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## EXTENDED REPORT

## Spectrum of lymphomas across different drug treatment groups in rheumatoid arthritis: a European registries collaborative project

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**ABSTRACT**

**Background** Lymphomas comprise a heterogeneous group of malignant diseases with highly variable prognosis. Rheumatoid arthritis (RA) is associated with a twofold increased risk of both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). It is unknown whether treatment with biologic disease-modifying antirheumatic drugs (bDMARDs) affect the risk of specific lymphoma subtypes.

**Methods** Patients never exposed to (bionative) or ever treated with bDMARDs from 12 European biologic registers were followed prospectively for the occurrence of first ever histologically confirmed lymphoma. Patients were considered exposed to a bDMARD after having received the first dose. Lymphomas were attributed to the most recently received bDMARD.

**Results** Among 124 997 patients (mean age 59 years; 73.7% female), 533 lymphomas were reported. Of these, 9.5% were HL, 83.8% B-cell NHL and 6.8% T-cell NHL. No cases of hepatosplenic T-cell lymphoma were observed. Diffuse large B-cell lymphoma (DLBCL) was the most frequent B-cell NHL subtype (55.8% of all B-cell NHLs). The subtype distributions were similar between bionative patients and those treated with tumour necrosis factor inhibitors (TNFi). For other bDMARDs, the numbers of cases were too small to draw any conclusions. Patients with RA developed more DLBCLs and less chronic lymphocytic leukaemia compared with the general population.

**Conclusion** This large collaborative analysis of European registries has successfully collated subtype information on 533 lymphomas. While the subtype distribution differs between RA and the general population, there was no evidence of any modification of the distribution of lymphoma subtypes in patients with RA treated with TNFi compared with bionative patients.

**INTRODUCTION**

Malignant lymphomas ('lymphomas') comprise a heterogeneous group of malignant diseases with presumably distinct aetiologies. Whereas the 5-year overall survival across all lymphomas is approximately 60%, there is great variation in survival depending on the lymphoma subtype, ranging from life expectancy comparable to the general population in nodular lymphocyte predominant Hodgkin's

lymphoma (HL) to 5-year survival of <40% for T-cell lymphomas.<sup>1</sup> Furthermore, clinical characteristics and therapy approaches vary to a great extent according to subtype. The age-standardised incidence rate (IR) in Europe of approximately 25/100 000<sup>2</sup> makes lymphoma one of the 10 most common cancer types in the general population. There are significant gender and age-dependent differences, with men having higher IRs in most subtypes and being diagnosed at younger ages.<sup>1</sup>

In rheumatoid arthritis (RA) the overall incidence of lymphoma is approximately doubled compared with that in the general population.<sup>3-9</sup> The association between RA disease activity and lymphoma risk is considered one reason for this increased risk.<sup>10</sup>

Evidence that chronic immune stimulation/chronic inflammation has a pathogenic effect in lymphomagenesis comes from the publication by Baecklund *et al.*<sup>10</sup> This study described an 'excess' risk strongly linked to the cumulative activity of the disease, especially for diffuse large B-cell lymphoma (DLBCL), the most common type of aggressive B-cell lymphomas.<sup>10</sup> Moreover, an association of methotrexate (MTX) treatment with Epstein-Barr virus (EBV)-positive lymphoproliferative disorders has been described.<sup>11</sup> Furthermore, a possible association between the use of tumour necrosis factor inhibitors (TNFi) and a rare but prognostically unfavourable hepatosplenic subtype of T-cell lymphoma has been reported.<sup>12</sup>

A number of European and other rheumatology registers have reported on the overall risk of lymphoma in patients with RA treated or not with TNFi<sup>5 13 14</sup> and did not find a further risk increase related to the treatment. However, the influence of TNFi is a matter of debate as recent reports from Asia and French data on Crohn's disease have shown a higher lymphoma risk in TNFi-treated patients.<sup>15-17</sup>

The notion that RA disease activity may be a strong risk determinant suggests that the overall lymphoma risk in TNFi-treated RA compared with the general population may represent a composite wherein a decreased risk for a disease-related lymphoma subset may be replaced by an increased risk for a treatment-related subtype. However, there is no definitive evidence for any influence of



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RA treatment on subtype distribution. In contrast to estimations of overall lymphoma risk in RA, which can be accomplished in individual registers, any analysis of subtype distribution requires large data sets and hence an international collaboration of RA registers.

The main aim of this collaborative analysis was, therefore, to explore whether there might be a switch in the subtype distribution of lymphomas in RA linked to specific antirheumatic treatments; if so, the finding would support the above-mentioned 'exchange of risks.' To this end, patients with RA never exposed to bDMARDs (bionative) were compared with patients with RA treated with bDMARDs, mainly TNFi, with respect to lymphoma subtypes across several European RA registries. To place the RA results into context, a second rationale of the study was to analyse the size and direction of any shift in the spectrum of lymphoma subtypes in patients with RA compared with the general population.

## PATIENTS AND METHODS

### Participating registers

Twelve European biologic registers from nine countries participated in this collaborative project of the European League Against Rheumatism (EULAR) Registers and Observational Drug Studies (RODS) Study Group: the French biologics register 'autoimmunity and rituximab' (AIR),<sup>18</sup> the Swedish ARTIS linkage of the Swedish Rheumatology Quality Register (SRQ) to other nationwide registers,<sup>13</sup> the Czech biologics register ATTRA,<sup>19</sup> the Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas (BIOBADASER),<sup>20</sup> the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA),<sup>5</sup> the Danish Rheumatologic database (DANBIO),<sup>21</sup> the Italian biologics register (GISEA),<sup>22</sup> the French biologics register 'Orencia and RA' (ORA),<sup>18</sup> the German biologics register 'Rheumatoid arthritis observation of biologic therapy' (RABBIT),<sup>23</sup> the French Research Axed on Tolerance of biOtherapies (RATIO),<sup>24</sup> the French Register Tocilizumab and RA (REGATE), and the Portuguese rheumatic diseases register (Reuma.pt).<sup>25</sup> To participate, registers were required to have at least one lymphoma reported and consequently several other European biologic registers were not able to contribute.

### Patients

Patients were required to have physician-diagnosed RA and to be prospectively followed up in one of the participating European RA registers. Patients with a history of lymphoma prior to registration were excluded. Patients diagnosed with a histology-confirmed lymphoma after study registration were included in the analysis. These patients were stratified according to their exposure status as follows: (1) bionative group: patients who were bionative at the diagnosis of the lymphoma; and (2) patients who were not bionative at the diagnosis of the lymphoma were stratified into four groups according to the biologic disease-modifying antirheumatic drug (bDMARD) they had received most recently prior to the development of the lymphoma: TNFi, rituximab, tocilizumab or abatacept.

### Outcome

The primary endpoint was the spectrum of lymphoma subtypes. The definition of lymphoma included HL and non-Hodgkin's lymphoma (NHL), but not plasma cell neoplasias. The subtypes were defined according to the pathology reports. The WHO 2008 classification of lymphomas was used to classify the respective subtype of lymphoma.<sup>26</sup> Crude IRs were also calculated.

Three registries received reports of histologically confirmed lymphoma through linkage of all participants to their national cancer registry: DANBIO, ARTIS and BSRBR-RA. The remaining registers (as well as BSRBR-RA) received reports of lymphoma from the patient's rheumatologist. For BSRBR-RA, histologically confirmed lymphomas were included if reported from either record linkage or rheumatologist.

### Statistical analysis

The spectrum of lymphoma subtypes was compared between RA cohorts in two steps. In the first step, the portion of HL and NHL classified into B-cell lymphoma (B-NHL) and T-cell lymphoma (T-NHL) was compared by  $\chi^2$  test and exact multinomial 95% CIs. HL, B-NHL and T-NHL with incomplete subtype information were included in this first step, whereas lymphomas not otherwise specified were excluded.

To describe the consistency of the findings, the results of analyses based on registers with at least 30 lymphomas each in the bionative cohort and the biologic-treated cohort are shown separately. In the second step, the subtype distributions of B-NHL were compared. In this comparison, B-NHLs with missing further subtype specification were excluded.

To compare the spectra of lymphomas observed within the RA cohorts with the spectrum of lymphoma subtypes in the general population, data from the HAEMACARE project were used.<sup>2</sup> HAEMACARE is a European cancer register-based project intended to improve the standardisation and availability of population-based data on haematological malignancies in Europe. It covers approximately 30% of the European population. Forty-eight cancer registers, operating in 20 countries, had incidence data for at least one of the predefined study years (2000–2002) and were hence included in the HAEMACARE analysis.<sup>2</sup>

To use these data for the comparison with the RA cohorts, we had to consider that the spectrum of lymphoma subtypes, especially the portion of HL versus NHL, depends on the underlying age distribution of the population being investigated. In the general population, approximately 50% of HL cases, but only 10% of NHL cases, are diagnosed in subjects aged 45 or below. In the HAEMACARE cohort, the percentage of subjects with age  $\leq 45$  years was clearly higher (55%) than that in our RA cohorts (16%). Therefore, a lower proportion of incident HL cases are expected in our cohorts. For that reason, we used direct standardisation methods and calculated the expected numbers of HL, B-NHL and T-NHL in a general population in which the age group  $\leq 45$  years has the same proportion as in our sample. These expected numbers were used to calculate percentages of the corresponding subtypes and were compared with those observed in the RA cohorts. No adjustment was made when the spectra of B-cell lymphoma were compared.

## RESULTS

Baseline characteristics of more than 120 000 patients with RA included in the analysis are shown in [table 1](#). In total, 533 lymphoma cases were identified. Since patient-years (pyrs) were not available in the RATIO and GISEA registries, we excluded the 27 lymphoma cases from RATIO and the 12 cases from GISEA in the calculation of the IR. A total of 494 lymphoma cases were reported in 584 236 pyrs in the remaining registers, corresponding to an overall crude IR of 85 per 100 000 pyrs (95% CI 77 to 92). The crude IR was similar between bionative and TNFi-treated patients with RA, whereas a lower incidence was reported in patients exposed to rituximab ([table 1](#)).

**Table 1** Baseline characteristics and crude incidence rate of lymphomas among biologic-naïve, TNFi, rituximab, tocilizumab or abatacept-treated patients with RA

	Bionai�ve	TNFi	Rituximab	Tocilizumab	Abatacept	Total
No. of patients	71 088	47 864*	9094	2029	1708*	124 997*
Follow-up time (pyrs)	322 167	242 260*	29810	2827	3352*	584 236*
Female (%)	72.1	74.8	79.0	80.1	78.0	73.7
Age mean (mean range)	61.1 (57–62)	55.0 (50–57)	57.9 (58–58)	55.9 (55–57)	57.5 (56–58)	58.5 (50–62)
No. of lymphomas	288	230	6	6	3	533
Incidence per 100 000 pyrs (95% CI)	89 (79–100)	81 (70–94)	20 (7–44)	177 (57–413)	60 (7–216)	85 (77–92)

\*Because of the type of the register these data are missing from RATIO and GISEA, 38 incident TNFi-exposed lymphoma cases (RATIO: 27, GISEA: 11) and one abatacept-exposed patient (GISEA) were for that reason excluded from the calculation of the incidence rate. GISEA, Italian Group for the Study of Early Arthritis; pyrs, patient-years; RA, rheumatoid arthritis; RATIO, French Research Axed on Tolerance of biOtherapies; TNFi, tumour necrosis factor inhibitor.

### Spectrum of lymphoma subtypes in patients with RA

The spectrum of lymphoma subtypes was analysed in multiple steps, corresponding to progressively more detailed classifications (tables 2 and 3).

To compare possible influences of the treatment on the subtype distribution of lymphomas we compared patients with RA by treatment groups. There were no significant differences in the distribution of HL versus B-NHL versus T-NHL between bionai ve patients and TNFi-treated patients (table 2). Similar results were found in each of two biologic registers (ARTIS and BSRBR-RA) with more than 30 lymphomas in both the bionai ve and TNFi groups, as well as in the subgroup of the remaining registers (table 2). Results of the remaining registers are provided in online supplementary table S1.

B-NHL cases were further stratified by subtype (table 3). The most frequent subtype in patients with RA was DLBCL, followed by follicular lymphoma and chronic lymphocytic leukaemia (CLL). No significant difference in B-NHL subtypes was observed between bionai ve and TNFi-treated patients (table 3).

The small numbers of HL and T-NHL cases did not allow further subtype analysis. No case of hepatosplenic T-cell lymphoma was detected.

### Comparison between RA and the general population

After standardisation for age, the distribution of HL versus B-NHL versus T-NHL observed in the RA group with 9.5% HL, 83.8% B-NHL and 6.8% T-NHL was similar to the values estimated from the general population data (10.1% HL, 82.6% B-NHL and 7.3% T-NHL, table 2).

Comparison within the B-NHL subtype, however, showed that DLBCL was significantly over-represented in subjects with RA compared with the general population (56% of all B-NHL in RA vs 30% in the general population; table 3); whereas CLL was significantly less frequent (16% of all B-NHL in RA vs 38% in the general population; table 3).

### DISCUSSION

The main aim of this collaborative study was to compare the distribution of lymphoma subtypes between TNFi-treated and bionai ve patients with RA. Interestingly, we did not find any significant differences in these subtype distributions, neither when comparing the broader groups of HL versus B-NHL versus T-NHL nor when comparing among the B-NHL subtypes. This is reassuring as it does not indicate any bidirectional effect

**Table 2** Lymphoma subtype distribution (Hodgkin's, B-cell and T-cell lymphomas) in patients with RA in treatment groups. ARTIS and BSRBR-RA, both with more than 30 lymphomas in the bionai ve and TNFi groups, are shown separately to describe the robustness of the results

	N total	Hodgkin's			B cell			T cell			NOS
		n	%	95% CI	n	%	95% CI	n	%	95% CI	N excluded
<b>Bionai�ve</b>											
ARTIS	197	13	6.6	3.3 to 11.8	174	88.3	82.1 to 93.0	10	5.1	2.6 to 8.8	19
BSRBR	30	5	16.7	5.1 to 37.0	22	73.3	50.9 to 88.6	3	10.0	1.8 to 29.1	4
Other	31	3	9.7	1.8 to 28.6	24	77.4	55.3 to 91.2	4	12.9	3.2 to 32.5	7
Total	258	21	8.1	4.7 to 12.9	220	85.3	79.3 to 90.0	17	6.6	3.6 to 11.2	30
<b>TNFi</b>											
ARTIS	52	6	11.5	4.0 to 26.2	40	76.9	61.1 to 88.3	6	11.5	4.0 to 26.2	7
BSRBR	77	11	14.3	6.5 to 25.9	63	81.8	69.4 to 90.6	3	3.9	0.7 to 12.1	10
Other	73	7	9.6	3.6 to 20.4	61	83.6	71.3 to 91.8	5	6.9	2.0 to 17.0	11
Total	202	24	11.9	7.0 to 18.3	164	81.2	74.1 to 87.3	14	6.9	3.3 to 12.3	28
Rituximab	6	0	0	0 to 50.0	5	83.3	32.9 to 99.7	1	16.7	0.3 to 67.2	0
Tocilizumab	5	0	0	0 to 56.0	5	100	44.0 to 100	0	0	0 to 56.0	1
Abatacept	3	0	0	0 to 74.4	3	100	25.6 to 100	0	0	0 to 74.4	0
RA total	474	45	9.5	6.6 to 13.2	397	83.8	79.3 to 87.6	32	6.8	4.3 to 10.0	59

BSRBR-RA, British Society for Rheumatology Biologics Register for Rheumatoid Arthritis; NOS, not otherwise specified; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

**Table 3** B-cell non-Hodgkin's lymphoma subtypes

	Chronic lymphocytic leukemia/ small cell lymphoma		Lymphoplasmacytic lymphoma (Waldenström macroglobulinaemia)		Marginal zone lymphoma		Follicular lymphoma		Mantle cell lymphoma		Diffuse large B-cell lymphoma		Burkitt lymphoma		
	N total	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Bionaive	184	28	15.2 (9.2 to 23.2)	4	2.2 (0.4 to 6.8)	1	0.5 (0 to 4.1)	33	17.9 (11.3 to 26.6)	5	2.7 (0.6 to 7.6)	113	61.4 (51.5 to 70.8)	0	0 (0 to 3.0)
TNF	151	26	17.2 (10.1 to 26.8)	6	4.0 (1.1 to 10.1)	10	6.6 (2.6 to 13.6)	34	22.5 (14.3 to 32.6)	0	0 (0 to 3.6)	75	49.7 (38.6 to 60.8)	0	0 (0 to 3.6)
RTX	5	1	20.0 (1.4 to 79.6)	1	20.0 (1.4 to 79.6)	0	0 (0 to 62.9)	1	20.0 (1.4 to 79.6)	0	0 (0 to 62.9)	2	40.0 (2.8 to 90.6)	0	0 (0 to 62.9)
TOC	5	2	40.0 (2.8 to 90.6)	0	0 (0 to 62.9)	0	0 (0 to 62.9)	0	0 (0 to 62.9)	0	0 (0 to 62.9)	3	60.0 (9.4 to 97.3)	0	0 (0 to 62.9)
ABA	3	0	0 (0 to 80.7)	0	0 (0 to 80.7)	0	0 (0 to 80.7)	2	66.7 (5.0 to 99.8)	0	0 (0 to 80.7)	1	33.3 (0.2 to 95.0)	0	0 (0 to 80.7)
RA total	348	57	16.4 (11.6 to 22.2)	11	3.2 (1.3 to 6.4)	11	3.2 (1.3 to 6.4)	70	20.1 (14.7 to 26.4)	5	1.4 (0.3 to 4.0)	194	55.8 (48.4 to 62.9)	0	0 (0 to 1.6)
General population	28747	11 019	38.3 (37.6 to 39.1)	1859	6.5 (6.1 to 6.9)	950	3.3 (3.0 to 3.6)	4881	17.0 (16.4 to 17.6)	1012	3.5 (3.2 to 3.8)	8538	29.7 (29.0 to 30.4)	488	1.7 (1.5 to 1.9)

ABA, abatacept; RA, rheumatoid arthritis; RTX, rituximab; TNFi, tumour necrosis factor inhibitor; TOC, tocilizumab.

of treatments by reducing the risk for some subtypes while increasing the risk of other subtypes. By contrast, the spectrum of lymphoma subtypes in our RA cohort showed significant differences from the spectrum described in the general population in Europe.<sup>2</sup> This has been suggested in previous studies,<sup>10 27</sup> and it is now confirmed by our analysis which is the largest to date. It is of great clinical importance as different lymphoma subtypes show different clinical behaviour, including wide heterogeneity in both prognosis and the preferred treatment approach.

The analysis of the spectrum of lymphoma subtypes is also of importance because there are hints that certain subtypes might be associated with certain therapies, for example, very rare cases of EBV-associated lymphoproliferative disease with MTX<sup>11</sup> and hepatosplenic T-cell lymphomas with TNFi.<sup>12</sup> Hepatosplenic T-cell lymphoma is a rare subtype with a very unfavourable prognosis and poor response to currently available treatment options. It occurs more often in chronically immunocompromised patients. There has been a safety concern regarding its occurrence in patients treated with TNFi, especially in young male patients with Crohn's disease.<sup>12</sup> However, a very thorough analysis of all T-cell lymphoma cases reported to the Food and Drug Administration between 2003 and 2010 suggested an increased T-cell NHL risk from TNFi use in combination with thiopurines but not from TNFi alone.<sup>28</sup> We did not find any cases of hepatosplenic T-cell NHL in our RA patient cohorts in over 240 000 pyrs of follow-up in patients with RA exposed to TNFi, in 320 000 bionaive pyrs or in the 36 000 pyrs in patients exposed to rituximab, abatacept or tocilizumab. Whether there were cases hidden among the group of 12 'T-cell NHL not otherwise specified,' of which five cases were in the TNFi group, remains speculative.

In a recent Swedish cohort, an increased risk of HL in patients with RA compared with the general population and compared with previously reported RA cohorts has been described.<sup>6</sup> There is a strong association between chronic inflammation and development of HL.<sup>6 29</sup> In our analysis, there was a slight numerical but not statistically significant increase in the proportion of HLs between bionaive and TNFi-treated patients.

The development of lymphomas can occur over a prolonged period of time, with several months or years elapsing between the onset of lymphomagenesis and diagnosis. Therefore, clinical trials with their short follow-up times are not an appropriate method of studying these malignancies, whereas registers provide a unique opportunity to do so. In addition to the large sample size of 533 lymphoma cases, the largest published RA-lymphoma cohort to date, the strength of our study is the usage of clearly stated definitions for the subtypes of lymphomas. All registers used the same template to define subtypes based on the WHO 2008 classification.<sup>30</sup> Ideally, central pathological review of lymphoma specimens would have been preferable to standardise the lymphoma subtype classification; however, for feasibility reasons, this was not possible.

Another strength is the long follow-up time for individual patients, which is the prerequisite for analysing these safety events. Thanks to the use of unselected patients without any exclusion criteria we are confident that our results are representative of patients with RA from across Europe.

Despite the huge data set of more than 120 000 patients we were not able to analyse all different RA treatments separately for subtype distribution due to small numbers. For example, only six, six and three lymphomas occurred in patients treated with rituximab, tocilizumab and abatacept, respectively, at lymphoma diagnosis. Another limitation is the fact that the bionaive patients are older than the bDMARD group (mean age 61

vs 55). Since age is an important factor in lymphomagenesis, the comparison between the treatment groups might be affected by this age difference.

Due to feasibility reasons, the patients were grouped into treatment groups according to the bDMARD that they have received most recently before the lymphoma diagnosis. A potential limitation is that we cannot exclude an influence of bDMARDs used prior to the last one. Furthermore, we could not analyse any potential influence of additional therapies with MTX or other conventional synthetic DMARDs.

The attribution of rare events such as lymphoma in RA to the respective RA treatment is complex. First, there is an increased lymphoma risk in patients with RA compared with the general population.<sup>3,4,31</sup> Second, the disease activity of RA has been identified as being of utmost importance for the development of lymphoma.<sup>10</sup> However, disease activity changes over time and is in itself dependent on the RA treatment. In addition, disease activity is one of the strongest factors in the treatment decision; therefore, there is a considerable confounding by indication when analysing this context. Hence, the bionative patients are different from the bDMARD-treated patients, since bDMARDs are used in those patients with more severe disease. It is therefore reassuring that in the bDMARD group with an even higher a priori lymphoma risk due to higher cumulative disease activity the risk is not higher than in the bionative patients.

We were confronted with other limitations typical for collaborative studies on register data, namely that collating data from different registers does not alter the quality of data from each register. We therefore depended on the validity of each subcohort. The impact of a possible heterogeneity in the results of the registers was partly examined in a descriptive manner by showing results of the two largest registers ARTIS and BSRBR separately. Separate results of all registers are furthermore shown in online supplementary table S1.

## CONCLUSION

The evidence is growing that the risk of lymphoma in RA is more dependent on RA itself and especially the disease activity than on the RA treatment.<sup>5,13</sup> Furthermore, our results are reassuring as the spectrum of lymphoma subtypes seems not to be altered by TNFi.

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