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Original article

The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis

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Abstract

Objective. To explore the influence of TNF inhibitor (TNFi) therapy and rituximab (RTX) upon the incidence of cancer in patients with RA and prior malignancy.

Methods. The study population comprised RA subjects with a prior malignancy reported to the UK national cancer registers, recruited to the British Society for Rheumatology Biologics Register from 2001 to 2013. We compared rates of first incident malignancy in a TNFi cohort, RTX cohort and synthetic DMARDs (sDMARD) cohort.

Results. We identified 425 patients with a prior malignancy from 18 000 RA patients in the study. Of these, 101 patients developed a new malignancy. The rates of incident malignancy were 33.3 events/1000 person-years (py) in the TNFi cohort, 24.7 events/1000 py in the RTX cohort and 53.8 events/1000 py in the sDMARD cohort. The age- and gender-adjusted hazard ratio was 0.55 (95% CI: 0.35, 0.86) for the TNFi cohort and 0.43 (95% CI: 0.10, 1.80) for the RTX cohort in comparison with the sDMARDs cohort. The 17.0% of patients in the sDMARDs cohort had a recurrence of the same cancer in comparison with the 12.8% and the 4.3% in the TNFi and RTX cohorts, respectively.

Conclusions. Although numbers are still low, it seems that patients with RA and prior malignancy selected to receive either a TNFi or RTX in the UK do not have an increased risk of future incident malignancy.

Key words: rheumatoid arthritis, cancer, anti-TNF, rituximab, cohort study

Rheumatology key messages

- Patients with prior malignancy selected to receive biologics do not have an increased risk of incident malignancy.
- The time between past cancer and first biologic was shorter among rituximab than TNFi patients.
- It remains unknown whether biologics can be used safely in all patients with prior malignancy.

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Introduction

RA is characterized by chronic inflammation. A substantial body of evidence supports the conclusion that chronic inflammation can predispose an individual to cancer. Chronic exposure to inflammatory mediators leads to increased cell proliferation, mutagenesis, oncogene activation and angiogenesis. The longer the inflammation persists, the higher the risk of associated carcinogenesis [1]. Data from several studies have suggested that the relative risk of certain types of malignancy such as lymphoma, leukaemia and lung cancer is increased in patients with RA [2, 3]. Factors such as disease activity and severity, and smoking have been recognized to increase the incidence of malignancies in patients with RA [3]. The effects of RA treatment on this risk remain less clear. Synthetic DMARDs (sDMARDs), such as MTX and AZA, have been linked to an increased risk of lymphoma whereas other studies have not found increased rates of cancer in sDMARD-treated patients [4].

TNF is one of the cytokines involved in the immunosurveillance of tumours and its inhibition may theoretically increase the risk of either tumour development or increased growth rate or malignant potential of established tumours. Recent publications studying the risk associated with TNF inhibitor (TNFi) have also not identified an increased risk of cancer overall [5–7], although there have been reports of increases in certain skin cancers (melanoma) [8, 9].

The majority of these meta-analyses and observational studies of cancer risk have been undertaken among patients without a history of pre-existing cancer, and therefore cannot necessarily be extrapolated to patients with this history prior to initiation of TNFi or other biologic therapies. This has been addressed in part by two publications, which have looked at the risk associated with TNFi therapy compared with sDMARD therapy. An analysis from the British Society for Rheumatology Biologics Register (BSRBR)-RA [10] showed that the rate of incident malignancy (IM) in patients with RA and prior malignancy who receive an TNFi was not increased in comparison with patients receiving sDMARDs after an average of 3 years follow-up. In this analysis, the age- and sex-adjusted incidence rate ratio was 0.58 (95% CI: 0.23, 1.43) for the TNFi-treated cohort compared with the sDMARD cohort. No significant association was also found in the German RABBIT registry (German acronym for Rheumatoid Arthritis – Observation of Biologic Therapy) [11] with an incidence rate ratio of 1.4 (95% CI: 0.5, 5.5) for the TNFi *vs* sDMARDS. Despite these reassuring results, both of these studies were small and only studied cancer risk over the short term (2–3 years). Given the latency of cancer, uncertainty about the use of TNFi in this situation remains unclear.

Rituximab (RTX) was licensed for RA in 2006 in the UK for use in TNFi inadequate responders. It had already been licensed as a successful treatment for B cell lymphoma [12]. As such, there is generally less concern about using this agent in patients with a history of cancer. The British Society for Rheumatology (BSR) guidelines for RTX did not include a warning regarding patients with past cancer, and therefore RTX as first-line biologic treatment outside of current licensed indications may be considered by physicians in patients with this history. That said, data on the risk of non-lymphoma malignancy among patients receiving RTX remain sparse and often complicated by previous exposure to TNFi [13, 14]. The aims of this study, therefore, were to explore the influence of RTX on the incidence of cancer in patients with RA and a prior malignancy and to update our previous report on cancer incidence in RA patients with prior malignancy treated with a TNFi.

Methods

Patient population

Patients included in this study were participants in the BSRBR-RA, which is a large national prospective observational cohort established primarily to assess the long-term safety of exposure to biologic therapies in patients with RA. Full details of the BSRBR-RA methodology have been published previously [15]. In brief, the study commenced in 2001 with the goal to recruit and follow patients with RA starting biologic therapies and compare these to a group of patients with similar disease not receiving these drugs to see if there were any differences in drug safety. Recruitment to TNFi cohorts occurred between 2001 and 2008 and re-opened again in 2010 with the primary aim to recruit a contemporary comparison cohort for the newer biologic therapies licensed in the UK. Recruitment of patients starting RTX as a first biologic occurred between 2008 and 2011. A comparison cohort of biologic-naïve patients with active RA defined as DAS28 $>$ 4.2 was recruited in parallel. These patients had active disease at the time of recruitment despite current treatment with sDMARDs.

Ethical approval

Ethical approval for the BSRBR-RA was granted by the North West Multi-Centre Research Ethics Committee in December 2000. All patients provided written informed consent. No additional approval was required for this specific analysis.

Patient selection

All patients with RA registered with the BSRBR-RA who were commencing a TNFi or RTX as their first biologic were eligible for inclusion in this analysis. A third cohort of the patients from the BSRBR-RA who had never received biologic agents was used for comparison.

Identification of prior malignancy

Analysis was limited to patients with prior malignancy, defined as diagnosed prior to start of first biologic drug (for the anti-TNF and RTX cohorts) or study registration (for the sDMARD comparison group). At registration, all patients were linked to the UK Health and Social Care Service Information Centre (HSCIC), which collates mandatory data from the eight regional English cancer

registers, in addition to similar registers in Wales, Scotland and Northern Ireland on the diagnosis of all malignancies in the UK. This linkage provided details of all historic cancers, including date of diagnosis, type and anatomic site. Carcinoma-*in situ* and non-melanoma skin cancer were excluded, as capture of these malignancies is less complete. Where patients had >1 prior malignancy, the most recent malignancy was reported.

Capture of new malignancy diagnoses following recruitment

Follow-up data, including changes to therapy and occurrence of serious adverse events were captured from the rheumatology team (6-monthly for 3 years and then annually) and the patient (6-monthly for 3 years). In addition, the linkage to the UK HSCIC also provides details (date and ICD-10 code) on any new cancers diagnosed within the cohort, although there can be a considerable delay (around 18 months) [16] in reporting to the BSRBR-RA while validation procedures are undertaken.

Definition of IM

IMs were defined as malignancies diagnosed after the first dose of biologic therapy or after the study registration date for the sDMARD cohort. New primaries, local recurrence and metastases were all included as incident cancers. Carcinoma-*in situ* and non-melanoma skin cancer were excluded, as were benign cancers. Once cancers were reported from any source, i.e. patient or HSCIC report, clinicians were asked to provide further information for these events in order to understand if there was any relation to the prior cancer.

Statistical analysis

Follow-up time was calculated from the date of the first TNFi or RTX use for the biologic cohorts, or from the registration date for the comparison cohort, to 31 May 2013, first IM or the death date, whichever occurred first. Within the TNFi cohort, patients could switch between different TNFi. The biologic cohorts contributed person-years (py) of follow-up even if the biologic therapy was stopped, but only for the period of the patient being off any biologic therapy. The follow-up was then censored at the initiation of a second biologic with a different target. Malignancies were attributed to biologic therapy irrespective of drug discontinuation. Patients initially registered in the comparison cohort who subsequently received a TNFi or RTX contributed person-years to the comparison cohort up to the date that the biologic drug was started, and contributed subsequent follow-up to the biologic cohort.

Crude incidence rates were calculated as the number of first episodes of IM per 1000 py of follow-up with a 95% CI. Survival analyses, performed using a Cox proportional hazards model, were used to compare the rates of IM between cohorts, adjusted for age and sex. All analyses were conducted using Stata version 11 (StataCorp, College Station, TX, USA). We performed a sensitivity analysis censoring all follow-up at 5 years to compensate for the shorter follow-up of the RTX cohort.

Results

In total, 14 168 patients from the BSRBR-RA received a TNFi as their first biologic. Of the 4179 patients in the BSRBR-RA who ever received RTX, for this analysis we selected the 257 who received it as their first biologic as we aimed to explore the incidence of malignancies in patients receiving a first biologic. The comparison cohort consisted of 3787 sDMARD-treated patients. After linkage with the HSCIC, 425 patients with a prior history of malignancy were identified: 243 (1.7%) of the 14 168 in the TNFi cohort, 23 (8.9%) of the 257 in the RTX cohort and 159 (4.2%) in the comparison cohort. All subsequent analyses were restricted to these patients.

The TNFi cohort was younger than the other two cohorts and comprised proportionally more women. The sDMARD cohort had less severe disease (Table 1). All three groups were much older than the mean age previously reported in this cohort [56 (12)] [17]. Sites of most recent prior malignancy were similar between cohorts with >80% of patients in the three cohorts having had a solid cancer, with the remainder divided into lymphoproliferative malignancies and melanomas. No patient with prior melanoma received RTX. Proportionally more prior malignancies were diagnosed >10 years before registration in the TNFi cohort (56.8%) compared with the RTX cohort (17.4%) and the comparison (37.1%) cohort.

The total follow-up time was 855 py for the sDMARD cohort, 1591 py for the TNFi cohort and 81 py for the RTX cohort. Patients in the RTX cohort contributed a median follow-up time of 3.9 [interquartile range (IQR): 3.3–4.6] years compared with 6.8 (IQR: 3.5–8.8) for patients in the TNFi cohort and 6.6 (IQR: 4.4–7.8) for patients in the sDMARD cohort.

Overall, there were 101 IMs: 46 in the sDMARD cohort, 53 in the TNFi cohort and 2 in the RTX cohort (Table 2). The unadjusted hazard ratio (HR) was 0.51 (95% CI: 0.33, 0.79) for the TNFi-treated patients and 0.45 (95% CI: 0.11, 1.87) for the RTX-treated patients compared with the sDMARD cohort.

A sensitivity analysis censored at 5 years of follow-up (total time sDMARD: 609 py, TNFi 971 py, RTX 81 py) identified 64 IMs: 36 in the sDMARD cohort, 26 in the TNFi cohort and 2 in the RTX cohort (Table 2). The unadjusted HR was 0.45 (95% CI: 0.27, 0.75) for the TNFi-treated patients and 0.42 (95% CI: 0.10, 1.75) for the RTX-treated patients compared with the sDMARD cohort, which did not differ substantially after adjustment for age and gender.

Since smoking is a risk factor for many types of cancer, a further adjustment analysis including the smoking status was done to check its influence in the recurrence or diagnosis of new cancers. This adjustment did not significantly change the HR for any of the biologic cohorts (Table 2).

Supplementary Table S1, available at *Rheumatology* Online, shows the distribution of anatomical sites of prior and incident malignancies. The most frequent prior malignancy in the three cohorts was the breast cancer followed by melanoma in the sDMARD and TNFi cohorts and by lymphoma in the RTX cohort. In the sensitivity

Table 1 Baseline patient characteristics

Characteristic	sDMARD (n = 159)	TNFi (n = 243)	Rituximab (n = 23)	P-value
Age, mean (S.D.), years	66.1 (10.0)	62.7 (9.5)	67.3 (9.9)	0.0005
Sex, female, n (%)	118 (74.2)	199 (81.9)	15 (65.2)	0.058
DAS28, mean (S.D.)	5.2 (1.2)	6.6 (1.1)	6.5 (0)	0.0001
HAQ score, mean (S.D.)	1.7 (0.7)	2.2 (0.5)	2.1 (0.3)	0.0001
Disease duration, median (IQR), years	8 (3–18)	12 (6–18)	14 (5–31)	0.0047
Prior sDMARDs, median (IQR)	2 (2–4)	4 (3–6)	3 (2–5)	0.0001
RF+, n (%)	100 (62.9)	156 (64.2)	17 (73.9)	0.588
Steroid use at baseline, n (%)	50 (31.5)	123 (50.6)	13 (56.5)	<0.001
Smoking, n (%)				0.050
Current	32 (20.4)	48 (19.9)	4 (17.4)	
Ex	78 (49.7)	87 (36.1)	11 (47.8)	
Never	47 (29.9)	106 (44.0)	8 (34.8)	
Entry year, n (%)				<0.001
Pre-2003	0	30 (12.4)	0	
2003	10 (6.3)	68 (28.0)	0	
2004	30 (18.9)	57 (23.5)	0	
2005	44 (27.7)	30 (12.4)	0	
2006 or after	75 (47.1)	58 (23.7)	23 (100)	
Prior malignancy, n (%)				0.014
Solid	133 (83.7)	213 (87.7)	19 (82.6)	
Lymphoproliferative	11 (6.9)	7 (2.9)	4 (17.4)	
Melanoma	15 (9.4)	23 (9.4)	0 (0)	
Time from most recent prior malignancy to registration				
Median (IQR), years	7.9 (3.0–13.3)	11.5 (5.8–17.6)	5.4 (3.0–9.2)	0.0001
>10 years preregistration, n (%)	59 (37.1)	138 (56.8)	4 (17.4)	<0.001

DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; sDMARDS, synthetic disease anti-rheumatic modifying drugs.

Table 2 Overall risk of new cancer

	Total follow-up			Censored at 5 years		
	DMARD (n = 159)	TNFi (n = 243)	Rituximab (n = 23)	DMARD (n = 159)	TNFi (n = 243)	Rituximab (n = 23)
Follow-up (py)	855	1591	81	609	971	81
Follow-up, median (IQR), years	6.6 (4.4–7.8)	6.8 (3.5–8.8)	3.9 (3.3–4.6)	5.0 (3.5–5.0)	5.0 (3.5–5.0)	3.9 (3.3–4.6)
Number of first IMs	46	53	2	36	26	2
Rate/1000 py (95% CI)	53.8 (39.4, 71.8)	33.3 (24.9, 43.6)	24.7 (3.0, 89.3)	59.1 (41.4, 81.9)	26.8 (17.5, 39.2)	24.7 (3.0, 89.3)
Unadjusted HR (95% CI)	Ref.	0.51 (0.33, 0.79)	0.45 (0.11, 1.97)	Ref.	0.45 (0.27, 0.75)	0.42 (0.10, 1.75)
Age and gender adjusted HR (95% CI)	Ref.	0.55 (0.35, 0.86)	0.43 (0.10, 1.80)	Ref.	0.47 (0.28, 0.80)	0.41 (0.10, 1.71)
Age, gender and smoking status adjusted HR (95% CI)	Ref.	0.56 (0.36, 0.88)	0.44 (0.11, 1.82)	Ref.	0.48 (0.28, 0.81)	0.41 (0.10, 1.71)

IM, incident malignancy.

analysis, 5% (13/243) of TNFi-treated patients had recurrence of the prior malignancy (either locally or metastases) compared with 4% (1/23) in the RTX cohort and 12% (19/159) in the sDMARD cohort.

Discussion

Despite biologics being used increasingly for the treatment of RA, their exact relationship with cancer still

remains unclear. The risk of cancer recurrence cannot be explored in trials either, as patients with a prior malignancy are systematically excluded. In this prospective observational cohort study, we have shown that in patients with RA and prior malignancy selected to receive a TNFi or RTX, the rate of first IM is not increased in comparison with patients receiving sDMARDs. Nevertheless, attending to the wide confidence interval of the HR in the RTX group, we cannot firmly rule out a clinically important increased or decreased risk of IM in patients receiving RTX.

The finding of a decreased rate of cancer incidence in patients with a prior malignancy receiving a TNFi in comparison with biologic-naïve patients is consistent with a previous report from the BSRBR-RA [10], although the present analysis extends the mean follow-up by 3 years. A cumulative incidence plot in our original publication suggested that the rate may accelerate with increasing duration of follow-up. Fortunately, we have observed that after a median follow-up of the 6.8 years, there has been no significant increase in the incidence of malignancies in TNFi-treated patients. In this analysis, the small number of each type of IM prevented us from analysing specific cancers risk.

A major threat to the validity of our results is the potential confounding due to the non-randomization of treatment. Patients' baseline characteristics were unbalanced between groups and some of these characteristics that are associated with cancer recurrence risk may have influenced treatment choices, particularly the choice to proceed with a biologic therapy. One of the most remarkable differences between cohorts was the proportion of patients with a history of prior cancer as well as the time from most recent prior malignancy to registration, which was much shorter for patients starting RTX as their first line biologic compared with both sDMARDs and TNFi. There were also differences in the site of previous cancer in those starting RTX, with a higher proportion of prior lymphoma. These differences may have led to an imbalance in the baseline risk of IM between the cohorts. Finally, many of the patients who started RTX did so in more recent years compared with those registered with the TNFi cohort. What is not known is whether those patients starting RTX would have also started a TNFi if RTX had not been available and therefore direct comparison of risk between the two biologic treatment cohorts should not be made.

Among RA patients, higher inflammatory activity is a major risk determinant of cancer, particularly lymphoma. On the other hand, no study has confirmed any treatment-related effect on cancer [18, 19]. In our study, there was also an imbalance in the disease activity measured by the DAS28 and the severity measured by the HAQ score between the groups. Patients treated with TNFi and RTX had significantly higher disease activity and disability than those only receiving sDMARDs. Although at first it would be expected that this imbalance increased the malignancy rate in the biologic-treated patients, it could also be hypothesized that the better control of the disease activity achieved by biologic therapies may cause the opposite effect. Details of disease activity and severity were not available at all follow-up visits in all patients to explore this further [20, 21].

Another possible difference between our cohorts is the cancer screening at registration. Because biologic-treated patients are registered with the BSRBR-RA at the initiation of the biologic therapy, it is presumed that those patients had some kind of cancer recurrence screening before they started receiving the biologic therapy. This may not be true for patients receiving sDMARD therapies. This may explain in part why a higher rate of recurrence of the same cancer was seen in the sDMARD cohort compared with the TNFi cohort. There may also have been prognostic factors associated with the prior cancer that led to a decision not to start a biologic in certain patients, details which were not captured in the BSRBR-RA.

One of the strengths of our cohort is its size and the length of the follow-up, being the largest and longest study to address this question to date. We also had assumed near complete capture of prior cancers (the one exception being if a cancer had been diagnosed and treated in another country) and incident cancers through linkage with the national cancer register and comprehensive physician and patient follow-up.

In conclusion, we have shown that after an average follow-up of 5 years, patients with RA and prior malignancy selected to receive treatment with either TNFi or RTX in the UK do not have an increased risk of recurrence or development of new IM. These results must be interpreted in the context of an observational study of routine clinical practice.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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