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ORIGINAL RESEARCH

Risk of malignancy in rheumatoid arthritis patients initiating biologics: an historical propensity score matched cohort study within the French nationwide healthcare database

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ABSTRACT

Objective To compare the risk of malignancy between patients with rheumatoid arthritis (RA) initiating their first biological disease-modifying antirheumatic drug (bDMARD) and those continuing conventional synthetic DMARDs (csDMARDs).

Methods Nine-year historical Propensity Score (PS) matched cohort study within the French national healthcare database (87% of the French population; ~57 million people), including adults RA without malignancy. Exposures started with the first use of any systemic treatment (csDMARDs and/or bDMARDs). Incident users of bDMARDs were matched on a dynamic PS to patients continuing csDMARDs. Their risk of malignancy was compared by Cox model.

Results From 1 January 2007 to 31 December 2014, 83 706 patients with RA started their first systemic treatment (63 837 remained on csDMARDs and 19 869 initiated a bDMARD during follow-up). After dynamic PS matching, 19 727 bDMARD initiators were compared with 19 727 RA remaining on csDMARDs. They did not statistically differ in risk of overall malignancies (HR 0.99 (95% CI 0.86 to 1.14)), solid cancer (HR 0.95 (95% CI 0.82 to 1.11)), nor lymphoma (HR 1.35 (95% CI 0.72 to 2.53)). Results were similar when bDMARDs were given as monotherapy or in association with csDMARDs. Analyses restricted to patients starting TNF inhibitor as first bDMARD compared with matched RA remaining on csDMARDs, provided similar results (HR for overall malignancy 1.03 (95% CI 0.88 to 1.21)). Sensitivity analyses, varying carry-over periods (up to 5 years) to define risk periods, provided similar results.

Conclusions In this historical cohort study within the French nationwide healthcare database, the risk of overall, solid or haematological malignancies did not significantly differ between patients with RA initiating bDMARD and those continuing csDMARDs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Biological disease-modifying antirheumatic drugs (bDMARDs) have considerably improved the prognosis of rheumatoid arthritis (RA).
⇒ Due to their mechanism of action, bDMARDs were suspected to increase the risk of malignancy.
⇒ Randomised controlled trials are underpowered to investigate this rare risk and previous observational studies have methodological pitfalls.

WHAT THIS STUDY ADDS

⇒ Among patients with RA included in the French national healthcare database (87% of the French population; ~57 million people), we run a propensity score matched cohort study using very stringent methodology to handle the risk of bias and analysed a large variety of malignancies.
⇒ No significant increased risk of overall malignancies, solid cancers, nor haematological malignancies, including lymphoma, was observed in patients initiating bDMARDs compared with those remaining on conventional synthetic DMARDs (csDMARDs).
⇒ Restricting the analysis to RA exposed patients initiating a first TNF inhibitor matched to unexposed patient with RA remaining on csDMARDs, provided similar results.

INTRODUCTION

The risk of malignancy in patients with rheumatoid arthritis (RA) is globally similar to that of the general population except for increased risk of lung cancer and lymphoma,[1–3] the former likely linked to smoking, and the latter to long-term activity of the disease.[4 5] Thus, acting by controlling disease activity, disease-modifying antirheumatic agents (DMARDs) might decrease the overall risk of lymphoma.[6] However, although biological DMARDs (bDMARDs) have considerably improved the prognosis of RA, they

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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Our study provided an important reassuring message for patients with RA and physicians treating them regarding the risk of malignancies associated with the use of bDMARDs.

⇒ Even in a national healthcare database (87% of the French population), some malignancies, such as lymphoma, remained rare events that deserve to be analysed in future studies including more recently treated patients.

have also been suspected to increase the risk of malignancy.[7]

Owing to their mechanism of action, antitumour necrosis factor alpha (TNF inhibitors) agents have been particularly suspected to facilitate cancer development. Following an alert on a possible increased risk of cancer in a meta-analysis of randomised controlled trials (RCTs) published in 2006, they have been contraindicated in case of recent cancer (<5 years).[8] This possible increased risk of cancer with TNF inhibitors was not confirmed by further meta-analyses of RCTs or registry data,[9–15] nor by the more recent updates from bDMARD registries worldwide.[16–21]

Nevertheless, many questions remain, among them the potential differential risk of lymphoma with TNF inhibitors according to their molecular structure (monoclonal antibodies or soluble receptor)[22 23] Effectively, specificities in their mechanism of action (same inhibition of soluble TNF but less inhibition of membrane TNF with the soluble receptor) were supposed to differentially impact the risk of different lymphoma subtypes.[24] Additionally, uncertainties remain regarding the risk of some specific cancers, particularly invasive melanoma,[23 25] that might be increased in northern countries,[26] and virus-related cancer such as cancer of the cervix[27–29] that can be triggered by immunosuppressants. Regarding other bDMARDs, studies are scarce and most of them are underpowered.[12 15 30]

RCTs are the best way to obtain an unbiased estimation of the efficacy of a treatment under 'ideal conditions'; however, due to their relatively short duration and small sample size, they are not designed to assess the potential risk of rare and/or long-term adverse events. In addition, they frequently exclude patients with significant comorbidities and high baseline risk. Therefore, observational cohort studies are useful to provide additional and complementary information regarding these risks in 'real-world' settings.[16 18 21 31 32] Nationwide healthcare databases may provide sufficient power to detect differences in risk of malignancy in an unselected population.[33] Nevertheless, such studies are prone to potential biases (particularly selection bias, indication bias, attrition bias, channelling bias, immortal time bias) inherent to their observational nature that are not always adequately handled.

The aim of this study was to compare the risk of malignancy in patients witn RA initiating a bDMARD and those continuing conventional synthetic DMARDs (csDMARDs) within the French nationwide health insurance claims database, using an incident user cohort with dynamic Propensity Score (PS) matching design to adequate handle methodological issues.

METHODS

Data source

The 'système national des données de santé' (SNDS) is the French nationwide healthcare database and contains individual claims and hospital discharge summary prospectively recorded since 2005 for every subject covered by French Health Insurance and pseudonymised. The general insurance plan covers both private and public sector employees, thus accounts for approximately 87% of the French population (~57 million people). The SNDS includes sociodemographic data, out-hospital health resource use including outpatient consultations and procedures, drugs and devices dispensation covered by the insurance, sick days, inpatient data and vital status. Inpatient data include discharge summaries including reason of admission and relevant patients' comorbidities described through International Classification of Diseases, 10th Revision (ICD-10) codes, procedures and highly expensive drugs dispensed during the stay (such as biologics). The SNDS also contained medical information on serious and costly long-term disabling diseases allowing 100% health insurance coverage based on the French Health insurance of 30 eligible chronic conditions (named 'ALD 30'), including malignancies, coded with ICD-10 with the date of disease onset.

Study design

We conducted a 9-year historical cohort study within the General Scheme of the (SNDS (see online supplemental file).[34 35] The period of inclusion was from 1 January 2007 to 31 December 2014 (online supplemental figure 1). The data extraction period was 1 January 2006 to 31 December 2015, for having a 1-year 'look-back' period and at least 1 year of follow-up.

Under optimal epidemiological conditions (new incident users of DMARDs with known exposures over time), we tested the hypothesis of an association between incident exposure to bDMARDs and risk of malignancies. Thus, to compare the risk of malignancy associated with initiating bDMARDs or continuing csDMARDs, we first identified all patients with RA ≥18 years old initiating their first csDMARD or bDMARD during the inclusion period (ie, did not receive any csDMARD or bDMARD during the 1-year look-back period). We excluded patients with history of malignancy. The 1-year look back period was used to define incident exposure (ie, exclude patients already exposed to systemic treatment), and exclude patients with history of malignancy. Patients initiating their first bDMARD were matched to patients continuing csDMARDs on a dynamic PS, time since initiation of the first DMARD at the time of matching, age at first DMARD initiation (<65 years or not) and gender.

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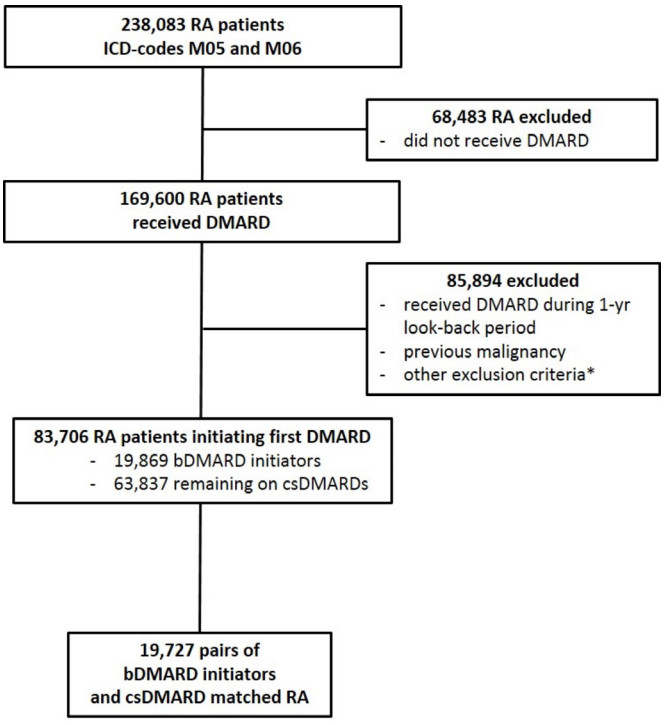

Figure 1 Flow chart. *Exclusion criteria were history of organ transplantation, HIV infection or malignancy. bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic agents; ICD, International Classification of Diseases; RA, rheumatoid arthritis.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

Study population

Adults (≥18 years old) with RA were identified from long-term disability status and/or hospital discharge summaries (main, related or an associated diagnosis) with ICD-10 codes M05 or M06.

The date of RA diagnosis was defined as the first occurrence of RA diagnosis in the database (ie, the earliest date between the first hospital discharge diagnosis of RA available and the date of declaration of long-term disability for RA).

To be included, RA adults had to be affiliated to the General Scheme of the French health insurance for more than 1 year, live in mainland France and have no history of organ transplantation, HIV infection or malignancy before the index date and initiate their first DMARD during the inclusion period.

Exposures

Exposures of interest were csDMARDs (including methotrexate, leflunomide, sulfasalazine, azathioprine, hydroxychloroquine) and/or or bDMARDs (including all TNF inhibitors: infliximab, adalimumab, etanercept, certolizumab and golimumab; rituximab; abatacept; tocilizumab; anakinra; ustekinumab). Among bDMARDs, TNF inhibitors being the most widely used first line therapy a separate analysis focused on this therapeutic class. The period covered by the last delivery/administration of each of the drugs are reported in online supplemental table 1.

Exposures were considered by therapeutic class and not by individual drug. Risk period for a therapeutic class, for example, bDMARDs, started from the first delivery (or inhospital administration) of any treatment of this class (first bDMARD), continued with the succession of different drugs of this class with no significant gap (ie, gap ≤90 days) and accounted for the period covered by the last delivery of each individual drug (online supplemental figure 2) and the lag and carry-over periods.

In the main analysis, the risk period was considered with a 90-day lag period after treatment initiation to avoid considering prevalent malignancies as attributable to the drug recently initiated and a 180-day carry-over period after the period covered by the last delivery administration. Sensitivity analyses varying duration of carry-over periods extended to 24 and 60 months were performed.

Outcomes: malignancies

Incident malignancies (all cancers except non-melanoma skin cancers (NMSCs)) were identified by the diagnostic algorithms developed by Ajrouche *et al* in the SNDS.[36 37]

The main outcome was any incident malignancy (excluding NMSCs). Secondary outcomes were any solid cancers (excluding NMSCs), the most frequent solid cancers separately (breast, prostate, lung, colorectal, liver, kidney, pancreatic cancers), invasive melanoma, invasive cancer of the cervix, haematological malignancies, lymphoma (and most frequent subtypes), and any other haematological malignancies. The ICD-10 codes used are reported in online supplemental table 2.

Covariates

PS methods were implemented to handle the non-randomised design (and thus potential indication bias). The following variables were considered to estimate PS: age at first DMARD initiation, year of the first RA code, year of the index date, number of previous DMARDs, Charlson's Comorbidity Index (version adapted to the SNDS),[38] smoking and/or alcohol-associated disorders (as proxies for heavy tobacco or alcohol consumption), number of hospitalisations for RA, cumulative corticosteroids dose and full health expense coverage for low income.

Statistical analyses

Descriptive statistics are reported as median (IQR) or number (%). To compare the risk of malignancy in patients initiating their first bDMARD to those

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Table 1 Characteristics of the bDMARD-exposed and csDMARD matched rheumatoid arthritis (RA) patient populations at the time of matching

	bDMARD-exposed RA N=**19 727**	csDMARD-matched RA N=**19 727**
Sex (women)	14 722 (74.63%)	14 722 (74.63%)
Age (years)	52.24 (42.19–61.13)	51.16 (40.94–60.72)
RA disease duration (years)	2.20 (1.08–5.15)	1.86 (0.77–4.85)
Comorbidities		
Hypertension	3349 (16.98%)	2951 (14.96%)
Diabetes	2438 (12.36%)	2261 (11.46%)
Cardiovascular disease	1169 (5.93%)	1273 (6.45%)
Smoking-related comorbidities	2504 (12.69%)	2629 (13.33%)
Alcohol-related comorbidities	409 (2.07%)	427 (2.16%)
Weighted Charlson's Comorbidity Index		
0	13 216 (66.99%)	13 280 (67.32%)
1–3	6361 (32.25%)	6302 (31.95%)
≥4	150 (0.76%)	145 (0.74%)
Full health expense coverage due to low income	1207 (6.12%)	1239 (6.28%)
RA therapeutic history		
No of hospital stays for RA in the previous year	0.18 (0.54)	0.12 (0.47)
No of csDMARDs received before matching		
0–1	14 617 (74.09%)	14 185 (71.91%)
2	3842 (19.48%)	4152 (21.05%)
≥3	1268 (6.43%)	1390 (7.05%)
Previous/ongoing csDMARDs		
Methotrexate	13 860 (70.26%)	15 844 (80.32%)
Leflunomide	3554 (18.02%)	3011 (15.26%)
Hydroxychloroquine	2340 (11.86%)	4797 (24.32%)
csDMARDs duration before matching (years)	0.80 (0.16–1.71)	0.96 (0.37–1.92)
Cumulative corticosteroids dose in the previous year (mg)	154.60 (175.14)	149.65 (177.12)
Cumulative corticosteroids dose from 1 January 2007 to matching (mg)	292.68 (393.18)	265.03 (358.55)

Data are number (%) or median (IQR), unless indicated.
bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic agents.

unexposed continuing csDMARDS, patients initiating a first bDMARD were matched with a 1:1 ratio to patients who did not initiate bDMARD at the time of matching, on a dynamic PS (with calliper of 0.20), time since the initiation of the first DMARD at the time of matching, age at first DMARD initiation (<65 years or not) and gender. For each pair of patients, follow-up for the analysis started from matching time (see online supplemental figure 3). The dynamic PS was constructed by using pooled logistic regression and was reassessed every 30 days. The risk period for a patient initiating a first bDMARD was the succession of all periods on bDMARDs for this patient, with no gap between them, taking into account the lag and carry-over periods. Likewise, for exposure to csDMARDs, the risk period was the succession of all periods on csDMARDs for this patient, with no gap between them or until bDMARD initiation, taking into account the lag and carry-over periods. In this later case, contribution of this patient to the unexposed period (ie, period on csDMARD) ended at the time of bDMARD initiation (taking into account the lag and carry-over periods), and the patient was then considered in the group of bDMARD initiators and matched to another patient remaining on csDMARD.

Patients contributed to this analysis until the earliest occurrence of the end of the risk period after matching, occurrence of malignancy, HIV infection, bone-marrow or organ transplantation, death from any cause, exit from the General Scheme of the French health insurance or the end of the observation period on 31 December 2015.

After dynamic PS matching, the risk of malignancy was compared between csDMARDs and bDMARDs by using a Cox proportional-hazards model, estimating HRs (HRs) and 95% CIs. The proportional hazard assumption was assessed by plotting the scaled Schoenfeld residuals against time. For the main outcome (overall malignancies) and the most frequent secondary outcomes (solid cancers, haematological

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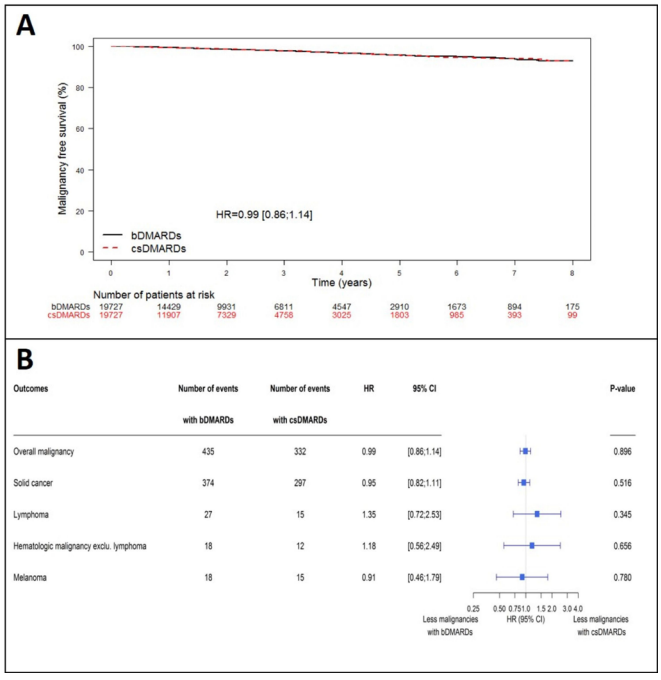

Figure 2 Comparison of the overall risk of malignancy and other major outcomes between patients with RA initiating bDMARD and matched patients continuing csDMARDs comparison of the risk of overall malignancy (A) and major outcomes (B) between csDMARDs and bDMARDs (time zero is time of matching). bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic agents; RA, rheumatoid arthritis.

malignancies and lymphomas), we also estimated the risk associated with exposure to bDMARDs as monotherapy or combined with a csDMARD versus csDMARD alone by introducing an interaction term in the model.

Since, TNF inhibitors are the most widely prescribed first line bDMARDs a separate analysis, using the same methodology with dynamic PS matching, comparing patients initiating TNF inhibitors as first bDMARD to patients continuing csDMARDs was also performed.

Also, since elderly patients have an increased risk of malignancy and lymphoma[39] and the matching was stratified on age (above 65 years old or not) and gender, subgroup analyses in men and women >65 years were performed for the main events of interest.

All analyses were performed with SAS V.9.4 (SAS Institute) and R V.4.0.0 (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org). Statistical significance was defined at p<0.05; all alternative hypotheses were two sided.

RESULTS

RA patient population

Between 2007 and 2015, 238 083 patients with RA were identified, including 169 600 received any DMARD during this period (figure 1). Considering the 90-day lag period and after excluding patients who had received a csDMARD or bDMARD in the 1-year look back period, 83 706 patients with RA initiated their first DMARD during the inclusion period. Among them, 63 837 received only csDMARDs and 19 869 initiated a bDMARD. Among the 83 706 DMARDs incident users, the median follow-up in the database since first DMARD initiation was 4.64 range (0.25–8.99) years.

Matched population

After dynamic PS matching, analyses were conducted on 19 727 patients in each group (table 1). Malignancy occurred in 332 patients continuing csDMARDs and 435 exposed to bDMARDs. The median risk-period duration after matching was 1.38 range (0.00–8.72) and 2.06 (0.00–8.74) years, with csDMARDs alone and bDMARDs, respectively.

Comparison of risk of malignancy between bDMARD initiators and patients continuing csDMARDs

The csDMARDs and bDMARDs groups did not differ in risk of overall malignancies (HR 0.99 (95% CI 0.86 to 1.14), figure 2 A), solid cancers (HR 0.95 (95% CI 0.82 to 1.11)), lymphomas (HR 1.35 (95% CI 0.72 to 2.53)) or other haematological malignancies (HR 1.18 (95% CI 0.56 to 2.49)) (table 2, figure 2 B). Results were similar when bDMARDs were given as monotherapy or associated with csDMARDs (table 3). Likewise, the groups did not significantly differ in the risk of organ-specific cancers (table 2). Of importance, for some cancers, the number of events was too small to drown any firm conclusion.

The analyses comparing patients initiating TNF inhibitors to those remaining on csDMARDs, provide similar results (table 4). The risk of overall malignancies (HR 1.03 (95% CI 0.88 to 1.21)), solid cancers (HR 1.08 (95% CI 0.91 to 1.28)) and lymphomas (HR 0.77 (95% CI 0.42 to 1.43)) did not differ between groups.

Sensitivity and subgroup analyses

Sensitivity analyses with a 90-day lag period and with any of the carry-over periods>180 days gave similar results (online supplemental eTables 3 and 4). The only differences were increased risk of haematological malignancies (HR 1.53 (95% CI 1.02 to 2.31), p=0.035) and a non-significant trend to increased risk of lymphoma (HR 1.70 (95% CI 0.97 to 3.00), p=0.052) with bDMARDs in the analysis with a 90-day lag period and 2-year carry-over period. These differences were no longer observed when extending the carry-over period to 5 years. When plotting scaled Schoenfeld residuals against time, the proportional hazard assumption was respected for all events in the main analysis (with 180 days of carry-over effect). However, for haematological malignancies and lymphoma we observed a variation of the effect over time in the sensitivity analyses with a 2-year carry over effect (increased risk in patients exposed to bDMARDs between 1 and 2 years after matching).

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Table 2 Risk of malignancy associated with bDMARDs initiation compared with continuing csDMARDs alone in patients with RA

Type of malignancy	Sex	No of bDMARD exposed/ csDMARD matched RA	No of cancer in bDMARD exposed patients	No of cancer in csDMARD matched patients	HR	95% CI	P value
All malignancies excluding non-melanoma skin cancers		19727/19 727	435	332	0.99	(0.86 to 1.14)	0.896
All solid malignancies excluding non-melanoma skin cancers		19727/19 727	374	297	0.95	(0.82 to 1.11)	0.516
Haematological malignancies		19727/19 727	45	27	1.27	(0.79 to 2.06)	0.316
Malignant lymphoma		19727/19 727	27	15	1.35	(0.72 to 2.53)	0.345
Hodgkin lymphoma		19727/19 727	2	2	0.77	(0.10 to 5.70)	0.802
Non-Hodgkin's lymphoma		19727/19 727	25	13	1.43	(0.73 to 2.80)	0.277
Haematological malignancies (excluding lymphoma)		19727/19 727	18	12	1.18	(0.56 to 2.49)	0.656
Invasive melanoma		19727/19 727	18	15	0.91	(0.46 to 1.79)	0.780
Invasive cancer of the cervix	Women	14722/14 722	7	4	1.40	(0.41 to 4.79)	0.582
Breast cancer	Women	14722/14 722	80	67	0.91	(0.66 to 1.26)	0.573
Lung cancer		19727/19 727	61	45	1.00	(0.68 to 1.48)	0.990
Colorectal cancer		19727/19 727	41	31	0.98	(0.61 to 1.57)	0.935
Prostate cancer	Men	5005/5005	24	24	0.73	(0.42 to 1.29)	0.294
Kidney cancer		19727/19 727	10	13	0.61	(0.27 to 1.42)	0.263
Liver cancer		19727/19 727	7	4	1.27	(0.37 to 4.40)	0.702
Pancreas cancer		19727/19 727	10	4	1.81	(0.57 to 5.74)	0.287

bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic agents; RA, rheumatoid arthritis.

No significant increased risk of overall malignancies, solid cancers or lymphomas was observed in men nor women >65 years (online supplemental eTables 5 and 6).

DISCUSSION

In this historical PS matched cohort study within the French nationwide healthcare database, covering 87% of the French population (~57 million people), the risk of overall malignancies, organ-specific cancers and haematological malignancies did not significantly differ between patients continuing csDMARDs and those initiating bDMARDs. Likewise, the risk of overall malignancies, organ-specific cancers and haematological malignancies did not differ between patients initiating TNF inhibitors and matched patients remaining on csDMARDs. Sensitivity analyses hypothesising a persistent risk after bDMARD withdrawal up to 5 years, and subgroup analysis in patients >65 years provided similar results.

This study aimed to investigate the risk of malignancy associated with bDMARDs. Thus, we compared, in incident users of any DMARD, the risk of malignancy in patients initiating bDMARDs to that those, having the same duration on csDMARD, but continuing csDMARDs, which allow to account for the recommendation to start bDMARD after inefficacy or intolerance of csDMARDs. This design corresponds to a relevant question in clinical practice, of the risk associated with initiating of a bDMARD versus continuing on csDMARDs in bDMARD

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Table 3 Comparison of the risk of malignancy in patients with RA initiating bDMARDs alone or in combination with csDMARDs to those continuing csDMARDs alone

Type of malignancy	Exposure	HR	95% CI	P value
All malignancies excluding non-melanoma skin cancer	csDMARD	REF		0.970
	bDMARD alone	1.00	(0.84 to 1.19)	
	bDMARD +csDMARD	0.98	(0.83 to 1.16)	
All solid malignancies excluding non-melanoma skin cancer	csDMARD	REF		0.798
	bDMARD alone	0.94	(0.78 to 1.13)	
	bDMARD +csDMARD	0.96	(0.80 to 1.15)	
Haematological malignancies	csDMARD	REF		0.350
	bDMARD alone	1.51	(0.87 to 2.62)	
	bDMARD +csDMARD	1.05	(0.59 to 1.89)	
Malignant lymphoma	csDMARD	REF		0.546
	bDMARD alone	1.52	(0.74 to 3.11)	
	bDMARD +csDMARD	1.18	(0.55 to 2.52)	

bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic agent; RA, rheumatoid arthritis.

Table 4 Risk of malignancy associated with TNF inhibitors initiation compared with continuing csDMARDs alone in patients with RA

Type of malignancy	Sex	No of TNF inhibitors exposed/ csDMARD matched RA	No of cancer in TNF inhibitors exposed patients	No of cancer in csDMARD matched patients	HR	95% CI	P value
All malignancies excluding non-melanoma skin cancers		16 333–16 333	332	277	1.03	(0.88 to 1.21)	0.702
All solid malignancies excluding non-melanoma skin cancers		16 333–16 333	290	232	1.08	(0.91 to 1.28)	0.405
Haematological malignancies		16 333–16 333	30	36	0.72	(0.44 to 1.17)	0.186
Malignant lymphoma		16 333–16 333	19	21	0.77	(0.42 to 1.43)	0.413
Hodgkin lymphoma		16 333–16 333	1	1	0.88	(0.06 to 13.72)	0.929
Non-Hodgkin's lymphoma		16 333–16 333	18	20	0.77	(0.41 to 1.44)	0.413
Haematological malignancies (excluding lymphoma)		16 333–16 333	11	15	0.65	(0.29 to 1.41)	0.277
Invasive melanoma		16 333–16 333	11	13	0.73	(0.33 to 1.62)	0.437
Invasive cancer of the cervix	Women	12 158–12 158	6	4	1.32	(0.38 to 4.68)	0.658
Breast cancer	Women	12 158–12 158	66	50	1.15	(0.80 to 1.66)	0.450
Lung cancer		16 333–16 333	43	35	1.04	(0.67 to 1.63)	0.853
Colorectal cancer		16 333–16 333	34	20	1.45	(0.83 to 2.53)	0.179
Prostate cancer	Men	4175–4175	22	26	0.7	(0.40 to 1.25)	0.235
Kidney cancer		16 333–16 333	7	14	0.44	(0.18 to 1.11)	0.081
Liver cancer		16 333–16 333	5	1	4.29	(0.50 to 37.14)	0.131
Pancreas cancer		16 333–16 333	8	8	0.85	(0.32 to 2.25)	0.748

csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic agents; RA, rheumatoid arthritis.

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naïve patients. By contrast, a classical new user design, where new users of csDMARDs would have been matched to new users of bDMARDs, would have not addressed the real question in practice as it would have compared patients at different stages of their disease and thus with possibly different baseline risk.

The main result—not observing any significant overall increased risk of malignancy in patients with RA initiating bDMARDs—is in concordance with RCT meta-analyses[10 12] and previous observational studies.[16–21]

Considering the use of bDMARDs in association or not with csDMARDs did not change the results. By contrast, in a previous study on the same database involving patients with inflammatory bowel disease (IBD), the use of conventional immunomodulating agents in adjunction to TNF inhibitors increased the risk of lymphoma. However, there are major differences between these two studies. First, the main csDMARD used in IBD is azathioprine and not methotrexate. Yet, azathioprine is known to have a higher immunosuppressive effect than methotrexate, and is itself associated with an increased risk of some cancers: all types of skin cancers[40–43] and lymphoma.[44–46] Also, this study included both incident and prevalent users making difficult the analysis of the impact of previous therapeutic lines. Finally, analyses considered only 'on-treatment' period, thus not accounting for the potential delayed effect of treatment on the risk of malignancy. Effectively, when analysing the risk of malignancy associated with treatments, an 'on-treatment' analysis is not appropriate, since such risk might appear with some delay but also may persist after treatment discontinuation. Effectively, to define risk periods, our analyses implemented lag and carry-over periods. The lag period avoids including malignancies that appear in the database immediately after treatment initiation and are unlikely to be related to this treatment. In addition, the carry over period is useful to account for the delay of cancer registering in the database and for the persistent treatment effect after its discontinuation. Here, sensitivity analyses hypothesising a persistent risk after bDMARD withdrawal up to 5 years accounted for this potential risk.

Regarding the risk of melanoma, results are conflicting in the literature, with a trend to an increased risk of melanoma with bDMARDs only in northern countries[23 26 31 47 48] We did not find an increased risk of invasive melanoma in any of our analyses. However, we only addressed the risk of invasive melanoma, usually leading to a long-term care, and thus adequately identified in the SNDS.

In line with the literature, we found no significant increased risk of lymphoma associated with initiating bDMARDs versus continuing csDMARD.[31 49] Of note, since the HR is higher (although not significant with a large 95% CI, with a small number of events) for lymphomas than for the other cancers (HR 1.35 (95% CI 0.72 to 2.53)), we cannot exclude a possible signal for this peculiar cancer. However, even if we did our best in matching the two groups of patients with proxy of disease activity, we cannot exclude that this slight non-significant increased risk of lymphoma may be linked to only a slight difference in disease activity between the groups. Nevertheless, in analyses comparing patients initiating TNF inhibitors and matched patients remaining on csDMARDs, HR for the risk of lymphoma was still non-significant and tended to be even lower (HR 0.77 (95% CI 0.42 to 1.43)). Also, in analyses with a 2-year carry over effect, we observed a variation of the bDMARD effect over time with a possible increased risk of lymphoma in patients exposed to bDMARDs between 1 and 2 years after bDMARD initiation. However, due to the relatively small number of events at each time period, we cannot definitely conclude on theses time variations. This point will be investigated in further analyses, planned integrating the most recent years of the SNDS database, when available.

The risk of bias in observational studies may be high, particularly in complex situations in which exposure and confounding factors are time-dependent, with a channelling phenomenon, and a long-term outcome (cancer) for which cumulative immunosuppressant exposure is an issue. As compared with previous studies, to adequately handle these methodological issues, we used a cohort of csDMARD incident users to eliminate the potential impact of previous therapeutic lines. We also implemented PS based methods with the use of a time-dependent—(ie, dynamic) PS. This means that every 30 days PS was recalculated after updating time dependent variables included in the PS. Matching was performed on this dynamic PS, age at first DMARD initiation (<65 years or not), gender, but also on time since initiation of the first DMARD at the time of matching. This last matching variable aimed to account for the marketing authorisations and therapeutic recommendations, which imply that bDMARDs should be prescribed only in case of csDMARD failure or contraindication, or in case of very severe RA (which represent a minority of patients). These methodological choices have reduced the study population size but leads to less-biased and more robust results. Thus, we acknowledge that for some secondary outcomes (site-specific cancers) our analyses might be underpowered. Nevertheless, the SDNS database account for nearly 90% of the French population which ensure a high representativeness of the whole population and a limited risk of selection bias. Also, the definition of RA cases, mainly based on ICD-10 codes, may be subject to misclassification. However, with a similar definition, previous work with a representative sample of the SNDS found the RA prevalence within the expected range.[50] In addition, our analyses included only patients receiving DMARDs, which strengthened the confidence regarding RA diagnoses. Finally, the use of a healthcare claim database has some pitfalls, particularly regarding the phenotyping of the RA cases with no data available on ACPA status and disease activity. Nevertheless, ACPA status has not been shown to be associated with the overall risk of malignancy, even though it remains uncertain regarding

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the risk of lymphoma.[4] Also, we tried to take into account disease severity/activity in our PS by incorporating proxies such as: disease duration, corticosteroid current and cumulative dose, number of previous DMARDs and of previous hospitalisations for RA. In addition, it is unlikely that our analyses on solid malignancies were impacted by the absence of formal measure of disease activity, since the link between disease activity and risk of malignancy, is only established for lymphoma.

CONCLUSIONS AND RELEVANCE

In this large 9-year cohort study within the French nationwide healthcare database, including almost all, thus representative of, the French population, the risk of overall malignancies and organ-specific cancers and haematological malignancies in adults with RA initiating bDMARDs did not significantly differ from that of matched patients with RA continuing on csDMARDs. The results were similar when considering the use of bDMARDs alone or in association with csDMARDs, when comparing patients initiating TNF inhibitors to patients continuing on csDMARDs, or in sensitivity analyses hypothesising a persistent risk after treatment withdrawal of up to 5 years.

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