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Original article

Lymphopenia in early arthritis: Impact on diagnosis and 3-year outcomes (ESPOIR cohort)



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ABSTRACT

Objectives: In patients with early arthritis naive to disease-modifying antirheumatic drugs, we evaluated the prevalence of initial and persistent lymphopenia, underlying diagnoses, and risk of infection or malignancy.

Methods: Eight hundred and thirteen patients with early arthritis included in the ESPOIR cohort had a clinical examination, laboratory tests (viral serology, immunological tests, and cytokine profile), and radiographs. We determined the prevalence of lymphopenia at baseline and after 3 years, associated factors, diagnoses, and risk of infection or malignancy.

Results: At baseline, 50/813 (6.2%) patients had lymphopenia. Lymphopenia was associated with positive rheumatoid factor ($P=0.02$), cytopenia ($P\leq 0.05$), hepatitis C ($P=0.05$), higher C-reactive protein and DAS28 ($P\leq 0.05$ for both). Cytokine profile and radiological progression were not significantly different between patients with and without lymphopenia. Suspected diagnoses at inclusion were rheumatoid arthritis (RA, $n=27$), unclassified arthritis ($n=15$), systemic lupus erythematosus (SLE, $n=3$), spondyloarthritis ($n=2$), Sjögren's syndrome ($n=1$), hematologic disease ($n=1$), and fibromyalgia ($n=1$). Fifteen patients out of 42 (35.7%) with initial lymphopenia had persistent lymphopenia after 3 years, including 5 with documented causes (lupus, hepatitis C, undernutrition, azathioprine, and tamoxifen); none had PVB19, HIV, or HBV infection and none experienced infections, solid or hematologic malignancies during follow-up. Final diagnoses in these 15 patients were RA ($n=6$), unclassified arthritis ($n=6$), SLE ($n=1$), spondyloarthritis ($n=1$), and fibromyalgia ($n=1$).

Conclusions: Lymphopenia is rare in early arthritis. The most common rheumatic cause is RA, in which marked inflammation and other cytopenias are common. Lymphopenia in early arthritis is often short-lived, even when methotrexate is prescribed.

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Lymphopenia occurs in various autoimmune, infectious, and/or hematological diseases. Lymphocytes play a central role in the pathogenesis of rheumatoid arthritis (RA) [1–4]. In daily practice, lymphopenia is a common finding during follow-up of patients with RA and is generally ascribed to the medications used to treat the disease (glucocorticoids, disease-modifying antirheumatic drugs [DMARDs], and biotherapies) [5–7].

Few studies have assessed the prevalence of lymphopenia in early RA, before the introduction of drugs known to affect lymphocyte counts. In a British cohort, among 66 RA patients, 10 (15%)

had persistent lymphopenia after 1 year in the absence of Felty's syndrome or drugs known to decrease lymphocyte counts [8]. Lymphopenia was associated with rheumatoid factor (RF) positivity and emerged as a possible marker for severe disease [8].

In patients with recent-onset inflammatory joint disease, a finding of lymphopenia may suggest specific diagnoses (e.g., connective tissue diseases, viral infections, and hematological diseases) or RA progression to a more systemic form of the disease. Furthermore, lymphopenia may indicate an increased risk of infection after the introduction of immunosuppressive drugs. Information is lacking on the prevalence, associated factors, diagnostic implications, and prognostic impact of persistent lymphopenia in patients with recent-onset inflammatory joint disease.

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In this observational descriptive study of the prospective longitudinal ESPOIR cohort of patients with recent-onset arthritis naive to drugs known to decrease lymphocyte counts, our objectives were to determine the baseline prevalence of lymphopenia and risk of persistent lymphopenia, as well as the diagnoses and risk of infection and malignancy in patients with lymphopenia.

1. Patients and methods

1.1. Study population

The French Society for Rheumatology established a nationwide, longitudinal, prospective cohort, the ESPOIR cohort [9], to enable investigations of the diagnosis, outcome markers, epidemiology, pathogenesis, and medico-economics of early arthritis and RA. General practitioners and rheumatologists referred patients with recent-onset arthritis to hospitals participating in the ESPOIR cohort project. Patients were eligible for inclusion if they had either a definite or probable clinical diagnosis of RA or polyarthritis not better explained by another etiology. Patients were included if they were older than 18 years and younger than 70 years, had swelling of at least two joints for 6 weeks with a symptom duration no longer than 6 months, and had no prior treatment with DMARDs or glucocorticoids; however, the use of glucocorticoids for ≤ 2 weeks in a mean dosage ≤ 20 mg/day and with discontinuation at least 2 weeks earlier did not prevent study inclusion. Patients who were included were evaluated every 6 months for 2 years, then once a year for at least 10 years. Definite diagnoses other than RA or undifferentiated arthritis were excluded during follow-up.

The study was approved by the institutional review board of the Montpellier University Hospital, the coordinating center for this nationwide study. Before inclusion, all patients gave their written informed consent to participate in this prospective longitudinal study.

1.2. Study design

The baseline assessment included a standardized interview, general physical examination; laboratory tests including blood cell counts, viral serologies (parvovirus B19 [PVB19], hepatitis B virus [HBV], hepatitis C virus [HCV], and human immunodeficiency virus [HIV]), immunological tests (ELISAs for IgM, IgG, and IgA rheumatoid factors [RFs]; tests for anti-citrullinated peptide antibodies [ACPAs], antinuclear antibodies [ANA]); HLA DR phenotype determination; a cytokine profile (IL-1 β , IL-1 receptor antagonist [IL-1Ra], IL-2, IL-4, IL-6, IL-10, IL-17, monocyte chemoattractant protein 1 [MCP-1], interferon γ [IFN γ] and tumor necrosis factor α [TNF α]); urine tests; and radiographs of the chest, pelvis, hands and feet in the posteroanterior view, feet in the oblique view. Each patient was evaluated by an ESPOIR study rheumatologist every 6 months for 2 years, then once a year. Monitoring was stopped if a diagnosis other than RA was established during the follow-up. Diagnoses retained were diagnoses considered by the rheumatologist at 3 years.

Serum interleukin IL-1 β , IL-1Ra, IL-2, IL-4, IL-6, IL-10, IL-17, MCP-1, TNF α and IFN γ levels were measured using Elisa test. Serum samples were collected from the ESPOIR cohort patients and all samples were stored immediately at -80°C . Laboratory tests were centralised. Serum concentrations of IL-1 β , IL-1Ra, IL-2, IL-4, IL-6, IL-10, IL-17, MCP-1, TNF α , and IFN γ were assayed using a commercially available multiplex bead immunoassay based on the Luminex platform (Fluorokine MAP Multiplex Human Cytokine Panel, R&D Systems, Minneapolis, MN, USA), as previously reported [10].

A set of radiographs was obtained for each patient at baseline then every 6 months, at each rheumatologist visit. The radiographs included posteroanterior views of the hands, wrists, and feet; as well as oblique views of the feet. They were sent to the coordinating center for independent interpretation by a rheumatologist (GJT), who had no information about the patients. For each radiograph, the reader followed a standardized procedure to assess the number of erosions and severity of joint-space narrowing scored according to the van der Heijde-modified Sharp system for posteroanterior views of the hands and feet [11,12]. The location of each abnormality was recorded. Finally, the reader indicated whether patients had at least one erosion at the hands or feet considered typical of RA [13].

In the literature, different threshold were used to define lymphopenia (peripheral blood lymphocyte count $< 1000/\text{mm}^3$ or $< 1500/\text{mm}^3$). In our study, lymphopenia was defined as a peripheral blood lymphocyte count $< 1000/\text{mm}^3$, cut-off considered as the most relevant in previous studies [14–20].

To determine the prevalence, associated factors, underlying diagnoses, and prognostic impact of persistent lymphopenia in patients with recent-onset inflammatory joint disease naive to lymphopenia-inducing drugs, we analyzed patients with lymphopenia at baseline and those with persistent lymphopenia after 3 years.

1.3. Statistical analysis

We calculated the prevalence of lymphopenia at baseline and after 3 years, as well as the prevalence of lymphopenia present at both time points.

To identify factors significantly associated with lymphopenia, we separated the patients into two groups based on presence or absence of lymphopenia. We then looked for factors associated with belonging to either group. The Chi² test or Fisher's exact test, as appropriate, and Mann-Whitney test were used for univariate analyses of variables collected at baseline and after 3 years. We used SPSS v15.0 software (SPSS Inc., Chicago, IL, USA). *P*-values ≤ 0.05 were considered statistically significant.

2. Results

2.1. Study group

The ESPOIR cohort included 813 patients, with 624 women (76.8%). The meantime from symptom onset to rheumatologist referral was 75 days. We evaluated 813 patients at baseline and 609 patients 3 years later.

2.2. Baseline lymphopenia (less than 1000/mm³)

The baseline prevalence of lymphopenia was 6.2% (50/813 patients). Mean age was similar in the groups with and without baseline lymphopenia (47.2 years and 47.6 years, respectively).

Table 1 lists the factors associated with baseline lymphopenia. We found no significant between-group differences for smoking or alcohol consumption. As shown in Table 2, the cytokine profiles were similar in the two groups.

The diagnoses considered most likely by the rheumatologists after 3 years in the 50 patients with baseline lymphopenia were RA in 27 (54.0%) patients, unclassified arthritis in 15 (30.0%), systemic lupus erythematosus (SLE) in 3 (6.0%), spondyloarthritis in 2 (4.0%), Sjögren's syndrome in 1 (2.0%), hematologic disease in 1 (2.0%), and fibromyalgia in 1 (2.0%).

Table 1
Factors associated with baseline lymphopenia < 1000/mm³ at inclusion in the ESPOIR cohort (n = 813).

Features	Baseline lymphopenia n = 50	No baseline lymphopenia n = 762	P-value
Females, n (%)	37/50 (74.0)	587/762 (77.0)	0.62
Age at onset, years, mean (SD)	47.2 (12.6)	47.6 (12.5)	0.63
DAS 28, mean (SD)	5.7 (1.4)	5.1 (1.3)	0.01
ESR, mm/h, mean (SD)	39.5 (33.4)	28.8 (23.8)	0.07
CRP, mg/L, mean (SD)	33.1 (43.6)	19.4 (31.4)	0.02
ACPA > 20 IU/L, n (%)	22/50 (44.0)	306/761 (40.2)	0.60
RF positivity, n (%)	29/50 (58.0)	313/759 (41.2)	0.02
Creatinine > 110 μmol/L, n (%)	2/50 (4.0)	15/751 (2.0)	0.29
Anemia ^a g/L, n (%)	22/50 (44.0)	218/759 (28.7)	0.02
Leukopenia < 3500/mm ³ , n (%)	3/50 (6.0)	7/759 (0.9)	0.02
Neutropenia < 1500/mm ³ , n (%)	4/50 (8.0)	11/753 (1.5)	0.01
HIV+, n (%)	0/50 (0.0)	1/762 (0.1)	1.00
HCV+, n (%)	2/50 (4.0)	4/762 (0.5)	0.05
HBV+, n (%)	0/50 (0.0)	3/762 (0.4)	1.00
Parvovirus B19+, n (%)	0/50 (0.0)	2/762 (0.3)	1.00
Modified Sharp Score change at 3 years, mean (SD)	0.7 (1.1)	0.8 (1.7)	0.31

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; HIV: human immunodeficiency virus; HCV: hepatitis C virus; HBV: hepatitis B virus.

^a Anemia defined as hemoglobin < 13 g/dL in men and < 12 g/dL in women.

Table 2
Cytokine profile.

	Baseline lymphopenia n = 50	No baseline lymphopenia n = 762	P-value
IL-1Ra, IU/L, mean (SD)	1724 (1988)	1259 (1055)	0.10
IL-1β, IU/L, mean (SD)	0.08 (0.39)	0.22 (2.29)	0.99
IL-2, IU/L, mean (SD)	1.03 (3.11)	0.82 (4.52)	0.97
IL-4, IU/L, mean (SD)	0.39 (1.38)	0.53 (6.77)	0.86
IL-6, IU/L, mean (SD)	45.0 (136.5)	15.6 (19.6)	0.08
IL-10, IU/L, mean (SD)	0.21 (0.70)	0.75 (11.25)	0.39
IL-17, IU/L, mean (SD)	0.39 (1.10)	0.38 (3.68)	0.05
MCP-1, IU/L, mean (SD)	304.3 (305.4)	214.2 (141.2)	0.09
INFγ, IU/L, mean (SD)	0.19 (0.80)	0.13 (0.64)	0.76
TNFα, IU/L, mean (SD)	4.36 (10.37)	2.53 (5.16)	0.34

IL-1Ra: IL-1 receptor antagonist; IL: interleukin; MCP-1: monocyte chemoattractant protein 1; INFγ: interferon γ; TNFα: tumor necrosis factor α.

2.3. Lymphopenia (< 1000/mm³) after 3 years

The prevalence of lymphopenia after 3 years was 6.2% (38/609 patients). Of the 567 patients without baseline lymphopenia, 23 (4.1%) had lymphopenia after 3 years. Among 42 patients with baseline lymphopenia assessed after 3 years, 15 (35.7%) had persistent lymphopenia after 3 years. Eight patients out of 50 (16.0%) with baseline lymphopenia were not assessed after 3 years, because 2 patients were removed from the study after 2 years for other diagnoses (lupus in 1 and Sjogren's syndrome in 1), 1 patient was excluded after 6 months for lymphoma, and 5 patients were lost to follow-up. Fig. 1 shows lymphocyte count changes from baseline to 3 years in the patients with baseline lymphopenia. All patients had lymphocyte count between 500 and 1000/mm³.

2.4. Lymphopenia (< 1000/mm³) both at baseline and after 3 years (Table 3)

Of 609 patients who were assessed after 3 years, 15 (2.5%) had lymphopenia both at baseline and after 3 years. Their mean age was 43 years, 10 (66.7%) were women, and their mean body mass index (BMI) was 23 kg/m²; 1 patient had malnutrition (BMI, 16 kg/m²). Hepatitis C was diagnosed in 1 (6.7%) of these 15 patients compared to 4/594 (0.7%) patients without persistent lymphopenia. No patients with persistent lymphopenia had positive tests for PVB19, HBV, or HIV infection.

At baseline, all 15 patients had arthritis and/or arthralgia of the hands, which was symmetric in 11 (73.3%) cases. Morning stiffness longer than 30 min was reported by 12/15 (80.0%)

patients. The DAS28 was > 3.2 in 13/14 (92.9%) patients and the CRP level > 5.0 mg/L in 8/15 (53.3%) patients. Tests were positive for RF in 4/15 (26.7%) patients, ACPA in 3/15 (20.0%) patients, and ANA in 7/15 (46.7%) patients (without specificity in 5 and anti-SSA in 2; none had anti-DNA). Another cytopenia was found in 5/15 (33.3%) patients (anemia in 4 and neutropenia in 1). None of these patients had serum creatinine levels > 110 mmol/L. The peripheral lymphocyte count was < 1500/mm³ at each visit in 14/15 (93.3%) patients, including 8/15 (53.3%) with lymphopenia < 1000/mm³.

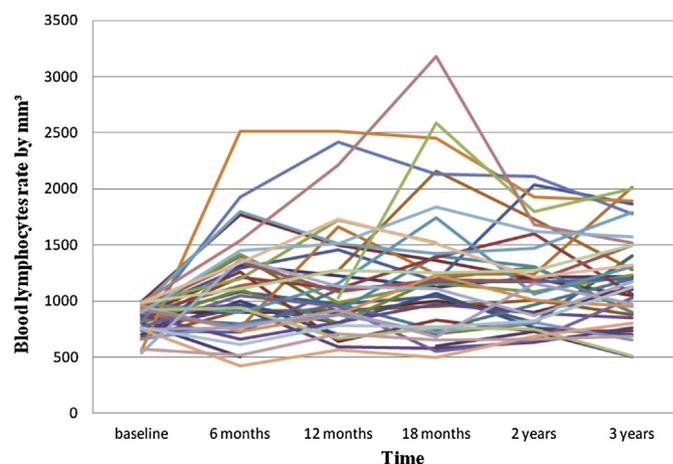


Fig. 1. Change in peripheral blood lymphocyte counts from baseline to 3 years in patients with baseline lymphopenia (< 1000/mm³) (n = 42).

Table 3
Description of the 15 patients with persistent lymphopenia (< 1000/mm³) after 3 years.

n = 15	Sex, age	Other cytopenia at baseline	CRP > 5.0 mg/L at baseline	Immunological tests at baseline	Possible etiologies of lymphopenia	Most likely diagnosis after 3 years
1	F 36 years	No	Yes	Negative		Unclassified arthritis
2	F 37 years	No	No	RF+ ACPA+		RA
3	F 47 years	Anemia	Yes	ANA+ without specificity		Unclassified arthritis
4	F 56 years	No	No	Negative	HCV, gabapentin	Unclassified arthritis
5	F 52 years	No	No	ANA+ without specificity	Azathioprine for multiple sclerosis	Unclassified arthritis
6	M 21 years	No	Yes	Negative	SLE	SLE
7	F 36 years	Anemia	Yes	ANA+ without specificity		RA
8	F 32 years	No	No	Negative		RA
9	F 43 years	Anemia	Yes	RF+ ANA+, 1/1000 anti-SSa		RA
10	M 56 years	No	No	Negative		Ankylosing spondylitis
11	M 36 years	No	Yes	RF+ ACPA+		RA
12	M 38 years	No	No	ANA+, 1/1280, anti-SSa		Fibromyalgia
13	F 66 years	Anemia	Yes	Negative	Breast cancer, tamoxifen	Unclassified arthritis
14	M 45 years	No	Yes	ANA+ without specificity		Unclassified arthritis
15	F 48 years	Neutropenia	No	RF+ ACPA+ ANA+ without specificity	Undernutrition with BMI 16 kg/m ²	RA

CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; ANA: anti-nuclear antibodies; RA: rheumatoid arthritis; HCV: hepatitis C virus; SLE: systemic lupus erythematosus; BMI: body mass index.

Table 4
Diagnosis after 3 years in patients with and without persistent lymphopenia (< 1000/mm³).

Diagnosis	Lymphopenia n = 15	No lymphopenia n = 594	P
RA	6 (40.0%)	368 (62.0%)	0.08
Other diagnoses ^a	9 (60.0%)	226 (38.0%)	

^a Others diagnosis in groups with and without persistent lymphopenia respectively, were: unclassified arthritis 6 (40.0%) 113 (19.0%); systemic lupus erythematosus 1 (7.0%) 5 (2.2%); Sjogren's syndrome 0 24 (10.6%); spondyloarthritis 1 (7.0%) 45 (19.9%); fibromyalgia 1 (7.0%) 3 (1.3%); other 0 36 (15.9%).

One patient had a blood lymphocyte count of 2688/mm³ with counts < 1000/mm³ at all other visits. At baseline, 6/15 (40.0%) patients had received drugs known to decrease leukocyte counts (gabapentin, azathioprine, lansoprazole, clomipramine, or tamoxifen). During the 3-year follow-up, none of the 15 patients received biotherapies and 10/15 (66.7%) patients received DMARDs; in the group without persistent lymphopenia, 92/594 (15.5%) patients were given biotherapies with or without DMARDs and 342/594 (57.6%) DMARDs without biotherapies. As shown in Table 3, a possible cause of lymphopenia was identified in 5/15 (33.3%) patients (lupus, hepatitis C, undernutrition, azathioprine, and tamoxifen). During follow-up, the only infection in these 15 patients was a case of bronchitis. None of the 15 patients was diagnosed with solid or hematological malignancies, and none died.

The most likely diagnoses after 3 years are listed in Table 4. Final diagnoses in these 15 patients were RA (n = 6), unclassified arthritis (n = 6), SLE (n = 1), spondyloarthritis (n = 1), and fibromyalgia (n = 1). The distribution of diagnoses was not significantly different between the groups with and without lymphopenia (Table 4) but the sample size was too small for a definite conclusion.

3. Discussion

In the prospective ESPOIR cohort of recent-onset arthritis, 6.2% of patients had lymphopenia (< 1000/mm³) at baseline, and a third of these still had lymphopenia 3 years later. Baseline lymphopenia

was associated with HCV infection, RF positivity, other cytopenias (anemia and neutropenia), systemic inflammation, and higher DAS28 values. In 5 of the 15 patients with persistent lymphopenia after 3 years, a possible cause of lymphopenia was identified. The underlying disease at 3 years was RA in 6 of the 15 patients. Persistent lymphopenia was not associated with infection, solid cancer, or hematologic malignancies, even when DMARD therapy was started during the 3-year follow-up. As none of the 15 patients with persistent lymphopenia received biotherapies, we were therefore unable to assess the potential risk of infection in this situation. Finally, none of the 15 patients had infection with PVB19, HBV, or HIV. None had Felty's syndrome, but this cohort of mixed population with early arthritis did not allow to analyze the correlation of lymphopenia and severe outcomes in RA patients.

In patients with SLE, lymphopenia is a very common finding and a risk factor for infection [21,22]. In primary Sjogren's syndrome, lymphopenia is also common [23] and indicates an increased risk of developing lymphoma [24]. During HIV infection, CD4+ lymphopenia is associated with opportunistic infections and malignancies [25,26]. PVB19 infection often manifests as arthralgia and/or arthritis and lymphopenia, a picture that may be clinically difficult to distinguish from other recent-onset inflammatory joint diseases (including RA) if the skin rash is lacking [27].

In RA, the risk of infection is increased both by the disease itself [28,29] and by the immunosuppressant drugs used to treat it. The risk of severe bacterial infections (intracellular and extracellular) is higher with anti-TNF α therapy than with DMARDs [30–32]. Despite the possibility of sustained lymphopenia in RA patients given biotherapies, these drugs were associated neither with substantial excess mortality nor with increased infection-related morbidity over 12 years of follow-up [33,34].

Several mechanisms can induce lymphopenia: decreased lymphocyte production (primary immune deficiencies and immune deficiencies secondary to malnutrition or zinc deficiency), increased lymphocyte destruction (chemotherapy, radiotherapy, immunosuppressive therapy, HIV infection, or SLE), alterations in lymphocyte distribution (splenomegaly, viral infections, septic shock, extensive burns, systemic granulomatosis, or glucocorticoid

therapy), and other poorly understood factors (Ethiopian ethnicity, lymphoma, renal dysfunction, and idiopathic CD4 lymphocytopenia) [35].

We chose not to exclude patients with differential diagnosis than RA when they were followed at 3 years for two reasons. Firstly, to analyze if a persistent lymphopenia in recent-onset inflammatory joint disease may suggest specific diagnoses (e.g., connective tissue diseases, viral infections, and hematological diseases). Secondly, as definite diagnoses other than RA or undifferentiated arthritis were excluded during follow-up, all patients with a 3-year follow-up were considered as possible RA.

The prevalence of lymphopenia in early arthritis is low and our study is the only one that assesses its impact in a large cohort of recent-onset arthritis, to demonstrate the absence of excess mortality, infections, solid cancer or hematological malignancies, and no more rapid radiographic disease progression.

There is no consensus about the cut-off that should be used to define lymphopenia. Some studies used 1500/mm³ [36] and others 1000/mm³ [14–20]. We used the lower of these two cut-offs, which was chosen for most of the previous studies.

Our study had three main limitations. First, the small number of patients with persistent lymphopenia did not allow a statistical analysis (15/609 patients after 3 years). With lymphopenia's cut-off of 1500/mm³, we would have more patients with persistent lymphopenia but we thought that this cut-off was less appropriate regarding to the literature. Few data are available on the prevalence of lymphopenia in RA patients naive to lymphocyte-depleting treatments or in the general population. In RA patients, lymphopenia could be a marker for disease activity, but the small number of RA patients with persistent lymphopenia did not allow to conclude. Second, we did not type the peripheral lymphocytes. Therefore, we do not know whether the lymphopenia reflected a decrease in B-cells, T-cells, or both. Several studies found low peripheral T-cell counts with normal peripheral B-cell counts [8]. Finally, assays of the cytokine IL-7 would have been of interest. IL-7 plays a major role in T-cell homeostasis (as both a growth factor and an anti-apoptotic factor) [37], induces the production of other cytokines, and stimulates the osteoclasts. IL-7 is produced not only by bone marrow stromal cells; but also by macrophages, dendritic cells, and synovial fibroblasts. High IL-7 levels have been reported in joint fluid from patients with RA [38]. In contrast, serum IL-7 levels were low and IL-7 production by bone marrow stromal cells was decreased, this decrease in serum IL-7 may explain the occurrence of lymphopenia and the poor early T-cell reconstitution seen in RA patients after drug-induced lymphodepletion [39].

Lymphopenia in recent-onset inflammatory arthritis may be a feature of RA. However, lymphopenia was rare in our patients with RA. Therefore, patients with recent-onset arthritis should be investigated for other causes or concomitants of lymphopenia such as SLE; Sjögren's syndrome; or infection with PVB19, HBV, HCV, or HIV. Two-thirds of patients with lymphopenia at baseline no longer had lymphopenia 3 years later, even when DMARD therapy had been started in the interval. However, most of the patients with persistent lymphopenia had a definite diagnosis of RA. Thus, lymphopenia may be a marker for disease activity associated with a greater degree of inflammation (higher CRP and DAS28 values) and with other cytopenias. Persistent lymphopenia was not associated with an increased risk of infection, solid cancer, hematological malignancies, or rapid radiographic disease progression.

Disclosure of interest

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