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ORIGINAL RESEARCH

Lymphoma complicating rheumatoid arthritis: results from a French case–control study

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ABSTRACT

Objectives To study the characteristics of B-cell non-Hodgkin's lymphoma (NHL) or Hodgkin lymphoma complicating rheumatoid arthritis (RA) and to identify RA-related factors associated with their occurrence.

Methods A multicentre case–control study was performed in France. Cases were patients with RA fulfilling ACR-EULAR 2010 criteria in whom B-cell NHL or Hodgkin lymphoma developed after the diagnosis of RA. For each case, 2 controls were assigned at random from the ESPOIR cohort and were matched on age at lymphoma diagnosis (cases)/age at the 10-year follow-up visit in the cohort (controls). Case and control characteristics were compared to identify parameters associated with the occurrence of lymphoma.

Results 54 cases were included and matched to 108 controls. Lymphomas were mostly diffuse large B-cell lymphoma (DLBCL, n=27, 50.0%). On immunochemistry, 4 of 27 (14.8%) lymphoma cases were positive for Epstein-Barr virus. On univariate analysis, factors associated with the occurrence of lymphoma were male sex (OR 3.3, 95% CI 1.7 to 6.7), positivity for ACPA (OR 5.1, 95% CI 2.0 to 15.7) and rheumatoid factor (OR 3.9, 95% CI 1.6 to 12.2), and erosions on radiographs (OR 3.8, 95% CI 1.7 to 8.3) and DAS28 (OR 2.0, 95% CI 1.5 to 2.7), both at the time of matching. Methotrexate, TNF blockers and a number of previous biologics were not associated with the occurrence of lymphoma. On multivariable analysis, erosions and DAS28 remained significantly associated with increased risk of lymphoma.

Conclusion Lymphomas complicating RA are mostly DLBCL. Risk of lymphoma in patients with RA was increased with markers of disease activity and severity, which supports the paradigm of a continuum between autoimmunity and lymphomagenesis in RA.

Key messages

What is already known about this subject?
► Risk of B-cell non-Hodgkin's lymphoma is increased in patients with rheumatoid arthritis (RA). Only two previous studies demonstrated high cumulative disease activity associated with increased risk of lymphoma.

What does this study add?
► This work revealed increased risk of lymphoma in patients with RA with active disease defined by DAS28 score as well as disease severity defined by the presence of erosions. There was no significant association between methotrexate and TNF-blocker treatment and occurrence of lymphoma.

How might this impact on clinical practice or future developments?
► This study is reassuring regarding RA treatments, including methotrexate, TNF inhibitors and other biologic agents, in that they are not associated with increased risk of lymphoma. Patients with structural damage should benefit from closer surveillance regarding the risk of lymphoma.

The risk of lymphoma is 1.5-fold to 3-fold higher in patients with RA than the overall population.[1] The lymphomas are mostly B-cell non-Hodgkin's lymphoma (NHL), particularly diffuse large B-cell lymphoma (DLBCL), but the risk of Hodgkin's lymphoma is also increased.[2 3]

The pathophysiology of lymphomas complicating RA remains unknown, and risk factors of this complication are not well identified. Disease activity is widely acknowledged to be associated with lymphomagenesis in

INTRODUCTION

Lymphoma is a rare but severe systemic complication of rheumatoid arthritis (RA).

RA, but only two studies to date found this association: the hypothesis was first explored in 1998 by a Swedish case–control study in which 42 cases of lymphoma were identified and matched to 126 controls with RA. Risk of lymphoma was 25.8-fold increased with the highest cumulative disease activity.[4] The same team confirmed these results in 2006, in a larger case–control study based on 378 cases of lymphoma complicating RA. For each patient, a 20-year cumulative activity score was calculated: for 10% of patients with the highest cumulative disease activity score, the risk of lymphoma was increased 60-fold.[5] Recently, in a case–control study nested in the Japanese IORRA cohort, high DAS28 was a risk factor of lymphoproliferative disorders (OR 1.57, 95% CI 1.12 to 1.57, p<0.01).[6] However, inflammation per se is not the driver of lymphomagenesis because other inflammatory rheumatic diseases such as autoinflammatory syndromes, spondyloarthritis and psoriatic arthritis are not associated with increased risk of lymphoma.[7]

In addition, the role of RA treatments was suspected. Indeed, several cases of Epstein-Barr virus (EBV)–induced lymphoma occurring in patients with RA receiving methotrexate (MTX) were reported. In one-third to two-thirds of cases after MTX discontinuation, some of these lymphoma cases regressed spontaneously.[8–11] However, two subsequent cohort studies did not demonstrate an association between lymphoma and MTX use in patients with RA. First, a French prospective study conducted by the *Club Rhumatismes et Inflammation* network collected 25 cases of lymphoma (18 B-cell NHL and 7 Hodgkin's lymphoma) occurring in patients with RA receiving MTX and found no difference with the overall French population in terms of incidence of B-cell NHL.[12] Nevertheless, the incidence of Hodgkin's lymphoma in patients with RA receiving MTX seemed higher than in the general population (standardised incidence ratio=7.4, 95% CI 3.0 to 15.3). The Swedish studies previously mentioned did not find an association between MTX and lymphoma occurrence regardless of duration of MTX exposure.[5] Regarding TNF blockers, the French RATIO study, following 57 000 patient-years with rheumatic diseases between 2004 and 2006, found increased risk of B-cell NHL in patients receiving TNF blockers (standardised incidence ratio=2.4, 95% CI 1.7 to 3.2), which is the known excess risk in active RA patient populations.[13] This risk was greater with infliximab or adalimumab but was not significant with etanercept. Nevertheless, the more recent study of the EULAR & RODS Study Group provided reassuring findings: among the 124 997 patients followed, 533 cases of lymphoma occurred, and the incidence rate of lymphoma with anti-TNF therapy was lower than in the total population and in biologic therapy–naive patients (81/100 000 vs 85/100 000 and 89/100 000 person-years, respectively).[14] In addition, the French CANIBIO study, using the national SNIIRAM database, found no difference in risk of lymphoma with TNF-blocker treatment as compared with other biological agents (HR 0.86, 95% CI 0.42 to 1.77, p=0.67).[15] Finally,

according to a recent Swedish cohort study based on nationwide registers, biologic agents might even reduce the risk of lymphoma in patients with RA (adjusted HR 0.69, 95% CI 0.47 to 1.00).[16] However, we cannot exclude a bias linked to the exclusion of biologic agents in more at-risk patients. Thus, to date, no study has demonstrated a deleterious role of treatments in RA-associated lymphomagenesis, and additional data are needed.

The aim of the present work was to study the characteristics of B-cell NHL and Hodgkin's lymphoma complicating RA and to identify among clinical, biological and treatment patterns, the factors associated with lymphomagenesis.

METHODS

Study design and population

In this French multicentre case–control study, cases were adults (age ≥18 years) with RA fulfilling ACR-EULAR 2010 criteria in whom B-cell NHL or Hodgkin's lymphoma developed after the diagnosis of RA. Exclusion criteria were T-cell lymphoma, a history of lymphoma before the RA diagnosis and a history of secondary Sjögren's syndrome, given that this autoimmune condition is associated with increased risk of lymphoma.[1 3] Cases were recruited following a call for observations mediated by the CRI-IMIDIATE network and among French Society of Rheumatology registries (AIR-PR, ORA, REGATE) and the Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort. The AIR-PR, ORA and REGATE registries and the ESPOIR cohort have been described in previous studies.[17–20] Cases were excluded if the case report form was not sent to the investigating centre (Kremlin-Bicêtre Hospital).

Controls were drawn at random from the ESPOIR cohort among patients with RA fulfilling ACR-EULAR 2010 criteria who completed a 10-year follow-up. Cases and controls were matched on age (age at lymphoma diagnosis for cases and age at 10-year ESPOIR visit for controls). This variable was chosen because of its well-known association with risk of B-cell lymphoma in the overall population.[21]

Lymphomas

B-Cell NHL and Hodgkin's lymphoma were considered. The diagnosis of lymphoma was histological and was performed on lymphatic nodes, bone marrow or solid-organ biopsy. Information was collected on the lymphoma subtype, EBV positivity on immunohistochemistry (EBV latent membrane protein LMP1 (n=26) or EBER in situ hybridisation (n=1)) and the grade of lymphoma according to Ann Arbor staging.

Collected data

In addition to information on characteristics of lymphomas, data were collected on patients' demographic, clinical and radiological features as well as autoantibody status (rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) positivity).

Disease activity was assessed by the last value of DAS28-ESR measured in the year before the diagnosis of lymphoma and was compared with the DAS28-ESR value at the 10-year ESPOIR visit for controls.

Severity was defined qualitatively by the presence of structure damage (at least one erosion) on hand and feet radiographs, at the diagnosis of lymphoma for cases and at the 10-year ESPOIR visit for controls. For cases, the presence of erosion was assessed on radiography full written results. For controls, radiographs were analysed by two trained readers with blinding to patients' clinical data and providing the results both quantitatively and qualitatively; for the purpose of this study, we considered only the qualitative description of structural damage in controls.

All treatments received during the RA course and before lymphoma diagnosis, including glucocorticoids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic agents, were recorded. For controls, because patients were followed up in the ESPOIR cohort since an early stage of their disease, all known RA treatments were collected from baseline until the 10-year visit. For both cases and controls, there was no minimum duration required to report the exposure to a given treatment.

Those data were collected for cases from a case report form, which was completed by the physician in charge of the patient. For controls, data were collected and available in the ESPOIR database.

Statistical analysis

Case and control characteristics were compared for variables associated with the occurrence of lymphoma. Fisher's exact test was used for qualitative variables and Mann-Whitney U test for quantitative variables. A multivariable logistic regression model was built with variables associated with B-cell NHL or Hodgkin lymphoma on univariate analysis at $p \leq 0.15$.

The statistical analysis was performed with R Studio V.3.5.1. For all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Population characteristics

Overall, 54 cases of B-cell NHL and Hodgkin's lymphoma were collected and matched to 108 controls from the ESPOIR cohort. The flow chart of the study is in figure 1. Characteristics of patients and controls are in table 1. Cases and controls did not significantly differ in age at RA onset (p=0.48), age at time of matching (p=0.46) or RA disease duration (p=0.40); of note, 11 lymphoma occurred after 20 years or more of disease duration. However, the median year of RA diagnosis was significantly earlier in cases than controls: 1998 (IQR 1971–2016) versus 2004 (2002–2005) (p<0.0001). In addition, cases had a significantly higher DAS28 (p<0.0001)
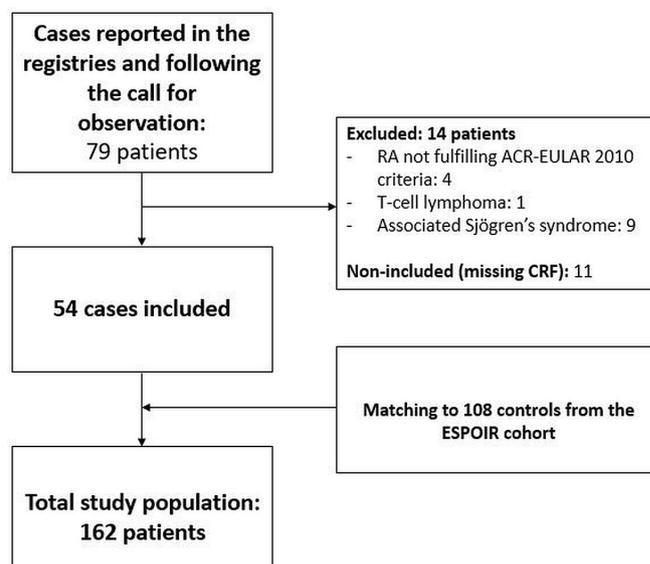

Figure 1 Flow chart of the study. CRF, case report form; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; RA, rheumatoid arthritis.

and more frequent erosions (p=0.0005) at the time of matching than did controls.

Lymphoma characteristics

Among the 54 cases of lymphomas, the most represented subtype was DLBCL (n=27, 50.0%). Among DLBCL cases, 21 had a more precise diagnosis: 11 were germinal centre (GC) DLBCL and 10 non-GC lymphoma. The other most-represented subtypes were follicular lymphoma (n=8, 14.8%) and marginal zone lymphoma (n=8, 14.8%). On immunochemistry, 4 of 27 (14.8%) patients were positive for EBV. More details regarding lymphoma characteristics are in table 2. One MALT lymphoma was observed, with gastric involvement; the patient had no clinical, immunological or histological features favouring Sjögren's syndrome, but *Helicobacter pylori* infection was found.

Lymphomas could involve several organs: they mostly involved lymphatic nodes (n=32, 59.3%), solid organs (n=12, 22.2%) and bone marrow (n=11, 20.4%). Several localisations could be observed in the same patient. Three patients had salivary gland involvement: the first had DLBCL of a submandibular gland, the second marginal zone lymphoma of a submandibular gland and the third mantle lymphoma localised to a parotid gland. The medical records of these three patients were checked and there was no clinical, biological or histological argument for underlying Sjögren's syndrome. Lymphoma was diagnosed most frequently at the Ann Arbor stage of limited organ involvement (stage I) or widespread involvement (stage IV) (n=19, 35.2% for both stages).

Overall, 50 (92.6%) cases received a specific treatment for the lymphoma, mostly chemotherapy (n=36), but 11 (20.4%) patients received rituximab monotherapy. Therapeutic abstention was decided in 4 (7.4%) cases.

Table 1 Characteristics of cases and controls and all participants

	Overall study population (n=162)	Cases (n=54)	Controls (n=108)
Male sex, n (%)	52 (32.1)	27 (50.0)	25 (23.2)
Age at RA diagnosis, years, mean (SD)	52.23 (11.1)	51.23 (12.90)	52.73 (10.12)
Age at the time of matching, years, mean (SD)	62.69 (10.4)	63.52 (10.90)	62.28 (10.11)
ACPA positivity, n (%)	120 (74.1)	49 (90.74)	71 (65.74)
RF positivity, n (%)	126 (77.8)	49 (90.74)	77 (71.3)
Erosions on radiographs at the time of matching, n (%)	102 (63.0)	44 (81.5)	58 (53.7)
DAS28 at the time of matching, mean (SD)	3.00 (1.59)	4.09 (1.62)	2.54 (1.35)
RA duration at the time of matching, mean (SD)	10.4 (6.1)	12.4 (10.5)	10.0 (0.1)
Year of RA diagnosis, median (IQR)	2003 (1971–2016)	1998 (1971–2016)	2004 (2002–2005)
Year of lymphoma diagnosis/10-year ESPOIR visit, median (IQR)	2013 (1987–2018)	2011 (1987–2018)	2014 (2012–2015)

The time of matching corresponded to the diagnosis of lymphoma for cases and the 10-year ESPOIR visit for controls
ACPA, anti-citrullinated peptide antibodies; DAS28, disease activity score in 28 joints; RA, rheumatoid arthritis; RF, rheumatoid factor.

The mean follow-up duration after the diagnosis of lymphoma was 5.2 years (SD 5.8). During this period, 14 (25.9%) deaths occurred: 11 were related to the lymphoma (10 recurrences and 1 non-response to first-line treatment).

Clinical and biological risk factors of lymphoma

The results of the univariate and multivariable analysis are in table 3. On univariate analysis, factors associated with increased risk of B-cell NHL or Hodgkin lymphoma were male sex (OR 3.3, 95% CI 1.7 to 6.7), positivity for ACPA (OR 5.1, 95% CI 2.0 to 15.7) and RF (OR 3.9, 95% CI 1.6 to 12.2) and erosions on radiographs (OR 3.8, 95% CI 1.7 to 8.3) and DAS28 (OR 2.0, 95% CI 1.5 to 2.7), both at the time of matching. Of note, DAS28 was significantly higher in men than women (mean DAS28 3.24 (SD 1.9) vs 2.91 (SD 1.41), p<0.0001).

Erosions and DAS28 remained significant on multivariable analysis, with a trend for ACPA positivity.

Relation between lymphoma and RA treatments

The results of the analysis of the relation between B-cell NHL or Hodgkin's lymphoma and RA treatments are in table 4. MTX, TNF blockers and number of previous biologic agents used were not associated with the occurrence of lymphoma (p=0.97, p=0.75 and p=0.58, respectively). Among the four patients with lymphoma positive for EBV, three were receiving MTX at the time of the lymphoma diagnosis, and the fourth was taking hydroxychloroquine. Previous use of hydroxychloroquine, sulfasalazine and 'ancient' RA therapies such as gold salts was associated with lymphoma on univariate analysis (OR 3.1 (95% CI 1.5 to 6.7), OR 3.1 (95% CI 1.4 to 6.6) and OR 3.0 (95% CI 1.00 to 9.0), respectively) but not multivariable analysis (table 5).

To clarify the association between RA treatments and the occurrence of lymphoma, we performed a sensitivity analysis of cases with RA diagnosed between 2003 and 2005 and their controls (ie, a total of 24 patients). No treatment was significantly associated with risk of lymphoma (online supplemental table S1).

DISCUSSION

In this case–control study, the most represented type of lymphoma complicating RA was DLBCL, and factors associated with the occurrence of lymphoma were disease activity and the radiographic presence of erosions at the time of matching between cases and controls; use of MTX and biologic agents was not associated with increased risk of lymphoma.

We included 54 cases of lymphoma complicating RA, one of the largest series in the literature. This type of study was appropriate because lymphoma in RA is a rare event and occurs about 10 years on average after the onset of rheumatic symptoms (12.4 years in this study); a prospective cohort study would have required a much larger sample and a longer follow-up.

Nevertheless, this work has the inherent limitations of case–control studies. A first limitation is its retrospective nature, which does not allow for estimating the incidence, prevalence and relative risk of lymphoma, and which potentially induces confounding or recall bias. Another limitation is the selection of controls: controls were randomly selected from the ESPOIR cohort and thus had RA diagnosed between 2002 and 2005, whereas cases had RA diagnosed in the late 1990s on average. This heterogeneity may explain at least in part some of the results, particularly those related to drug management. However, despite this time lag, the duration of RA was the same in cases and controls (about 10 years). Moreover, a major advantage of the ESPOIR cohort is that the controls from this cohort represent RA and its treatment in real-life conditions, just as do patients with lymphoma.

Table 2 Characteristics of the 54 cases of B-cell non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma

Histology	
DLBCL	27 (50.0)
Follicular	8 (14.8)
Marginal zone	8 (14.8)
Hodgkin lymphoma	3 (5.6)
Mantle cell	3 (5.6)
NHL (not specified)	3 (5.6)
Lymphocytic	1 (1.8)
MALT	1 (1.8)
EBV positivity on immunochemistry*	4 (14.8)
Ann Arbor staging†	
I	19 (35.2)
II	7 (13.0)
III	6 (11.1)
IV	19 (35.2)
Malignant transformation from indolent lymphoma	4 (7.4)
Localisation	
Lymphatic nodes	32 (59.3)
Solid organs	12 (22.2)
Bone marrow	11 (20.4)
Blood	3 (5.6)
Salivary gland	3 (5.6)
Skin	3 (5.6)
Bone	2 (3.7)
ENT	2 (3.7)
Spleen	2 (3.7)
Lymphoma-specific treatment	50 (92.6)
Chemotherapy	36 (66.7)
Rituximab only	11 (20.4)
Radiotherapy	7 (13.0)
Surgery	4 (7.4)
Therapeutic abstention	4 (7.4)
Remission after 1st line	32 (59.3)
Remission after 2nd line	7 (13.0)
Remission after 3rd line	0 (0.0)
Deaths	14 (25.9)
Lymphoma-related	11 (20.4)
Non lymphoma-related	3 (5.6)
Follow-up duration after lymphoma onset, years, mean (SD)	5.2 (5.8)

Data are n (%) unless otherwise indicated.
Of note, EBV-positive lymphomas were DLBCL (2/4) and Hodgkin's lymphoma (2/4).
*Total number of patients tested for EBV: 27
†Total number of patients with available data for Ann Arbor staging: 51
DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; ENT, ear nose throat; MALT, mucosa-associated lymphoid tissue

The treatment strategy being at the discretion of the investigators limits bias in treatment exposure. In addition, cases were identified by using various sources and registers to obtain the most accurate reflection of the disease and a less selected population. Thus, although unavoidable, selection bias has been limited as much as possible. Another potential limitation is that we did not have the possibility to match cases and controls on disease duration since 11 cases occurred after more than 20 years of disease duration, and there is no French cohort of RA with such long follow-up. The 10th year ESPOIR visit was chosen as comparator given that it was the closest to cases' mean disease duration, to minimise impact of disease duration. Nevertheless, as the disease duration is the same for all controls, the association between disease duration and risk of lymphoma cannot be analysed and we cannot draw any conclusion on the role of disease duration on the risk of lymphoma. Lastly, the qualitative evaluation of structural damage is another limitation of the study.

This study confirms data in the literature concerning the characteristics of lymphoma in RA: the most frequent histological type was DLBCL, which was found in 50% of our cases. Moreover, this proportion is comparable with that in series in the literature.[2 4 21 22] In addition, among the 21 patients for whom information was available, 11 had the DLBCL-GC subtype, which also confirms data from previous studies.[2 22 23] Detection of EBV on histological samples was not searched for systematically, but the proportion of EBV-positive patients also agreed with data from previous studies, about 15%.[4] This observation raises the question, at least in some cases, of the role of induced immunosuppression in the lymphomagenesis process occurring in patients with RA.

In this case series, 66% of patients received specific chemotherapy for their lymphoma, and 20% received rituximab monotherapy; the latter strategy was used in indolent lymphomas (follicular, lymphocytic or marginal zone lymphomas), with good efficacy both in lymphoma progression and control of RA activity. The four patients for whom it was decided to abstain from therapy had indolent lymphomas at an early stage. In our study, the 5-year survival was close to that of patients without RA with all types of lymphoma of the same age and sex in the general population: 74% versus 60% to 70%.[24] Thus, our study did not find a trend towards excess mortality in individuals with lymphoma complicating RA, in contrast to a previous report.[25]

The second part of this work aimed to identify the clinical and biological factors associated with the occurrence of lymphoma. This study supports the two previous studies that established the role of disease activity, with elevated DAS28 at the time of matching significantly associated with increased lymphoma risk on both univariate and multivariable analyses. However, this result should be interpreted with caution because DAS28 was available at only one time point, which does not reflect the full RA disease activity history. Given the retrospective nature and the 'real life setting' of the study, we could not collect disease activity history for cases. The association between lymphoma and radiographic erosions at the time of matching highlights the association between disease severity and risk of lymphoma; moreover, because

Table 3 Results of the univariate and multivariable analyses for the association between clinical and biological features and risk of B-cell NHL or Hodgkin's lymphoma

	Univariate analysis				Multivariable analysis
Variables	Cases (n=54)	Controls (n=108)	OR (95% CI)	P value	OR (95% CI)
Sex					
Male	27 (50.0)	25 (23.2)	3.3 (1.7 to 6.7)	*0.0006*	2.1 (0.7 to 5.8)
Female	27 (50.0)	83 (76.9)	Reference	–	Reference
Age at RA diagnosis, years, mean (SD)	51.2 (12.9)	52.7 (10.2)	1.0 (0.9 to 1.1)	0.48	–
Age at the time of matching, years, mean (SD)	63.5 (10.9)	62.2 (10.1)	1.0 (0.9 to 1.1)	0.46	–
ACPA positivity	49 (90.7)	71 (65.7)	5.1 (2.0 to 15.7)	*0.0006*	–
RF positivity	49 (90.7)	77 (71.3)	3.9 (1.6 to 12.2)	*0.005*	–
RF or ACPA positivity	49 (90.7)	80 (74.1)	3.4 (1.3 to 10.6)	*0.01*	3.4 (0.8 to 16.0)
Erosions on radiographs at the time of matching	44 (81.5)	58 (53.7)	3.8 (1.7 to 8.3)	*0.0005*	10.6 (4.1 to 31.0)
DAS28 at the time of matching, mean (SD)	4.1 (1.6)	2.6 (1.4)	2.0 (1.5 to 2.7)	*<0.0001*	1.9 (1.3 to 2.8)
RA duration at the time of matching, years, mean (SD)	12.4 (10.5)	10.0 (0.1)	1.1 (1.0 to 1.2)	0.40	–

Data are n (%) unless otherwise indicated.
ACPA, anti-citrullinated peptide antibodies; DAS28, disease activity score in 28 joints; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis; RF, rheumatoid factor.

erosive and thus more severe RA is associated with high disease activity, this result is also an indirect argument favouring the role of disease activity in lymphomagenesis. In this work, erosions were qualitatively assessed without quantitative evaluation. An association was found between immunopositivity and the occurrence of lymphoma on univariate but not multivariable analysis. Positivity for autoantibodies, particularly ACPAs, is classically considered a poor prognostic factor in RA, with an association with disease activity and joint destruction,[26–28] which could explain the association observed on univariate analysis. In addition, the association between RF positivity and lymphoma raises the question of the role of chronic antigenic stimulation by immune complexes in the occurrence of a lymphomagenesis process in RA, as well described in primary Sjögren's syndrome.[29] Finally, we found an association between male sex and lymphoma in RA; this finding is consistent with current knowledge of lymphomas in the general population since men have a 1.5-fold increased risk of developing lymphoma.[30] Furthermore, we found an association between male sex and RA activity, and male sex was no longer associated with the risk of lymphoma in multivariable analysis, which is probably due to a more important weight of disease activity in our study population.

Concerning the treatments, our results must be interpreted with caution because of the possible biases linked to the retrospective nature of the study. Except for two participants, all cases had received DMARDs before the diagnosis of lymphoma, and all the controls had received DMARDs during follow-up in the ESPOIR cohort. This study found no association between use of MTX and biologic agents and lymphoma, which supports the results of recent studies on this topic.[14 15]

More specifically, regarding TNF blockers, our results are consistent with those provided by Wolfe *et al* in a longitudinal study, which did not show an increased incidence of lymphoma in 19 591 patients with RA over 89 710 person-years of follow-up (p=0.87).[31] We found a numerically higher use of rituximab in cases versus controls but without reaching the threshold of significance. A direct pro-lymphoma effect of rituximab is more than unlikely. This result is probably due to an indication bias: patients considered at risk of lymphoma (because of the presence of a monoclonal component or lymphadenopathies) and patients with more advanced disease (because rituximab is recommended as a second-line biologic agent) were probably likely to receive this treatment. The association between the occurrence of lymphoma and treatment with hydroxychloroquine, sulfasalazine or 'ancient' RA treatments (such as gold salts) was more unexpected. Indeed, to date, no study has found such an association. This result probably reflects that cases had an RA diagnosis before controls (1998 vs 2004), with less efficient treatment available at that time and more frequent use of csDMARDs.[32 33] This hypothesis is supported by the multivariable analysis, in which the association between lymphoma and treatments was not significant after adjusting on sex, autoantibodies, erosions and DAS28 (table 5), and by the sensitivity analysis showing no more impact of treatment when focusing on the most recent cases (online supplemental table S1). Nevertheless, the conclusions of the sensitivity analysis must be taken with caution given the small number of analysed participants. Of note, the association between Janus kinase inhibitor treatment and lymphoma could not be assessed in the present work because these treatments were not available at the time of the study.

Table 4 Univariate analysis of the association between RA treatments and probability of B-cell NHL or Hodgkin's lymphoma

	Cases (n=54)	Controls (n=108)	OR (95% CI)	P value
Glucocorticoids	35 (64.8)	78 (72.2)	1.0 (0.5 to 2.3)	0.93
Methotrexate	45 (83.3)	97 (89.8)	1.0 (0.3 to 3.4)	0.97
Hydroxychloroquine	20 (37.0)	19 (17.6)	**3.1 (1.5 to 6.7)**	**0.002**
Sulfasalazine	19 (35.2)	19 (17.6)	**3.1 (1.4 to 6.6)**	**0.003**
Leflunomide	9 (16.7)	22 (20.4)	0.9 (0.4 to 2.1)	0.81
Other	8 (16.7)	6 (6.5)	**3.0 (1.0 to 9.0)**	**0.05**
Gold salts	*3 (5.6)*	*3 (2.8)*	*–*	*–*
Tiopronin	*3 (5.6)*	*3 (2.8)*	*–*	*–*
D-Penicillamine	*2 (3.7)*	*0 (0.0)*	*–*	*–*
TNF blockers	*21 (38.9)*	*38 (35.2)*	*1.1 (0.6 to 2.2)*	*0.75*
Adalimumab	*7 (13.0)*	*21 (19.4)*	*0.6 (0.2 to 1.5)*	*0.30*
Certolizumab	*1 (1.9)*	*3 (2.8)*	*0.7 (0.1 to 5.3)*	*1.00*
Etanercept	*13 (24.1)*	*17 (15.7)*	*1.7 (0.7 to 3.8)*	*0.19*
Golimumab	*0 (0.0)*	*4 (3.7)*	*–*	*0.30*
Infliximab	*7 (13.0)*	*25 (23.2)*	*0.6 (0.2 to 1.3)*	*0.21*
Rituximab	6 (11.1)	1 (2.8)	4.3 (1.0 to 21.4)	0.06
Abatacept	3 (5.6)	5 (4.6)	1.2 (0.2 to 5.2)	0.71
Tocilizumab	5 (9.3)	4 (3.7)	2.1 (0.5 to 9.3)	0.44
Anakinra	1 (1.9)	1 (0.9)	2.0 (0.2 to 159.7)	0.99
Lines of bDMARDs				0.58
0	*26 (48.2)*	*70 (64.8)*	*Reference*	*–*
1	*12 (22.2)*	*23 (21.3)*	*1.4 (0.6 to 3.2)*	*–*
2	*4 (7.4)*	*9 (8.3)*	*1.2 (0.3 to 4.0)*	*–*
3	3 (5.6)	3 (2.8)	2.7 (0.5 to 15.4)	–
4	*2 (3.7)*	*2 (1.8)*	*2.7 (0.3 to 23.4)*	*–*
5	1 (1.9)	1 (0.9)	2.7 (0.1 to 69.8)	–

Data are n (%).
bDMARD, biologic disease-modifying anti-rheumatic drugs; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

Only two previous studies showed RA activity as a risk factor of lymphoma.[5 6] Here, we confirmed this assumption. However, measuring activity at a single time is an obvious limitation. Hence, our demonstration that severity of RA measured by radiographic assessment,

Table 5 Multivariable analysis of the association between RA treatments and risk of B-cell NHL or Hodgkin's lymphoma, adjusting for sex, autoantibodies, erosions and DAS28

	OR (95% CI)
Hydroxychloroquine	3.48 (0.69 to 19.19)
Sulfasalazine	1.32 (0.26 to 6.49)
Male sex	3.13 (1.00 to 10.56)
RF or ACPA positivity	1.67 (0.39 to 9,10)
Erosion on radiographs at the time of matching	9.87 (3.51 to 31.49)
DAS28 at the time of matching	2.09 (1.41 to 3.38)

ACPA, anti-citrullinated peptide antibodies; DAS28, disease activity score in 28 joints; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis; RF, rheumatoid factor.

which well reflects long-term disease activity, is associated with risk of lymphoma may have clinical implications, such as a closer surveillance of these patients with structural damage.

In conclusion, this national multicentre case–control study, comparing 54 cases of lymphoma complicating RA with 108 controls, confirms the data in the literature regarding the characteristics of these lymphomas. It also confirms the role of disease activity and provides reassuring information regarding MTX and biologic agent safety in RA. In addition, this study shows an association between lymphoma and RA severity (erosions) and raises the hypothesis of the role of autoimmunity in lymphomagenesis, given that ACPA and RF positivity was significantly associated with lymphoma occurrence on univariate analysis. A precise identification of the factors involved in B-cell activation is a challenge in the search for new therapeutic targets, both in the field of autoimmunity and oncohematology.

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