible sacroiliac joints available at baseline and at least one follow-up time-point (year 2, 4, 6). Based on the reading of the sacroiliac joint radiographs, 15 patients (35.7%) were classified at baseline as r-axSpA and 27 (64.3%) as nr-axSpA. The change of the sacroiliitis sum score (mean±SD) was 0.13±0.73, -0.27±0.76 and -0.09±0.68, in the time intervals baseline - year 2, year 2 - year 4, and

year 4 - year 6, respectively. In the longitudinal mixed model analysis, elevated C-reactive protein (ß=0.58, 95%CI 0.25-0.90) and osteitis score (ß=0.06, 95%CI 0.03-0.10) in the MRI of the sacroiliac joints were independently associated with progression of the sacroiliitis sum score.

Conclusions: Long-term treatment with TNF inhibitor etanercept seems to decelerate the progression of structural damage in the sacroiliac joints. Elevated levels of CRP and the presence of osteitis on MRI were independently associated with radiographic progression of the sacroiliac joints.

(German)

Hintergrund: Verschiedene Beobachtungsstudien zeigten ein zwar gering ausgeprägtes, jedoch signifikantes Voranschreiten struktureller Schäden der Iliosakralgelenke (ISG) über 2 bis 5 Jahre bei Patienten mit axialer Spondyloarthritis (axSpA). Als Prädiktoren einer solchen Progression konnten ein erhöhtes C-reaktives Protein (CRP) und aktive entzündliche Veränderungen in der Magnetresonanztomographie (MRT) identifiziert werden – größtenteils bei Patienten, die nicht mit TNF-Inhibitoren (TNFi) behandelt wurden. Unklar bleibt, ob diese Prädiktoren auch für Patienten unter TNFi gelten und inwiefern eine Therapie mit TNFi in der Lage ist, die radiografische Progression der ISG zu verzögern.

Ziel: Ziel der vorliegenden Studie war die Analyse der radiographischen Progression der ISG unter Langzeittherapie (bis zu 6 Jahren) mit dem TNFi Etanercept in Patienten mit früher axSpA, sowie die Identifizierung möglicher prädiktiver Faktoren.

Methoden: Patienten mit früher axSpA, die im Rahmen der ESTHER-Studie bis zu 6 Jahre lang mit Etanercept behandelt wurden, wurden nach Verfügbarkeit von Röntgenaufnahmen der ISG in die Auswertung eingeschlossen. Zwei verblindete Reader bewerteten unabhängig voneinander die ISG-Röntgenaufnahmen in zufällig ausgewählter Reihenfolge nach der Gradeinteilung der modifizierten New Yorker Kriterien (Bereich von 0-4 pro ISG). Die Patienten wurden als röntgenologische axSpA (r-axSpA) klassifiziert, wenn beide Reader eine definitive radiografische Sakroiliitis (mindestens Grad 2 bilateral oder Grad 3 unilateral) feststellten. Andernfalls wurden die Patienten als nicht-röntgenologische (nr-)axSpA klassifiziert. Ein Summenscore der Sakroiliitis beider ISG (Gesamtbereich 0-8) wurde als Mittelwert aus den Werten beider Reader berechnet. Aktive und chronische entzündliche Veränderungen im MRT

der ISG, die zu Studienbeginn, Jahr 2 und Jahr 4 erfolgten, wurden anhand des Berlin MRI Scoring Systems analysiert. In einer longitudinalen gemischten Modellanalyse wurden mögliche Prädiktoren für die radiografische Progression der ISG evaluiert.

Ergebnisse: Von den 76 ursprünglich in der ESTHER Studie eingeschlossenen Patienten verfügten 42 über ISG-Röntgenaufnahmen zu Studienbeginn und mindestens einem Follow-up-Zeitpunkt (Jahr 2, 4, 6). Nach der Bewertung der ISG wurden 15 Patienten (35,7%) zu Studienbeginn als r-axSpA und 27 (64,3%) als nr-axSpA klassifiziert. Die Veränderung des Sakroiliitis Summenscores betrug 0,13±0,73; -0,27±0,76 und -0,09±0,68 (Mittelwert±Standardabweichung) in den Zeitintervallen von Baseline - Jahr 2; Jahr 2 - Jahr 4 und Jahr 4 - Jahr 6. Die longitudinale gemischte Modellanalyse zeigte eine unabhängige Assoziation von erhöhtem C-reaktiven Protein (ß=0,58; 95%CI 0,25-0,90) und dem Osteitis Score der ISG im MRT (ß=0,06; 95%CI 0,03-0,10) jeweils mit der Progression des Sakroiliitis Summenscores.

Schlussfolgerung: Eine Langzeittherapie mit TNFi scheint das Fortschreiten struktureller Schäden der ISG verlangsamen zu können. Erhöhte CRP-Werte sowie das Vorhandensein einer Osteitis im MRT waren unabhängig voneinander mit der Progression der radiografischen Sakroiliitis assoziiert.

SYNOPSIS

CURRENT STATE OF RESEARCH

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that mainly involves the axial skeleton (sacroiliac joints and spine), and its frequently associated to HLA-B27. Its prevalence is between 0.32% and 1.4% (Sieper and Poddubnyy, 2017). The main symptoms are chronic inflammatory back pain and stiffness. The back pain is typically located in the pelvis or lower back but can also affect any part of the spine. The back pain is characteristically inflammatory, as improves with exercise, worsens by resting, and awakes patients on the second part of the night. Typical SpA features besides chronic back pain that patients suffering from this condition can develop are: peripheral arthritis (usually mono- or oligoarthritis of the lower limbs), dactylitis, and enthesitis, and extra-articular manifestations: uveitis, psoriasis and inflammatory bowel disease(Sieper and Poddubnyy, 2017).

AxSpA is a term that covers non-radiographic (nr-axSpA) and radiographic axSpA (r-axSpA), this second one also known as ankylosing spondylitis (AS) depending on the absence or presence of structural damage in the sacroiliac joints on plain radiographs, respectively. This structural damage in the sacroiliac joints, visible on radiographs as erosions, sclerosis, joint space narrowing, partial and total ankylosis of the joint, is called sacroiliitis. According to the modified New York (mNY) criteria, definite radiographic sacroiliitis is defined by the presence of sacroiliitis at least grade 2 bilaterally or grade 3-4 unilaterally (van der Linden et al., 1984). The current tendency is to relate nr-axSpA and r-axSpA as two poles of the same disease. Certainly, there is a group of patients with nr-axSpA who progress to the stage of r-axSpA over time, but not all patients follow this pattern, and some might never develop such structural damage, remaining as nr-axSpA(Poddubnyy et al., 2012).

Due to the absence of radiographic changes in the nr-axSpA, magnetic resonance imaging (MRI) is used to detect inflammation in the SI joints and/or spine. Therefore it has been included in the 2009 Assessment in SpondyloArthritis international Society (ASAS) classification criteria for axSpA (Rudwaleit et al., 2009a, Rudwaleit et al., 2009b). According to these, a patient can be classified as having a nr-axSpA by the

presence of chronic back with age at onset under 45 years, not fulfilling the radiographic criterion of the mNY criteria for AS, and still having active inflammation in the sacroiliac joints detected on the MRI (plus at least on another SpA feature) (Rudwaleit et al., 2009a, Rudwaleit et al., 2009b).

It is particularly relevant to highlight that inflammation may activate bone repair mechanisms that triggers the new bone formation, aiming for joint stabilization (Lories, 2011). The characteristic inflammation of SpA takes place at the interface between cartilage and bone in the sacroiliac joints, spine, and entheses. Mechanical stress might have an important role for the initiation and maintenance of inflammation. New bone formation in axSpA coexists with the process of bone resorption. Therefore one can objectify appearance of syndesmophytes and bone erosions in the vertebra's bodies or erosions and partial ankylosis in the sacroiliac joint in the same patient. The ossification of the spine could have a severe impact on the quality of life of the patients, since it translates into a restriction of the spinal mobility (Landewe et al., 2009, Poddubnyy et al., 2018). Recent data suggested that structural damage in the sacroiliac joints might have also an impact on mobility and functional relevance in patients with axSpA independently of the structural damage in the spine (Protopopov et al., 2017).

Progression of structural damage in the spine in patients with axSpA has been long and detailed investigated for years. There is a clear relationship between structural damage and functional impairment (Landewe et al., 2009, Poddubnyy et al., 2018, Machado et al., 2010). To quantify the radiographic progression of the spine, studies usually use the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)(Creemers et al., 2005). It has been just recently that the scientific community has gained interest in the investigation of the progression of structural damage in the sacroiliac joints. The development of the concept "nr-/r-axSpA", together with the improvement of the early diagnosis of axSpA, has increased the interest in the natural course of the disease also at the early stages. Until the date, there is no specific scoring system to quantify the structural damage of the sacroiliac joints. The studies that addressed this subject used the scoring system from the mNY criteria.

One of the main difficulties related to evaluating the structural damage in the sacroiliac joints on plain radiographs is the wide intra- and inter-reader variability, and variations remain large without improvement even when readers have received targeted training (van Tubergen et al., 2003). Reading radiographs of the sacroiliac joints can be challenging due to the anatomical complexity of the sacroiliac joints, their oblique orientation in the pelvis, and the often interference of the bowel, leading to a poor visualization on plain radiographs. It seems particularly challenging to score early lesions in the sacroiliac joints, specifically grades 1 or 2 according to the mNY criteria (van Tubergen et al., 2003). This has an important implication for the radiographic progression assessment when it comes to the dichotomical question of nr-axSpA versus r-axSpA, according to the mNY criteria. Therefore, it would be reasonable to believe that in the future plain radiograph becomes obsolete, and newer imaging techniques such as computed tomography (CT) and MRI gain more relevance for detecting structural damage in the sacroiliac joints and spine improving the reliability intra- and inter-reader (Diekhoff et al., 2017).

Since the 80's observational studies have been trying to quantify the progression rates to radiographic sacroiliiitis. Most of the available studies showed rates between 10 to 40% over a time period of 2 to 10 years. A Brazilian cohort reported that 10% of the patients included in their study progressed from undifferentiated SpA to AS over 2 years, and 24.3% of the patients progressed to AS over a time period of 5 to 10 years (Sampaio-Barros et al., 2001, Sampaio-Barros et al., 2010). In the German Spondyloarthropathy Inception Cohort (GESPIC), radiographic progression from nr-axSpA (n=95) to AS was observed in about 12% of the patients after 2 years. The strongest predictor of progression for radiographic sacroiliitis was elevated CRP level with odds ratio = 3.65, $p<0.05$; indicating the importance of objective signs of inflammatory activity (Poddubnyy et al., 2011). The Devenir des Spondyloarthropaties Indifférenciées Récentes (DESIR) cohort is a longitudinal observational study of patients presenting with recent-onset inflammatory back pain suggestive of axSpA. A total 708 patients have been recruited in France, 449 had radiographs at baseline and on the follow-up visits. From those, 326 patients were classified as nr-axSpA. The progression rate to r-axSpA was 4-9% and 5.8% after 2 and 5 years of follow-up, respectively. As "net" progression, the rates were 2.0% and 5.1% after 2 and 5 years of follow-up, considering as "net" progression the difference between patients who

presented progression and regression over the total number of patients included (methodology described by DESIR cohort)(Dougados et al., 2016, Dougados et al., 2017). The ASAS cohort included 295 patients with axSpA showing a progression rate of 18% after 5 years of follow-up, with a “net” progression of 5% (Sepriano et al., 2016). A more detailed analysis of this cohort is currently in progress.

According to the Assessment of ASAS and European League Against Rheumatism (EULAR) recommendations, the first-line therapy for patients with axSpA are NSAIDs including selective cyclo-oxygenase-2 (COX-2) antagonists parallel to education and continuous exercise and/or physiotherapy (van der Heijde et al., 2017). For those patients who have an unsatisfactory response, contraindication or intolerance to NSAIDs, the recommended effective treatment currently available is biological therapy with tumor necrosis factor (TNF)-alpha inhibitors or monoclonal antibody anti-interleukin-17 (van der Heijde et al., 2017).

One could ask if radiographic progression could be stopped, retarded or even regressed. This question has been and is a main focus for the research groups focused on the SpA field. For years the interest was on how or if treatment could be a disease-modifier, retarding/stopping the structural damage in the spine. Concerning radiographic progression in the spine, there is contradictory evidence on the effect of NSAIDs if taken continuously (Wanders et al., 2005, Sieper et al., 2015). Celecoxib (a COX-2 inhibitor) given continuously seemed to have an inhibitory effect on radiographic progression of the spine compared to on-demand NSAIDs, specifically in those patients with elevated CRP levels (Wanders et al., 2005). However, these results could not be verified by the ENRADAS study, where diclofenac was used (Sieper et al., 2015). Whether non-selective NSAIDs, like ENRADAS study used, such as diclofenac, or COX-2 inhibitors, such as celecoxib, have different effects on new bone formation remains still unclear. The data on the effect of TNF inhibitors on radiographic spinal progression showed at first no clear evidence of such an effect (van der Heijde et al., 2008a, van der Heijde et al., 2009). However, recent studies have been published suggesting a positive effect by a longer duration or higher dose of the TNF inhibitor use on progression of the structural damage on the spine (Baraliakos et al., 2014). Results reported by GO-RAISE trial (golimumab) (Braun et al., 2014) and RAPID-axSpA phase III trial (certolizumab pegol) (van der Heijde et al., 2018)

confirmed low mSASSS progression over 4-year time period. Similar results have been shown in the MEASURE 1 study where patients with AS received secukinumab, a monoclonal antibody anti-interleukin-17 (Braun et al., 2017). In addition, it has been suggested the possible synergic effect of NSAIDs and TNF inhibitors, which is currently under investigation.

There is a lack of clinical trials regarding the effects of NSAIDs or biological treatment on the radiographic progression of the SI joints. The results of possible retardation on spinal radiographic progression by long duration treatment with biological drugs raise the question of whether it also has such an effect on the SI joint. So far there are very few studies evaluating the change in structural radiographic SI joint damage in patients receiving biological therapy.

This is the case of the Study Comparing Etanercept Against a Placebo for Etanercept on a Background Nonsteroidal Antiinflammatory Drug in the Treatment of Early Spondyloarthritis Patients Who Do Not Have X-ray Structural Changes (EMBARK trial), an analysis of the 2-year progression rate from nr-axSpA to r-axSpA in patients with axSpA treated with etanercept, showing almost no progression over 2 years: 4.9% switched from nr-axSpA to r-axSpA and the mean ± SD change in the total sacroiliac joint score (sacroiliitis sum score) was 0.1 ± 0.8. As possible predictors for progression they highlighted smoking status, HLA-B27 positivity and presence of inflammation on the MRI of the sacroiliac joints (Dougados et al., 2018).

The aim of our study was to investigate the long-term course, up to 6 years, of radiographic progression in the sacroiliac joints in patients with early active axSpA treated with etanercept (TNF inhibitor), and to explore possible predictor factors for such progression.

METHODS

Study Design and Patients Selection

Patients were selected from the Etanercept versus Sulfasalazine in Early Axial Spondyloarthritis (ESTHER) trial (Clinicatrials.gov Identifier: NCT00844142). The main objective of the ESTHER trial was to assess the efficacy of etanercept versus

sulfasalazine in patients with moderate to severe active early axSpA. The main outcome was the change of active inflammatory lesions in sacroiliac joints and spine as detected by MRI at 12 months. Early disease duration was defined as ongoing axial symptoms of less than 5 years; active disease was defined as BASDAI score of >=4, back pain score (BASDAI question 2) of >= 4 despite concurrent NSAID therapy, and active inflammatory lesions (osteitis) on MRI in either the sacroiliac joint or the spine.

A total of 76 patients were enrolled in the ESTHER study and randomized to receive treatment with etanercept 25mg subcutaneous twice weekly (n=40) or sulfasalazine 2000-3000mg per os daily (n=36) for 1 year. After the first year, all patients who were not in remission continued treatment with etanercept until the end of year 6. Those who were in remission discontinued the therapy and were followed up until the end of year 2. Remission was defined as reaching ASAS partial remission plus absence of active inflammation in the axial skeleton on MRI. If a patient experienced a disease flare during the year of follow up, etanercept was introduced and continued until the end of year 6. A disease flare was defined as a BASDAI increase of at least 2 points compared to the BASDAI at the end of year 1. Patients who did not flare were taken off the study at the end of year 2 according the study protocol, as they were considered in permanent drug-free remission. The detailed clinical and MRI outcome data have been already reported previously (Song et al., 2011, Song et al., 2012, Song et al., 2014a, Song et al., 2014b).

For the present work we selected patients from ESTHER study based on the availability of radiographs of the sacroiliac joints at baseline and at least at one follow-up time point. Radiographs were performed during the study at baseline and every 2 years thereafter.

The study was approved by the central ethics committee of the Landesamt für Gesundheit und Soziales – LaGeSo – Ethikkommission Berlin; approval number ZS EK 14 EA4/100/05. All patients included in the ESTHER study signed the written informed consent.

Radiographic assessment

Radiographs of the sacroiliac joints were obtained at up to 4 timepoints per patient: at baseline, year 2, year 4 and year 6. Two readers scored the sacroiliac joints from the radiographs (myself – VRR, and DP) for the current analysis. We were blinded for all clinical data as well as for the time points of the radiographs and scored independently the sacroiliac joints according to the grading system of the mNY criteria for AS (range from 0 to 4 per sacroiliac joint) (van der Linden et al., 1984):

- Grade 0 - normal
- Grade 1 - suspicious changes
- Grade 2 - minimal abnormality: small localized areas with erosion or sclerosis, without alteration in the joint width
- Grade 3 - unequivocal abnormality: moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis
- Grade 4 - severe abnormality: total ankylosis.

If both readers (VRR and DP) scored grade 2 bilaterally or at least grade 3 unilaterally on the sacroiliac radiographs, that was recorded as presence of definite radiographic sacroiliitis and patients were classified as having r-axSpA. Otherwise, patients were classified as having nr-axSpA.

MRI assessment

Whole-body MRIs with STIR and T1 sequencing images were obtained at baseline, year 2, and year 4 in all patients, as it was described on the study protocol. From those MRIs, we obtained the MRI imaging of the sacroiliac joints. Two trained and calibrated radiologists, blinded for all clinical data and MRI time points, scored the images according to the Berlin MRI scoring system with some small modifications concerning the fatty deposition sub-score (Song et al., 2016). On this scoring system, osteitis and fatty lesions were evaluated per sacroiliac joint per quadrant; the scoring ranged from 0 (no lesion) to 3 (at least 66% of the quadrant area) with a total scoring from 0 to 24 per type of lesion. Erosions, subchondral sclerosis and ankylosis were scored per sacroiliac joint: erosions on a scale from 0 to 3, subchondral sclerosis on a scale from 0 to 1 and ankylosis on a scale from 0 to 2. I calculated the mean of the 2 readers' scores for this analysis.

Statistical analysis

For the descriptive analysis, we used the Mann-Whitney U test for statistical analysis of continuous variables, and Fisher's exact test for the categorical variables, taking in consideration that the variables might not have a normal distribution. To calculate the sacroiliitis sum score, we summed the grades for the right and left sacroiliac joints for each patient at each time point. The range of the sacroiliitis sum score was from 0 (no signs of radiographic sacroiliitis in either sacroiliac joint) to 8 (total ankylosis of both sacroiliac joints). We assessed the mean of sacroiliitis sum score of both readers for each patient at each time point for the analysis. To determine the variability of the scoring between readers, we used the intra-class correlation coefficients for the sacroiliitis sum score. Intra-class correlation coefficient describes how strongly units in the same group resemble each other; it reflects not only degree of correlation but also agreement between measurements. It can be used for quantitative measurements and the value ranges are from 0 to 1, with values closer to 1 representing stronger reliability. It is commonly interpreted as: values less than 0.50 are indicative of poor, 0.50-0.75 as moderate, 0.75-0.90 as good and greater than 0.90 as excellent reliability (Koo and Li, 2016).

Radiographic progression was defined by the following definitions:

1. Absolute change in the sacroiliitis sum score;
2. Progression of at least 1 grade in the absolute sacroiliitis sum score;
3. Progression of at least 1 grade in at least one SIJ in the opinion of both readers;
4. Progression from nr-axSpA to r-axSpA in the opinion of both readers.

"Regression" was considered when there was an improvement on the radiographic progression. "Net progression" refers to the difference between the observed progression and regression rates in the opinion of both readers. For the definitions 2, 3, and 4, corresponding rates of "regression" were calculated.

To identify possible factors associated with radiographic sacroiliitis progression over time, we chose to perform a longitudinal linear mixed model analysis. Indeed, using this model, we had the opportunity to analyze the whole available dataset over 6 years of observation increasing, therefore, statistical power and precision of the effect estimations. Longitudinal analysis is conducted when outcomes are measured

repeatedly over time on the same subject, highlighting the changes over time in the response, and the changes in the relationship of the response to the subjects' characteristics (Cheng et al., 2010). For that reason, this is the most appropriate way to analyze longitudinal data with repeated measures that allows a precise and valid estimation of the effects of different factors on the outcome of interest, in this case progression of radiographic sacroiliitis. Specifically, we defined the outcome variable as the change in the sacroiliitis sum score on a 2-year interval (up to 3 intervals per patient: baseline-year 2, year 2 – year 4, year 4 – year 6). This way of analysis was already developed some years ago in the analysis of radiographic progression in rheumatoid arthritis (van der Heijde et al., 2008b), and most recently in the analysis of radiographic spinal progression in axSpA (e.g., in the OASIS cohort) (Ramiro et al., 2014). In the univariable analysis we identified the predictor candidates to be tested then in the multivariable analysis, where effects were adjusted for probable confounders. Variables included in the analysis as possible predictors were: age, sex, HLA-B27 positivity, treatment with sulfasalazine in the first year of the study, duration of the treatment with etanercept, intake of NSAIDs, symptom duration, CRP levels, active and chronic inflammatory changes on MRI of the sacroiliac joints, and radiographic sacroiliitis sum score. For the multivariable analysis, we created two multivariable models in order to avoid the multicollinearity since both strongest predictors of progression (CRP and osteitis on MRI) reflected active inflammation and had to be analyzed, therefore, in separate models. Parameter estimates (ß) with corresponding 95% confidence intervals were calculated. To perform the statistical analysis, we used SPSS version 25 (IBM Corp., Armonk, NY, USA), and SAS version 9.4 (SAS Institute).

RESULTS

Partial results of the present study were published in: "*Rios Rodriguez V, Hermann KG, Weiß A, et al. Progression of Structural Damage in the Sacroiliac Joints in Patients With Early Axial Spondyloarthritis During Long-Term Anti-Tumor Necrosis Factor Treatment: Six-Year Results of Continuous Treatment With Etanercept. Arthritis Rheumatol 2019;71(5):722-28. doi: 10.1002/art.40786".*

Patient characteristics

From the 76 patients included in the ESTHER study, a total of 55 patients performed radiographs of the sacroiliac joints at baseline. From these 55 patients, 42 of them had at least 1 follow-up radiograph available to assess the radiographic progression of the sacroiliac joints. Radiographs were available for assessment of sacroiliitis progression in 42 patients between baseline and year 2, in 32 patients between year 2 and year 4, and in 27 patients between year 4 and year 6. The two readers scored a total of 156 radiographs of the sacroiliac joints.

Based on the radiographs of the SI joints at baseline, 15 patients (35.7%) were classified as having r-axSpA and 27 (64.3%) were classified as having nr-axSpA. The baseline characteristics of the patients included in this analysis were similar to those of the whole group of patients enrolled in the ESTHER study (Table 1 from Publication). Sixty-two percent were men; their mean±SD age was 34.1 years, 81% were HLA-B27 positive and all patients had high disease activity (mean±SD): CRP 11.2±15.4 mg/l, BASDAI 5.6±1.2 and ASDAS 3.3±0.8.

Agreement between readers

The agreement between both readers on the sacroiliitis sum score for all time points was a good to excellent: baseline (ICC 0.83; 95% CI: 0.71-0.90), year 2 (ICC 0.82; 95% CI: 0.67-0.90), year 4 (ICC 0.72; 95% CI: 0.45-0.86), and year 6 (ICC 0.76; 95% CI: 0.49-0.89).

Radiographic sacroiliitis progression

Most of patients had a low-level sacroiliitis sum score (low score of sacroiliitis according to the mNY criteria for grading radiographic damage in the sacroiliac joints) at baseline, reflecting the early stage of the disease in the patients included in the study. The distribution of the sacroiliitis sum score at baseline is illustrated in the Figure 1 of the publication. No patient had a complete ankylosis of both SI joints (sacroiliitis sum score of 8) at baseline. The radiographic progression regarding the absolute change in the sacroiliitis sum score was (mean±SD) 0.13 ± 0.73 from baseline to year 2, -0.27 ± 0.76 from year 2 to year 4, and -0.09 ± 0.68 from year 4 to year 6. Similar results were obtained when progression was analyzed only in those patients in whom x-rays for all time points were available (n = 27): change of the sacroiliitis sum score

of 0.20 ± 0.72 between baseline and year 2, -0.22 ± 0.8 between year 2 and year 4, and -0.09 ± 0.68 between year 4 and year 6. For progression from nr-axSpA to r-axSpA, 5 (18%) patients out of the 27 progressed to r-axSpA from baseline to year 2. For all 4 definitions of progression, the highest rate of progression was observed during the period between baseline and year 2 (Table 2 of publication).

Regarding the treatment that patients received during the first year of the study (etanercept versus sulfasalazine), the change in the sacroiliitis sum score was higher over the first 2 years in patients who received etanercept during this period of time (n=24) than in patients who were treated with sulfasalazine in the first year and then switched to etanercept in the second year (n=18) (0.31 ± 0.62 versus -0.11 ± 0.82; p= 0.04). In the following years, no impact of sulfasalazine treatment in the initial study phase on radiographic sacroiliitis progression was observed. Similar results were observed when the radiographic progression was defined by nr-/r-axSpA. From the 27 patients that were classified as nr-axSpA at baseline, 4 patients progressed to r-axSpA from the group receiving etanercept during the first 2 years, and 1 patient from the group who received sulfasalazine.

Predictors of radiographic sacroiliitis progression

A longitudinal mixed model analysis was performed in the entire group of patients with registered data on 2-year intervals from baseline until the end of year 6 to find possible factors related to a change in the total sacroiliitis sum score. In the univariable analysis, from all the included variables, elevated CRP levels (ß = 0.45, 95%CI: 0.14 to 0.75) and the SI joint osteitis score on MRI (ß = 0.05, 95% CI: 0.02 to 0.08) were significantly associated with an increase of the sacroiliitis sum score in a 2-year interval (Table 3 of publication).

For the multivariable analysis, we developed 2 models, one included CRP levels and the other one osteitis on MRI, as both variables are parameters reflecting active inflammation that showed a significant association in the univariable analysis, and they are correlated. Both models were adjusted for age, sex, HLA-B27 positivity, symptom duration, treatment duration with etanercept, and the sacroiliitis sum score. The strength of the association for elevated CRP and SI joint osteitis score on MRI became

even stronger compared to univariable analysis with ß = 0.58 (95% CI: 0.25 to 0.90) and ß = 0.06 (95% CI: 0.03 to 0.10), respectively (Table 3 of publication).

RESULTING CLINICAL APPLICATIONS

The results of this study suggest that the treatment with a TNF inhibitor, in this case etanercept, for a long period of time (several years, and in our case up to 6 years), may influence the development and evolution of the disease by slowing down the radiographic progression observed in the sacroiliac joints of patients diagnosed with an early and active axSpA.

This is congruent with other studies that indicate that in order to reduce progression of structural damage in the spine, patients needed at least 4 years of treatment with TNF inhibitors. Therefore, one could assume that in general, in the spine as well as for the SI joints, radiographic progression seems to decelerate with long-term TNF inhibitor treatment. In addition, initiation of TNF inhibitors seems to be associated with a reduction of radiographic spinal progression especially within the first years of the disease. This latter observation could have similar results for radiographic progression of the SI joints, as nr-axSpA might be considered as an early stage into the SpA spectrum. This has an special relevance, if we consider that recent data suggested that structural damage in the SI joint might have an impact on functional status and spinal mobility in patients with axSpA, independent of the structural damage already present on the spine (Protopopov et al., 2017). Therefore, it might be crucial to make an early diagnosis of axSpA to detect rapidly those patients who have a high disease activity and start an anti-inflammatory treatment. One big impact that may derivate from this strategy is the great weight that these biological therapies could cause on the national health budgets. For that reason, the merge of biosimilars drugs is a big hope to provide a more cost-effective alternative treatment options for patients with axSpA.

It is logical to deduce if active inflammation and high disease activity are associated to radiographic progression, patients receiving TNF inhibitors, which are strong anti-inflammatory drugs, would lower their inflammation in their spine and sacroiliac joints, and consequently inhibit the radiographic damage. A study done by the Swiss Clinical Quality Management Cohort observed that the radiographic spinal progression was

significantly lower by those patients who were in remission under TNF inhibitor therapy (Molnar et al., 2018). The remission status was defined by the ASDAS status of inactive disease. The cut-off values for disease activity states are < 1.3, >= 1.3 to < 2.1, >= 2.1 to < 3.5, and >= 3.5 for inactive disease, moderate, high and very high disease activity, respectively. This parameter combines patient-reported outcome questions and CRP. The results of the Swiss cohort are strongly relevant for the treat-to-target strategy, declaring remission as the main treatment target in axSpA. Treat-to target is the design of a specific target-driven therapeutic approach, which would have a superior efficacy to the standard clinical care for a specific disease. That was first developed for chronic diseases such as diabetes and then rheumatoid arthritis (Smolen et al., 2017). A prospective study with a treat-to-target approach for axSpA proving the association between structural outcomes of an anti-inflammatory therapy remains still undone.

The data from our study, together with the latest studies published in regards to associated factors for radiographic progression, provide meaningful information for clinicians who in their daily regular practice would like to determine the risk of radiographic progression in a single patient, using simple baseline parameters such as already presence of radiographic structural damage, elevated CRP levels and presence of osteitis in the MRI of the SI joints. Identification of patients that are at high risk to develop progression of structural damage in the axial skeleton including the sacroiliac joints, together with the identification of treatment approaches able to prevent such a progression would mean to find real disease-modification strategies in axSpA.

DETAILED OVERVIEW OF THE AUTHOR'S OWN ACHIEVEMENTS

My doctoral project took place after the data collection of the patients enrolled in the ESTHER trial. I discussed and elaborated the idea of the doctoral project mentored by Prof. Poddubnyy. Then I selected the patients included in my project, based on the availability of conventional pelvic radiographs at baseline and at least one follow-up time point with visible sacroiliac joints.

With the aim of scoring the radiographic images of my project, Prof. Poddubnyy trained me for several months before we performed the scoring by discussing radiological cases together. Parallel to those meetings, I attended the regularly twice a month clinical/radiographic sessions in our Rheumatology department co-organized by Prof. Hermann (senior radiologist consultant with sub-specialization in musculoskeletal radiology); and I attended the ASAS course for axSpA as well as several workshops focused on axSpA imaging.

I anonymized and randomized the images; then Prof. Poddubnyy and I scored the radiographs independently and blinded for all clinical data and time points. After that I un-blinded the images, added the scorings to the clinical database and prepared it for the analysis. I performed all the statistical analysis and evaluated the results together with Prof. Poddubnyy.

At first, I presented my early analysis as a poster in the European Rheumatology Congress (EULAR) and the American Congress of Rheumatology (ACR) in 2016. After a deeper analysis of the data, I presented my further results as an oral communication in the EULAR congress in 2018. The manuscript was accepted for publication and published in May 2019.

During the analysis of the agreement between the two readers (me and PD) who scored the images for the SI joints, further questions in relationship to the SI joint scoring came to my mind. Most of the images that we scored were basically conventional pelvic radiographs, but some were antero-posterior lumbar radiographs with visible SI joints. It was not until the period that I was writing the manuscript, that I could construct a clear new idea about my questions regarding radiographs and SI joint scoring. Soon after I elaborated a hypothesis and new project, which I could perform also under the support of Prof. Poddubnyy and the results are currently under revision of a specialized rheumatology journal.

In relationship with SI joint radiograph scoring I am currently involved in the development and validation of an artificial intelligence-based network for the detection of definite radiographic sacroiliitis.

Parallel to those projects I am participating in the patient's recruitment and data collection of a prospective cohort of patients suffering from AS with criteria to start a bDMARD therapy to evaluate the changes in body composition after 6-12 months of treatment as well as the impact of the body composition on the response to the therapy. I am very involved in another project of a prospective cohort with patients affected with Crohn's disease to identify factors associated with the presence of SpA. I am currently analyzing from both projects the baseline microbiota characteristics for the identification of a possible phenotype pattern. At the same time, I am analyzing the food intake characteristics of those patients for further research into their microbiota and as possible parallel complement therapy.

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Statutory Declaration

"I, Valeria Rios Rodriguez, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic "Progression of structural damage in the sacroiliac joints in patietns with early axial spondyloarthritis during long-term anti-tumor necrosis factor treatment [Progression der Strukturschäden in den Iliosakralgelenke bei Patienten mit früher axialer Spondyloarthritis bei langfristiger Anti-Tumornekrosefaktor-Therapie]", independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date 06. MAY 2020 Signature

Declaration of your own contribution to the publications

Valeria Rios Rodriguez contributed the following to the below listed publications:

Publication 1: Valeria Rios Rodriguez, Kay-Geert Hermann, Anja Weiß, Joachim Listing, Hildrun Haibel, Christian Althoff, Fabian Proft, Olaf Behmer, Joachim Sieper, and Denis Poddubnyy. Progression of Structural Damage in the Sacroiliac Joints in Patients With Early Axial Spondyloarthritis During Long-Term Anti-Tumor Necrosis Factor Treatment: Six-Year Results of Continuous Treatment With Etanercept. Arthritis & Rheumatology, 2019
Contribution (please set out in detail): discussion and participation in the study conception and design. Selection of the patients included in the project, based on the availability of conventional pelvic radiographs at baseline and at least one follow-up time point with visible sacroiliac joints. Anonymization and randomization of the images; scoring the radiographs independently and blinded for all clinical data and time points. Adding the scoring results to the clinical database and preparation for the analysis. Data analysis and statistical evaluation using SPSS version 25 for the descriptive analysis, and SAS version 9.4 to perform a longitudinal mixed model analysis. Writing of the manuscript, creation of the 3 tables (Table 1, 2 and 3) and figure (Figure 1), and following revisions during the peer review process.

06.05.2020

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Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	Nature Reviews Rheumatology	7,761	18.545	0.021650
2	ANNALS OF THE RHEUMATIC DISEASES	44,754	14.299	0.082820
3	Arthritis & Rheumatology	10,169	9.002	0.046120
4	RHEUMATOLOGY	19,897	5.149	0.029990
5	SEMINARS IN ARTHRITIS AND RHEUMATISM	6,124	5.072	0.011650
6	Therapeutic Advances in Musculoskeletal Disease	817	5.045	0.002060
7	OSTEOARTHRITIS AND CARTILAGE	16,264	4.879	0.027140
8	ARTHRITIS CARE & RESEARCH	16,725	4.530	0.024540
9	ARTHRITIS RESEARCH & THERAPY	16,287	4.148	0.028820
10	CURRENT OPINION IN RHEUMATOLOGY	4,866	3.851	0.008140
11	Current Rheumatology Reports	2,855	3.645	0.005610
12	JOURNAL OF RHEUMATOLOGY	23,342	3.634	0.022670
13	RHEUMATIC DISEASE CLINICS OF NORTH AMERICA	2,234	3.527	0.003600
14	JOINT BONE SPINE	3,601	3.278	0.005480
15	CLINICAL AND EXPERIMENTAL RHEUMATOLOGY	8,671	3.238	0.012830
16	BEST PRACTICE & RESEARCH IN CLINICAL RHEUMATOLOGY	3,614	3.016	0.005500
17	LUPUS	7,708	2.924	0.009100
18	SCANDINAVIAN JOURNAL OF RHEUMATOLOGY	3,238	2.706	0.003880
19	Pediatric Rheumatology	1,290	2.673	0.003320
20	CLINICAL RHEUMATOLOGY	8,011	2.293	0.014140

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	RHEUMATOLOGY INTERNATIONAL	6,529	2.200	0.009990
22	BMC MUSCULOSKELETAL DISORDERS	9,916	2.002	0.021440
23	Modern Rheumatology	3,046	1.973	0.005600
24	International Journal of Rheumatic Diseases	2,276	1.938	0.005410
25	JCR-JOURNAL OF CLINICAL RHEUMATOLOGY	1,674	1.897	0.002470
26	Revista Brasileira De Reumatologia	946	1.163	0.001490
27	ZEITSCHRIFT FUR RHEUMATOLOGIE	842	0.901	0.000970
28	Acta Reumatologica Portuguesa	432	0.776	0.000630
29	AKTUELLE RHEUMATOLOGIE	62	0.289	0.000030
30	Archives of Rheumatology	81	0.274	0.000160
31	Advances in Rheumatology	0	Not Available	0.000000

Selected JCR Year: 2018; Selected Categories: “RHEUMATOLOGY”

PUBLICATION

The publication of the original article does not appear in the electronic version of my Dr. Arbeit for reasons of data protections.

Rios Rodriguez V, Hermann KG, Weiß A, et al. Progression of Structural Damage in the Sacroiliac Joints in Patients With Early Axial Spondyloarthritis During Long-Term Anti-Tumor Necrosis Factor Treatment: Six-Year Results of Continuous Treatment With Etanercept. Arthritis Rheumatol 2019;71(5):722-28. doi: 10.1002/art.40786".

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CURRICULUM VITAE: Valeria Ríos Rodríguez

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

LIST OF PUBLICATIONS

1. Proft F, Muche B, Spiller L, **Rodriguez VR**, Rademacher J, Weber AK, Lüders S, Protopopov M, Redeker I, Spiller I, Sieper J, Poddubnyy D. Performance of the Ankylosing Spondylitis Disease Activity Score based on a quick quantitative C-reactive protein assy in patients with axial spondyloarthritis. Joint Bone Spine. 2019 Jul 29. pii: S1297-319X(19)30113-7. doi: 10.1016/j.jbspin.2019.07.007. [Epub ahead of print] PMID:31369867

2. Llop M, **Rios Rodriguez V**, Redeker I, Sieper J, Haibel H, Rudwaleit M, Poddubnyy D. Incorporation of the anteroposterior lumbar radiographs in the modified Stoke Ankylosing Spondlitis Spine Score improves detection of radiographic spinal progression in axial spondyloarthritis. Arthritis Res Ther. 2019 May 24;21(1):126. doi: 10.1186/s13075-019-1913-z. PMID:31126334

3. **Rios Rodriguez V**, Hermann KG, Weiß A, Listing J, Haibel H, Althoff C, Proft F, Behmer O, Sieper J, Poddubnyy D. Progression of Structural Damage in the Sacroiliac Joints in Patients With Early Axial Spondyloarthritis During Long-Term Anti-Tumor Necrosis Facotr Treatment: Six-Year Results of Continuous Treatment With Etanercept. Arthritis Rheumatol. 2019 May;71(5):722-728. doi: 10.1002/art.40786. Epub 2019 Mar 7. PMID: 30625261

4. **Rios Rodriguez V**, Llop M, Poddubnyy D. Hematopoietic and mesenchymal stem cells: a promising new therapy for spondyloarthritis? Immunotherapy. 2017 Sep;9(11):899-911. doi: 10.2217/imt-2017-0034.

5. **Rios Rodriguez V**, Poddubnyy D. Tumor necrosis factor-α (TNFα) inhibitors in the treatment of nonradiographic axial spondyloarthritis: current evidence and place in therapy. Ther Adv Musculoskelet Dis. 2017; 9(8):197-210.

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8. **Rios Rodriguez V**, Poddubnyy D. Etanercept for the treatment of non-radiographic axial spondyloarthritis. Expert Rev Clin Immunol. 2016; 12(5):493-500.

9. **Rios Rodriguez V,** Poddubnyy D.Old and new treatment targets in axial spondyloarthritis. RMD Open. 2016; 1(Suppl 1):e000054.

10. Almodóvar R1, **Ríos V**, Ocaña S, Gobbo M, Casas ML, Zarco-Montejo P, Juanola X. Association of biomarkers of inflammation, cartilage and bone turnover with gender, disease activity, radiological damage and sacroiliitis by magnetic resonance imaging in patients with early spondyloarthritis. Clin Rheumatol. 2014 Feb;33(2):237-41. doi: 10.1007/s10067-013-2349-5. Epub 2013 Aug 7.

11. J Narváez, **V Ríos-Rodríguez**, D de la Fuente, P Santo, JM Nolla. Rituximab therapy in refractory neuropsychiatric lupus: current clinical evidence. Semin Arthritis Rheum 41 (3):364-72 (2011)

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