Effect of Gut Involvement in Patients with High Probability of Early Spondyloarthritis: Data from the DESIR Cohort

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ABSTRACT. ***Objective.*** Inflammatory bowel disease (IBD) is a well-known extraarticular feature of spondyloarthritis (SpA). The aims of this study were to evaluate factors associated with IBD and incidence over 5 years of followup in the DESIR cohort.

Methods. DESIR is a prospective observational cohort of patients with recent-onset inflammatory back pain suggestive of axial SpA. All available variables in the database were compared between patients with and without IBD at baseline and 5 years, and occurrence over 5 years of followup, with uni- and then multivariable analysis.

Results. At baseline, of 708 patients, 35 had IBD (prevalence 4.94%, CI 95% 3.3–6.5). IBD was associated (multivariable) with history of uveitis, levels of Dickkopf-1, and tumor necrosis factor, but not with phenotypic presentation (peripheral arthritis, enthesitis, dactylitis, uveitis) or baseline serum levels of other cytokines. At 5 years, 480 patients were analyzed, 58 with IBD. IBD was associated (multivariable) with fulfillment of modified New York criteria, sick leave, Bath Ankylosing Spondylitis Disease Activity Index, and smoking. There was no association with magnetic resonance imaging scores, enthesitis, psoriasis, and bone mineral density. Twenty-three incident cases of IBD were recorded: estimated occurrence rate of 0.95/100 (95% CI 0.57–1.35) patient-years (PY). Incidence of IBD is associated (multivariable) with HLA-B27 (OR 0.36, 95% CI 0.22–0.59), fulfillment of modified New York criteria (OR 3.35, 95% CI 1.85–6.08), and familial history of IBD (OR 3.31, 95% CI 1.62–6.77).

Conclusion. In early SpA, IBD occurs with an incidence of 1/100 PY, and is associated with poor outcome, familial history of IBD, absence of HLA-B27, and fulfillment of modified New York criteria.

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Interrelations between gut inflammation and spondyloarthritis (SpA) are recognized from progress in recent years and are represented by the coexistence of inflammatory bowel diseases (IBD) with SpA, findings of subclinical microscopic gut inflammation in both bowel and rheumatologic conditions in an important proportion of patients with SpA, and also implication of infectious agents and interleukin 23 (IL-23)/Th17 pathway[1,2,3].

A previous study demonstrated that bowel involvement was associated with disease activity assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; OR 2.05, 95% CI 1.06–3.95), with a similar prevalence of

microscopic gut inflammation between ankylosing spondylitis (AS) and nonradiographic axial SpA (axSpA)[4], and with a relationship between gut inflammation and degree of magnetic resonance imaging (MRI) bone marrow edema in the sacroiliac (SI) joints[5]. Calprotectin, a biomarker of gut inflammation, was found to be more elevated in patients with axSpA from the GESPIC cohort with radiographic progression, compared to patients without radiographic progression over 2 years[6]. The IL-23/Th17 axis is involved in the current pathophysiological hypothesis of the disease[7]; gut is an important source of IL-23[8,9], with evidence of recirculation of gut-derived IL-23R+ cells to blood, bone marrow, and joint[10]. The implication of infectious agents and gut microbiota in SpA represents another link between SpA and the gut[11].

Altogether, these data argue for a close relationship between gut inflammation and occurrence and severity of SpA. However, data concerning early phases of SpA are scarce. In the DESIR cohort, IBD history (defined as Crohn disease or ulcerative colitis, with medical confirmation) was present at baseline in 5% of the patients included[12].

The aims of our study were to evaluate (1) the factors associated with the presence of IBD at baseline, (2) the factors associated with the presence after 5 years of followup, and (3) the occurrence of new cases of IBD over a 5-year period and baseline factors associated with this occurrence.

MATERIALS AND METHODS

Patients. The DESIR cohort is a prospective, multicenter French cohort of patients (18–50 yrs) with early inflammatory back pain of > 3 months and < 3 years of duration, with symptoms suggestive of SpA according to the local investigator's assessment (score ≥ 5 on a 0–10 numerical rating scale in which 0 = not suggestive and 10 = very suggestive of SpA). The plan is to follow them up to 10 years. This cohort included 708 patients and recorded this data: epidemiologic (age, sex), clinical (all items for evaluation of classification criteria and disease assessment), biological [erythrocyte sedimentation rate, C-reactive protein (CRP), creatinine, cholesterol, hematology, and at baseline the levels of vitamin D, tumor necrosis factor (TNF)-α, IL-6, IL-17, IL-23, Dickkopf-1 (DKK-1), sclerostin], imaging by radiographs of the spine [modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)] and SI joints (New York staging) and by spine and SI MRI [Berlin and Spondyloarthritis Research Consortium of Canada (SPARCC) scores] using the centralized reading results. In addition, treatment and socioeconomic data were recorded. Details of the organization of the cohort, as well as the protocol and case report form (CRF), are available on the Website (www.lacohortedesir.fr). The main characteristics of the cohort and the patients at baseline have been reported previously[12]. Briefly, at baseline, 92% of the patients fulfill at least 1 classification criterion system: 26% modified New York (mNY), 79% Amor, 78% European Spondylarthropathy Study Group, and 70% Assessment of Spondyloarthritis international Society. HLA-B27 is present in 58% of the cases, with 46% male, and mean age at inclusion is 34 years. Axial involvement is present in all the cases, arthritis in 37%, enthesitis in 49%, and dactylitis in 13% of the patients. Thirty-six percent of the patients are smokers. Skin psoriasis is recorded in 16% and uveitis in 8.5% of the cases. High disease activity is present in 63%. Followup was scheduled with visits every 6 months for the first 2 years, and then annually; radiographs were performed again after 2 and 5 years.

Methods. History of or current IBD was collected in the CRF (Crohn disease or ulcerative colitis with medical confirmation) at each visit.

According to the aims of the study, 3 analyses were performed: (1) presence or history of IBD at baseline, and baseline factors associated with IBD; (2) presence or history of IBD at 5 years (60 mos; M60) and factors at the 5-year visit associated with IBD, in the population with complete followup over 5 years; (3) incident cases over 5 years and baseline factors associated with incidence of new IBD between baseline and 5 years, in the population with complete followup over 5 years.

The analysis of factors associated with IBD was done by comparison of IBD+ patients versus IBD– patients, using OR ± 95% CI and Fisher's tests for categorical variables, and unpaired t tests/Mann-Whitney for continuous variables, in uni- and then multivariable analysis (logistic regression). Potential interaction and confounding factors were assessed using Mantel-Haenszel and interaction chi-square tests. In multivariable analysis, using a logistic regression method, covariates significantly associated with IBD in the univariable analysis ($p < 0.3$) were included. The most likely multivariable model was then selected using likelihood ratio tests.

The statistical analyses were performed using R software on the database locked on June 20, 2016. Significance was $p < 0.05$.

Ethics. The study was approved by the Comité de protection des personnes Ile de France III (number 2457); European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2007-A00608-45; clinicaltrials.gov (NCTO1648907).

RESULTS

At baseline, 35 patients out of 708 had current or personal history of IBD, providing an estimated prevalence of 4.94% (95% CI 3.3–6.5%).

In the univariable analysis, factors associated with IBD are summarized in Table 1. There was no association between IBD and age, sex, disease duration, body mass index, smoking, dactylitis, enthesitis, chest wall involvement, BASDAI, Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index (BASFI), Health Assessment Questionnaire (HAQ), Medical Outcomes Study Short Form-36 (SF-36), Ankylosing Spondylitis Quality of Life score (ASQoL), levels of CRP, cholesterol, sclerostin, periostin, vitamin D, IL-6, IL-17, IL-23, imaging scores (spine and SI MRI inflammatory or structural, mSASSS), bone mineral density (BMD), or body composition results.

In the multivariable analysis, significant associations ($p < 0.05$) for IBD were found with history of uveitis (OR 3.62, 95% CI 1.95–6.74), DKK-1 levels (OR per unit 1.03, 95% CI 1.02–1.05), TNF serum levels (OR per unit 1.17, 95% CI 1.08–1.26).

At the 5-year (M60) endpoint, 58 cases of patients with IBD are recorded out of 480 with complete followup, indicating an estimated prevalence of 12.08% (95% CI 9.17–14.99).

In univariable analysis, past history or current IBD at M60 was associated with anti-TNF use, disease-modifying antirheumatic drug (DMARD) use, nonsteroidal antiinflammatory drug (NSAID) Score, ASDAS CRP, BASFI, SF-36 physical, SF-36 mental, HAQ, sick leave, and number of tender joints (Table 2).

In multivariable analysis, IBD was associated with the following: sick leave (OR 1.01, 95% CI 1.005–1.014; p = 0.04); mNYcriteria (OR 4.85, 95% CI 2.23–10.57;

Table 1. Factors associated with inflammatory bowel disease (IBD) at baseline (univariable analysis).

Variables	IBD+ vs IBD–, Prevalent M0 OR (95% CI) or mean (SD)	p
HLA-B27	0.47 (0.21–0.98)	0.03
mNY criteria at M0	2.28 (0.94–5.12)	0.05
Uveitis history	3.80 (1.49–8.90)	0.003
Familial history of IBD	3.97 (1.11–11.57)	0.02
Psoriasis	0.09 (0.02–0.24)	< 0.0001
DMARD use	3.74 (1.63–8.19)	< 0.001
Steroid use	4.21 (1.83–9.25)	< 0.001
NSAID score at 6 mos	30.2 (36.0) vs 45.5 (40.5)	0.005
Sick leave, days	33.9 (49.3) vs 32.7 (69.1)	0.09
ESR, mm/h	22.6 (26.7) vs 13.3 (14.5)	0.04
Hemoglobin, g/dl	15.7 (19.0) vs 16.0 (18.0)	0.02

M0: Month 0; mNY: modified New York criteria; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug; ESR: erythrocyte sedimentation rate.

Table 2. Factors associated with inflammatory bowel disease (IBD) at the 5-year visit (M60; univariable analysis).

Variables	IBD+ vs IBD–, Prevalent M60 OR (95% CI) or mean (SD)	p
DMARD use	2.58 (1.35–5.08)	0.002
NSAID score at 6 months	17.00 (31.20) vs 19.87 (30.37)	0.03
Sick leave, days	20.80 (59.16) vs 11.35 (39.19)	0.03
Anti-TNF use (yes/no)	2.11 (1.06–4.31)	0.02
ASDAS CRP	2.28 (0.85) vs 2.02 (0.83)	0.03
BASFI	29.04 (20.14) vs 22.08 (21.18)	0.02
SF-36 physical	39.26 (9.91) vs 43.59 (9.60)	0.004
SF-36 mental	41.2 (11.62) vs 45.2 (11.06)	0.013
HAQ	0.75 (0.58) vs 0.50 (0.51)	0.004
ASQoL	8.72 (5.65) vs 6.59 (5.37)	0.012
No. tender joints	5.84 (9.77) vs 2.37 (5.80)	0.009

M60: Month 60; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug; anti-TNF: anti-tumor necrosis factor; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; BASFI: Bath Ankylosing Spondylitis Functional Index; SF-36: Medical Outcomes Study Short Form-36 questionnaire; HAQ: Health Assessment Questionnaire; ASQoL: Ankylosing Spondylitis Quality of Life score.

p = 0.04); BASDAI (OR per unit 1.10, 95% CI 1.05–1.16; p = 0.04); and smoking (yes/no; OR 2.79, 95% CI 1.53–5.07; p = 0.04; data not shown).

Incidence. Twenty-three new cases of incident IBD were recorded from baseline to M60 in the 480 patients followed over 5 years, leading to an estimated incidence of 0.95/100 patient-years (PY; 95% CI 0.57–1.35). Incidence seems stable over time: six cases in the period M0–M12, six cases in the period M12–M24, five cases in the period M24–M36, and six cases in the period M36–M60.

In univariable analysis, IBD was associated with history of psoriasis, SF-36 physical component, familial history of IBD, fulfillment of mNY criteria, and lower lumbar and femoral BMD T scores at baseline (Table 3).

In multivariable analysis, incident IBD was significantly (p = 0.04) associated with HLA-B27 (OR 0.36, 95% CI 0.22–0.59), fulfillment of mNY criteria at M0 (OR 3.35, 95% CI 1.85–6.08), and familial history of IBD (OR 3.31, 95% CI 1.62–6.77; data not shown).

DISCUSSION

In this study using a prospective cohort of patients with high probability of early axSpA (at baseline, 92% of the patients fulfilled at least 1 set of classification criteria)[12], we found a prevalence of IBD of 5% at baseline and of 12% after 60 months of followup, demonstrating an increase in disease duration. These rates are in line with previous (cross-sectional) studies[13,14]. We may estimate from this analysis an IBD incidence of 0.95/100 PY in the DESIR cohort, roughly 10 times more than in the general population in Europe and France[15,16]. On the other hand, in the case of IBD, the probability of occurrence of SpA was assessed in a metaanalysis of 71 studies: SpA occurs in up to 13% of patients with IBD. Pooled prevalences were calculated for sacroiliitis (10%; 95% CI 8–12%), AS (3%; 95% CI 2–4%), and arthritis (13%; 95% CI 12–15%)[17].

Presence of IBD was associated with worse outcome of the rheumatologic condition in DESIR cohort, with higher disease activity (assessed by BASDAI and ASDAS) but also impaired function and quality of life (ASQoL, HAQ, SF-36), and more sick leave, as mentioned in the OASIS cohort[14,18].

IBD was not associated with spine imaging scores (mSASSS, Berlin MRI spine score) or SI MRI scores (SPARCC) for inflammatory changes. This is not in accordance with the results of van Praet, *et al*[5], but in their study they evaluated the degree of microscopic gut inflammation in correlation with the SI score. Nevertheless, IBD is independently associated with fulfillment of mNY criteria (i.e., presence of significant structural damage of SI joints). At the opposite end, in the Brazilian Registry of Spondyloarthritis, there was a significantly lower prevalence of radiographic sacroiliitis and lower radiographic score (assessed by Bath Ankylosing Spondylitis

Table 3. Baseline factors associated with incidence of new cases of inflammatory bowel disease (IBD) between baseline and 5 years (univariable analysis).

Variables	IBD+ vs IBD– OR (95% CI) or mean (SD)	p
mNY criteria at M0	2.58 (0.88–6.81)	0.006
Familial history of IBD	3.97 (0.92–13.02)	0.032
Psoriasis	0 (0–0.73)	0.013
SF-36 physical	36.75 (8.75) vs 40.34 (9.04)	0.047

mNY: modified New York criteria; M0: Month 0; SF-36: Medical Outcomes Study Short Form-36 questionnaire.

Radiological Index) in enteropathic arthritis compared to other types of SpA[19].

As expected, IBD occurrence is associated with familial history of IBD, but no particular phenotype of SpA could be individualized in association with IBD (axial, peripheral, enthesitis, dactylitis) even if the association with mNY criteria suggests that IBD occurs more often in AS than in nonradiographic axSpA. A previous metaanalysis concluded that pooled prevalence of IBD was similar in AS and nonradiographic axSpA[20]. In the Brazilian cohort, enteropathic arthritis was associated with lower incidence of enthesitis[19]. An association was found in our cohort with uveitis in multivariable analysis at baseline, and lesser association with psoriasis in univariable analysis at baseline and for incident cases. In a case control study, Cantini, *et al*[21] found that dactylitis, enthesitis, and anterior uveitis were less frequent in IBD SpA than in other types of SpA.

One particular finding was the low association with HLA-B27 in the case of IBD, suggesting the implication of other genetic factors in the case of SpA with IBD. This low prevalence of HLA-B27 was also found in another study[18] and was previously reported[22].

Some other biologic markers were assessed. Even if a single cytokine serum level may be difficult to interpret, TNF levels at baseline were higher in patients with IBD at baseline; this may argue for a more important inflammatory potential in these patients. Elevated DKK-1 levels at baseline were associated with IBD presence at baseline. DKK-1 involvement has been described in gut inflammation and mucosal repair[23].

Regarding treatments, patients with associated IBD had lower NSAID scores and more frequent use of glucocorticoids, conventional synthetic DMARD at baseline[19], and anti-TNF agents at 5 years. A lower rate of NSAID use seems logical in the case of IBD history, as well as more frequent use of glucocorticoids and DMARD, such as sulfasalazine.

Some factors at baseline were associated with occurrence of IBD during the 60-month followup (and may be discussed as predictive factors): absence of psoriasis, absence of HLA-B27, familial history of IBD, impaired SF-36, and fulfillment of mNY criteria.

Our study has some strengths and limitations. The strengths are the initial number of patients included in the cohort (> 700), and the prospective followup over 5 years, with many clinical, biological, and imaging evaluations. One limitation is the absence of systematic gut investigation, avoiding recognition of asymptomatic gut inflammation. The other limitations are the number of patients lost to followup on one hand, and the low number of events that may induce a lack of power in statistical analysis, on the other hand. However, the analyses were conducted on patients with complete followup, reducing the bias of missing data.

Finally, in patients with potentially early SpA followed for 5 years, IBD is frequent, with an estimated annual incidence of 0.95/100 PY. IBD is associated with worse outcome, familial history of IBD, absence of HLA-B27, and fulfillment of mNY criteria.

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