Impact of gut involvement in patients with high probability of early spondyloarthritis. Data from DESIR cohort.

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Word count ~~1780~~

Key words : spondyloarthritis, inflammatory bowel disease,

Running title : IBD in early SpA

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Abstract : (word count 250)

Inflammatory bowel disease (IBD) is a well-known extra articular feature of spondyloarthritis (SpA). The aims of this study were to evaluate in DESIR cohort factors associated with IBD and incidence over 5 years follow-up.

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 follow-up, with uni and then multivariable analysis.

Results

At baseline, 708 patients, 35 had IBD : prevalence 4.94% [CI 95% : 3.3 – 6.5]. IBD was associated (multivariable) with history of uveitis, levels of DKK-1 and TNF, 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, BASDAI, and smoking. No association with MRI scores, enthesitis, psoriasis, BMD. 23 incident cases of IBD were recorded: estimated occurrence rate of 0.95/100 [0.57 – 1.35] patient-years. Incidence of IBD is associated (multivariable) with : HLA B27 : OR 0.36 [0.22 – 0.59], fulfillment of modified New York criteria: OR 3.35 [1.85 – 6.08], familial history of IBD : OR 3.31 [1.62 – 6.77] .

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

1.Introduction.

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

A recent study demonstrated that bowel involvement was associated with disease activity assessed by BASDAI (OR : 2.05 95% CI :1.06-3.95), with a similar prevalence of microscopic gut inflammation between ankylosing spondylitis and non radiographic axial spondyloarthritis [4], and with a relationship between gut inflammation and degree of MRI bone marrow edema in the sacroiliac joints [5]. Calprotectin, a biomarker of gut inflammation was found to be more elevated in patients with axial SpA 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 spondyloarthritis represents another link between spondyloarthritis and the gut [11].

Altogether, these data argue for a close relation between gut inflammation and occurrence and severity of spondyloarthritis. But data concerning early phases of spondyloarthritis are scarce. In the DESIR cohort, IBD history (defined as Crohn's Disease or Ulcerative Colitis, with medical confirmation) was present at baseline in 5 % of the patients included [12].

The aims of this study were to evaluate i) the factors associated with the presence of IBD at baseline ii) the factors associated with the presence after 5 years of follow-up, iii) the occurrence of new cases of IBD over a five-year-period, and baseline factors associated with this occurrence.

2.Methods

2.1.Patients

The DESIR cohort is a prospective, multicenter French cohort of patients (18 – 50 years) with early inflammatory back pain (IBP) of more than 3 months and less than 3 years of duration, with

symptoms suggestive of SpA according to the local investigator's assessment (score ≥ 5 on a 0 to 10 numerical rating scale [NRS] in which 0=not suggestive and 10=very suggestive of SpA), planned to be followed up to 10 years. This cohort included 708 patients, recording epidemiologic (age, gender), clinical (all items for evaluation of classification criteria and disease assessment, biological (ESR, CRP, creatinin, cholesterol, haematology, and at baseline the levels of vitamin D, TNF alpha, IL-6, IL-17, IL-23, DKK-1, sclerostin), imaging by X-Rays of the spine (mSASSS score) and sacro iliac joints (New York staging) and by spine and sacro iliac MRI (Berlin and SPARCC scores), using the centralized reading results, treatment and socio economic data. Details of the organization of the cohort, as well as the protocol and case report form are available at 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 fulfil at least one classification criteria system; 26% mNew York, 79% Amor, 78% EESSG, 70% ASAS. HLA-B27 is present in 58% of the cases, with 46% male, and mean age at inclusion of 34 years. Axial involvement is present in all the cases, arthritis in 37%, enthesitis in 49%, dactylitis in 13% of the patients. 36% of the patients are smokers. Skin psoriasis is recorded in 16% and uveitis in 8.5% of the cases. 63% are In high disease activity. Follow-up was scheduled with visits every 6 months for the first two years, and then annually; X-rays were performed again after 2 and 5 years.

2.2.Methods.

Past or present history of IBD was collected in the CRF (Crohn's disease or ulcerative colitis with medical confirmation) at each visit.

According to the aims of the study, three analyses were performed : i) presence or history of IBD at baseline, and baseline factors associated with IBD, ii) presence or history of IBD at five years (60 months, M60) and factors at the five years visit associated with IBD, on the population with complete follow-up over five years, iii) incident cases over five years and baseline factors associated with incidence of new IBD between baseline and 5 years on the population with complete follow-up over five years.

The analysis of factors associated with IBD was done by comparison of patients IBD + vs patients IBD -, using odds-ratio +/- 95% CI and Fisher 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 20th 2016. Significance was p less than 0.05.

Ethics: the study was approved by the “Comite de protection des personnes CPP Ile de France III” Number 2457; EUDRACT number 2007-A00608-45; clinicaltrials.gov: NCT01648907

3. Results

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

In univariable analysis, factors associated with IBD are summarized in table 1. There was no association between IBD and age, gender, disease duration, BMI, smoking, dactylitis, enthesitis, chest wall involvement, BASDAI, ASDAS, BASFI, HAQ, SF-36, ASQoL, levels of CRP, cholesterol, sclerostin, periostin, Vitamin D, IL-6, IL-17, IL-23, imaging scores (spine and sacro iliac MRI inflammatory or structural, mSASSS), bone mineral density (BMD) and body composition results.

In multivariable analysis, significant associations (p less than 0.05) for IBD were found with history of uveitis: OR 3.62 [1.95 – 6.74], DKK1 levels : OR (per unit) 1.03 [1.02 – 1.05], TNF serum levels : OR (per unit) 1.17 [1.08 – 1.26].

3.2. At the five years (M60) endpoint, 58 cases of patients with IBD are recorded out of 480 with complete follow-up, indicating an estimated prevalence of 12.08 % [9.17 – 14.99] %.

In univariable analysis, past history or current IBD at M60 was associated with (Table 2) : Anti-TNF use, DMARD use, NSAID Score, ASDAS CRP, BASFI, SF36 physical, SF36 mental, HAQ, Sick leave, Number of tender joints.

In multivariable analysis, IBD is associated with :

- Sick leave : OR 1.01 [1.005 – 1.014] ; $p = 0.04$
- Modified New York criteria: OR 4.85 [2.23 – 10.57]; $p = 0.04$
- BASDAI : OR (per unit) 1.10 [1.05 – 1.16] ; $p = 0.04$
- Smoking (y/n) : OR 2.79 [1.53 – 5.07] ; $p = 0.04$

3.3. Analysis of incident cases :

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, 95% CI [0.57 – 1.35]. Incidence seems stable over time : 6 cases in the period M0-M12, 6 cases in the period M12-M24, 5 cases in the period M24-M36 and 6 cases in the period M36-M60.

In univariable analysis, IBD was associated (Table 3) with History of psoriasis, SF36 physical component, Familial history of IBD, fulfillment of modified New York criteria, lower lumbar and femoral BMD T scores at baseline.

In multivariable analysis, incident IBD was significantly ($p=0.04$) associated with :

- HLA B27 : OR 0.36 [0.22 – 0.59] ;
- Fulfillment of modified New York criteria at M0 : OR 3.35 [1.85 – 6.08] ;
- Familial history of IBD : OR 3.31 [1.62 – 6.77].

4. Discussion

In this study using a prospective cohort of patients with high probability of early axial SpA (at baseline, 92% of the patients fulfill at least one set of classification criteria)[12], we found a prevalence of IBD of 5% at baseline and of 12 % after 60 months follow up, demonstrating an increase with 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 patients-years in the DESIR cohort, roughly ten times higher than the data in the general population in Europe and in our country [15,16]. On the other side, in case of IBD, the probability of occurrence of SpA was recently assessed in a meta analysis of 71 studies: spondyloarthritis occurs in up to 13% of patients with IBD. Pooled prevalences were calculated for sacroiliitis (10%; 95% confidence interval [CI] 8-12%), ankylosing spondylitis [3%; 95% CI 2-4%], and arthritis [13%; 95% CI 12-15%] [17].

Presence of IBD is 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), 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 sacro iliac MRI scores (SPARCC) for inflammatory changes. This is not in accordance with the results of van Praet (5), but in their study they evaluated the degree of microscopic gut inflammation in correlation with the sacro iliac score. Nevertheless, IBD is independently associated with fulfillment of modified New York criteria, i.e. presence of significant structural damage of sacro iliac joints. At the opposite, in the Brazilian Registry of Spondyloarthritis, there was a significantly lower prevalence of radiographic sacro iliac and lower radiographic score (assessed by BASRI) in enteropathic arthritis compared to other types of spondyloarthritis [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 non radiographic axial SpA. A recent meta analysis concluded that pooled prevalence of IBD was similar in AS and non radiographic axial SpA [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 compared with other types of SpA.

One particular finding was the low association with HLA-B27 in case of IBD, suggesting the implication of other genetic factors in case of SpA with IBD. This low prevalence of HLA-B27 was also found in another study [18] and 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 NSAIDs scores, and more frequent use of glucocorticoids, csDMARDs at baseline [19], and anti TNF agents at 5 years. A lower rate of NSAID

use seems logical in case of IBD history, as well as more frequent use of glucocorticoids and DMARDs such as sulfasalazine.

Some factors at baseline are associated with occurrence of IBD during the 60 months follow up (and may be discussed as predictive factors): absence of psoriasis, absence of HLA-B27, familial history of IBD, impaired SF-26 and fulfillment of modified New York criteria.

This study has some strengths and limitations. The strengths are the initial number of patients included in the cohort (more than seven hundred), and the prospective follow-up over five years, with many clinical, biological and imaging evaluations. The limitations are the absence of systematic gut investigation, avoiding recognition of asymptomatic gut inflammation. The other limitations are the number of patients lost of follow-up at one hand, and the low number of events that may induce a lack of power in statistical analysis at the other hand. However, the analyses were conducted on patients with complete follow-up, 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 patients. IBD is associated with worse outcome, familial history of IBD, absence of HLA-B27 and fulfillment of modified New York criteria.

Highlights:

- IBD is frequent in early axial SpA
- Estimated incidence of IBD in DESIR cohort is about 1/100 patient-years
- Prevalent cases of IBD are associated with disease activity and severity
- Incident cases of IBD are associated with familial history of IBD, low HLA-B27 frequency and modified New York criteria fulfillment.

For Peer Review

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Acknowledgements:

The DESIR study is conducted as a Programme Hospitalier de Recherche Clinique with Assistance Publique Hopitaux de Paris as the sponsor, and also under the umbrella of the French Society of Rheumatology, which financially supports the cohort. An unrestricted grant from Pfizer has been allocated for the first 10 years. The DESIR cohort is conducted under the control of Assistance publique Hopitaux de Paris via the Clinical Research Unit Paris Centre and under the umbrella of the French Society of Rheumatology and Institut national de la recherche et de la recherche médicale (Inserm). Database management is performed within the Department of Epidemiology and Biostatistics (Professeur Jean-Pierre Daures, D.I.M., Nimes, France). We also wish to thank the different regional participating centres : Pr Maxime Dougados (Paris-Cochin B), Pr Andre Kahan (Paris-Cochin A), Pr Philippe Dieudé (Paris-Bichat), Pr Bruno Fautrel (Paris-La Pitie-Salpetriere), Pr Francis Berenbaum (Paris-Saint-Antoine), Pr Pascal Claudepierre (Creteil), Pr Maxime Breban (Boulogne-Billancourt), Dr Bernadette Saint-Marcoux (Aulnay-sous-Bois), Pr Philippe Goupille (Tours), Pr Jean Francis Maillefert (Dijon), Dr Emmanuelle Dernis (Le Mans), Pr Daniel Wendling (Besancon), Pr Bernard Combe (Montpellier), Pr Liana Euller-Ziegler (Nice), Pr Pascal Richette (ParisLariboisiere), Pr Pierre Lafforgue (Marseille), Dr Patrick Boumier (Amiens), Pr Martin Soubrier (ClermontFerrand), Dr Nadia Mehse (Bordeaux), Pr Damien Loeuille (Nancy), Pr Rene-Marc Flipo (Lille), Pr Alain Saraux (Brest), Pr Xavier Mariette (LeKremlin-Bicetre), Pr Alain Cantagrel (Toulouse), Pr Olivier Vittecoq (Rouen). We wish to thank the research nurses, the staff members of the Clinical Research Unit of Paris Centre, the staff members of the Biological Resource Center of Bichat Hospital, the staff members of the Department of Statistics of Nimes and all the investigators, and in particular Jerome Allain, Emmanuelle Dernis, Salah Ferkal, Clement Prati, Marie-Agnes Timsit, Eric Toussiro for active patient recruitment and monitoring.

Funding The DESIR-cohort is financially supported by unrestricted grants from both the French Society of Rheumatology, and Pfizer Ltd, France.

The authors declare no conflict of interest concerning the data of this paper.

Legends :

Table 1 : factors associated with IBD at baseline(univariable analysis). IBD = inflammatory bowel disease; mNY = modified New York criteria; DMARD = disease modifying anti rheumatic drug; NSAID = non steroidal anti inflammatory drug; ESR = erythrocyte sedimentation rate

Table 2 : factors associated with IBD at the five year visit (M60) (univariable analysis). IBD = inflammatory bowel disease; mNY = modified New York criteria; DMARD = disease modifying anti rheumatic drug; NSAID = non steroidal anti inflammatory drug; ESR = erythrocyte sedimentation rate

(univariable analysis). IBD = inflammatory bowel disease; mNY = modified New York criteria; DMARD = disease modifying anti rheumatic drug; NSAID = non steroidal anti inflammatory drug; ESR = erythrocyte sedimentation rate

Table 3 : baseline factors associated with incidence of new cases of IBD between baseline and 5 years (univariable analysis). IBD = inflammatory bowel disease; mNY = modified New York criteria; DMARD = disease modifying anti rheumatic drug; NSAID = non steroidal anti inflammatory drug; ESR = erythrocyte sedimentation rate

variable	OR [95% CI] or mean (SD) (IBD+ vs IBD -)	p value
	Prevalent M0	
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
Steroids use	4.21 [1.83 – 9.25]	< 0.001
NSAID score (6 months)	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
Haemoglobin (g.dl)	15.7 (19.0) vs 16.0 (18.0)	0.02

Table 1

variable	OR [95% CI] or mean (SD) (IBD+ vs IBD -)	p value
	Prevalent M60	
DMARD use	2.58 [1.35 – 5.08]	0.002
Steroids use		
NSAID score (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 (y/n)	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
SF36 physical	39.26 (9.91) vs 43.59 (9.60)	0.004
SF36 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
Number of tender joints	5.84 (9.77) vs 2.37 (5.80)	0,009

Table 2

variable	OR [95% CI] or mean (SD) (IBD+ vs IBD -)	p value
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
SF36 physical	36.75 (8.75) vs 40.34 (9.04)	0.047

Table 3