Rates of Serious Infections and Malignancies Among Patients with Rheumatoid Arthritis Receiving Either Tumor Necrosis Factor Inhibitor or Rituximab Therapy

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ABSTRACT. ***Objective.*** Because of the role of tumor necrosis factor (TNF) in host defense, it was hypothesized that its inhibition might lead to an increased risk of malignancies and infections. The objective of our study was to assess the incidence of serious infections leading to hospitalization and malignancies among patients with rheumatoid arthritis (RA) receiving either TNF inhibitor or rituximab (RTX) therapy.

Methods. The study population was identified from the National Register for Biologic Treatment in Finland and the hospital records of Central Finland Central Hospital for conventional disease-modifying antirheumatic drug (cDMARD) users. Data on infections and malignancies were acquired from national healthcare registers. A Poisson model was used to calculate the adjusted incidence rate ratios (aIRR) and was composed of age, sex, time from diagnosis, year of the beginning of the followup, rheumatoid factor status, Disease Activity Score at 28 joints, Health Assessment Questionnaire, prior malignancy, prior serious infection, prior biologic use, and time-updated use of methotrexate, sulfasalazine, hydroxychloroquine, and oral corticosteroids as confounders.

Results. In total, during the followup of 10,994 patient-years, 92 malignancies and 341 serious infections were included in the analyses. The aIRR of infections compared to cDMARD users were 1.2 (95% CI 0.63–2.3), 0.84 (95% CI 0.53–1.3), 0.98 (95% CI 0.60–1.6), and 1.1 (95% CI 0.59–1.9) for the patients treated with infliximab (IFX), etanercept, adalimumab, and RTX, respectively. The crude rates of malignancies were highest among the users of cDMARD and RTX, and lowest among patients treated with IFX with no differences in aIRR.

Conclusion. Our results provide some reassurance of the safety of biologic treatments in the treatment of RA. (First Release Jan 15 2015; J Rheumatol 2015;42:372–8; doi:10.3899/jrheum.140853)

Key Indexing Terms:

RHEUMATOID ARTHRITIS	ANTIBODIES	MONOCLONAL
INFECTION	NEOPLASMS	EPIDEMIOLOGY

According to the current Finnish care guidelines, the treatment of rheumatoid arthritis (RA) should commence with methotrexate (MTX), and in severe cases with the combination of MTX, sulfasalazine (SSZ), hydroxychloroquine, and low-dose prednisolone[1]. In case of insufficient treatment response or intolerance to the conventional disease-modifying antirheumatic drugs (cDMARD), treatment with biologic drugs, primarily tumor necrosis factor inhibitors (TNFi), may be commenced. Should the treatment with TNFi be unsuccessful, other biologics, such as rituximab (RTX), may be considered. Currently, 21% of patients with RA in our outpatient specialized healthcare are treated with biologics, with the majority of them using cDMARD concomitantly[2].

Patients with RA have been reported to have an increased risk for infections, possibly attributable to both immunosuppressive medication and the disease process itself[3]. A high disease activity has been associated with an increased risk for some lymphomas[4]. Because of the role of TNF in the defense against cancer, it was hypothesized that its blockade

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might lead to increased risk of malignancies. Current evidence does identify some types of hematological malignancies that may be affected by the drug exposure, but the overall risk is not affected[4,5,6,7,8]. Nevertheless, TNFi are avoided in patients with a history of cancer. Some safety data on TNFi have been published based on both randomized clinical trials and observational studies[9,10,11,12,13]. Mostly, current evidence suggests that TNFi seem to elevate the risk for serious infections in general and are known to predispose to some specific infections such as reactivation of latent tuberculosis (TB).

Although fewer data are available for RTX, it has been reported that compared to cDMARD, it does not predispose patients to either infections or malignancies[14,15].

Regardless, further research is warranted considering the differences between countries in treatment guidelines, healthcare systems, comorbidities such as latent TB, and cancer history. The objective of our study was to assess the incidence of serious infections and malignancies among patients with RA receiving infliximab (IFX), etanercept (ETN), adalimumab (ADA), or RTX therapy in Finland.

MATERIALS AND METHODS

Patients and followup. The study population was identified from the National Register for Biologic Treatment in Finland (ROB-FIN) and the hospital records of Central Finland Central Hospital with the latter providing all cDMARD users. The ROB-FIN is a prospective cohort study designed to monitor the effectiveness and safety of biologic drugs in treatment of rheumatic diseases based on structured data collection forms submitted by rheumatologists on patients' routine care visits to outpatient specialized healthcare. It has followup data dating to 1999 while the electronic hospital records collected using GoTreatIT (DiaGraphIT) patient monitoring software were retrieved from 2007 onward.

To be included in the present analysis, patients had to have a confirmed diagnosis of RA (either meeting the 1987 American College of Rheumatology criteria or a clinical diagnosis), at least 1 recorded visit, and have started their medication prior to December 31, 2011. Biologic drugs included in the analysis were limited to IFX, ETN, ADA, and RTX, but prior use of any biologic drug did count as a prior biologic treatment. Additionally, only biologic-naive cDMARD users were included. The patient could contribute to several medication groups as long as they did not violate the inclusion criteria. No additional exclusion criteria were applied.

Followup time was defined either as the reported medication start and stop date, or alternatively in the absence of this information, as the time between the first and the last visit while being treated with drugs. Additionally, a 6-month lag time was introduced to identify the adverse events taking place soon after the discontinuation of the exposure and to avoid possible bias caused by not being able to pinpoint the discontinuation date more accurately than the of-the-last-visit date while receiving treatment. However, the followup was truncated at the initiation of another biologic treatment or at December 31, 2011. Baseline visit was defined as the first visit during the exposure or at most 3 months before the treatment onset unless the patient was treated with another biologic.

Infections and malignancies. Data on study endpoints, infections and malignancies, were acquired from the National Hospital Discharge Register and the National Cancer Registry, respectively[16,17]. For our study, a serious infection was defined as any infection requiring hospitalization. Infections and malignancies were classified using the International Classification of Diseases (ICD) 10th ed. and ICD-O-3 classifications, respectively. Data on infections were available from 1998 to 2011 while the data on malignancies covered 1953 to 2011. No evaluations of causality between the exposure and outcome were made; instead, all hospitalizations because of infections and malignancies occurring during the followup period were included. However, postoperative infections were excluded. Further, hospital transfers were not considered as hospitalizations. As a sensitivity analysis, we included only the first hospitalization because of each unique type of infection.

Ethical considerations. An ethical statement and study permission were granted by the Helsinki University Central Hospital ethical committee and the Finnish National Institute for Health and Welfare, respectively. Additionally, all patients enrolled in the ROB-FIN gave their informed consent. Data from different sources were merged on patient level using unique social security numbers and anonymized to conceal patient identity.

Statistical analyses. The results were reported as medians with interquartile ranges (IQR), counts, incidence rates (IR), and incidence rate ratios (IRR). The 95% CI for IR were retrieved from Poisson distribution based on the crude rates, while the IRR were modeled using Poisson regression. A dispersion test was used to assess the Poisson model assumption of equal expected means and variances[18]. Adjustment for overdispersion accompanied by robust standard errors was used where appropriate. We executed 4 statistical models, all including the categorical variable on biological or nonbiological treatment of the patient. First model ("full model") was composed of all relevant predefined explanatory variables listed in Table 1, except prior biological treatments. Age and the use of cortisone, MTX, SSZ, and hydroxychloroquine were included as time-updated confounders using information from the most recent routine care visit to the rheumatologist. The second model reduced the number of variables in the model using Akaikes information criterion ("best model"). The third model included age and sex as explanatory variables while the fourth model had no additional variables other than the medication. Finally, we repeated the regression analyses comparing pooled TNFi to RTX with all prior biologic treatment-related variables included in the model. Baseline differences between the groups were analyzed using the ANOVA, the chi-square test, or the Kruskal-Wallis test, as appropriate. We used multiple imputation with predictive mean matching and 20 imputed datasets to create the imputed data, which guarantees that the imputed values were in the range of the observed values. For comparison, we also performed the analysis on the subset of complete cases. The data were analyzed using SPSS 22.0 (IBM SPSS) and R 3.1.0 (R Foundation for Statistical Computing).

RESULTS

Patients and followup. Of the 3762 patients included in our study, 2217 and 1545 were identified from the ROB-FIN and Central Finland Central Hospital, respectively. Four patients whose data were available from both sources were merged into single cases. Of the 4932 medication periods included in the study, 1400 were DMARD therapies, and 642, 1245, 1207, and 438 were IFX, ETN, ADA, and RTX therapies, respectively. Patient characteristics at baseline are presented in Table 1.

Followup took place between 1999 and 2011. Altogether, the study medications accumulated 10,994 patient-years, lag time included. The median followup times in years in DMARD, pooled TNFi, IFX, ETN, ADA, and RTX groups were 2.3 (IQR 1.2–2.9), 1.5 (IQR 0.57–3.4), 1.6 (IQR 0.81–3.4), 1.5 (IQR 0.50–3.5), 1.3 (IQR 0.50–3.4), and 1.1 (IQR 0.50–2.4), respectively, while corresponding sums of patient-years were 3119, 7163, 1700, 2842, 2620, and 712, respectively.

Table 1. Patient characteristics at the beginning of the followup. Values are median (IQR) or % unless otherwise specified.

Characteristics	cDMARD, n = 1400	TNFi, n = 3094	IFX, n = 642	ETN, n = 1245	ADA, n = 1207	RTX, n = 438	p*
Age	62 (53–72)	54 (45–61)	52 (44–59)	54 (45–61)	55 (47–62)	59 (52–67)	< 0.001
Female sex	69	75	72	76	76	77	< 0.001
Time from diagnosis, yrs	9.4 (5.0–13)	11 (6.0–19)	11 (5.8–17)	11 (5.8–19)	12 (6.4–20)	15 (8.7–23)	< 0.001
Beginning of followup, yr	2009 (2008–2010)	2006 (2004–2008)	2003 (2002–2007)	2006 (2004–2009)	2006 (2005–2008)	2009 (2008–2010)	< 0.001
RF-positive	65	78	78	77	78	88	< 0.001
DAS28	3.2 (2.2–4.3)	4.4 (3.2–5.5)	4.8 (3.6–5.8)	4.2 (3.0–5.3)	4.3 (3.2–5.4)	4.5 (3.3–5.4)	< 0.001
HAQ-DI	0.8 (0.28–1.4)	1.0 (0.50–1.5)	1.1 (0.62–1.7)	1.0 (0.50–1.5)	1.0 (0.48–1.5)	1.1 (0.6–1.7)	< 0.001
Prior malignancy	5.5	3.2	3.0	3.3	3.3	10	< 0.001
Hospitalization because of an infection during past 24 mos	3.6	4.0	4.2	3.9	3.9	7.8	< 0.001
Baseline use of MTX	75	54	54	54	56	41	< 0.001
Baseline use of sulphasalazine	31	22	22	22	22	17	< 0.001
Baseline use of HCQ	41	28	28	28	28	25	< 0.001
Baseline use of oral corticosteroids	53	75	78	75	73	78	< 0.001
Prior biologic	0	31	12	37	36	63	> 0.001
Prior TNFi	0	30	12	36	35	61	< 0.001
Prior biologic other than TNFi	0	2.1	1.6	2.6	1.8	6.4	< 0.001
1 prior biologic	0	25	5.0	32	28	26	< 0.001
More than 1 prior biologic	0	6.1	7.0	4.6	7.2	36	< 0.001
Duration of prior biologic treatment ≥ 1.60 yrs	0	14	4.4	16	18	40	< 0.001

* Pooled TNFi column excluded from baseline statistical comparison. IQR: interquartile range; cDMARD: conventional disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitors; IFX: infliximab; ETN: etanercept; ADA: adalimumab; RTX: rituximab; RF: rheumatoid factor; DAS28: Disease Activity Score at 28 joints; HAQ-DI: Health Assessment Questionnaire–Disability Index; MTX: methotrexate; HCQ: hydroxychloroquine.

The total amount of missing data was 12.4%, ranging from 0–26.9% across the variables in the dataset. Complete data were available from 58.2% of the patients. Results based on the complete cases were not statistically different from those reported below and data were assumed to be missing at random. The same variables showed statistically significant effect in both the "full" and "best" models; therefore, we reported results only from the former.

Hospitalizations because of an infection. Altogether, there were 341 hospitalizations because of infections during the followup period, of which 61 were subsequent hospitalizations because of the same infection diagnosis (Table 2). The

Table 2. Rates of hospitalization because of an infection.

Characteristics	cDMARD	TNFi	IFX	ETN	ADA	RTX
Patient-yrs	3119	7162	1700	2842	2620	712
No. hospitalizations	106	198	53	68	77	37
Length of hospitalization, days, mean (SD)	6.3 (3.7)	7.8 (6.7)	9.5 (7.9)	7.3 (5.5)	7.3 (6.7)	7.9 (6.2)
IR/1000 patient-yrs (95% CI)	34 (28–41)	28 (24–32)	31 (23–41)	24 (19–30)	29 (23–37)	52 (37–72)
IRR (95% CI)	Ref.	0.80 (0.58–1.1)	0.89 (0.58–1.4)	0.70 (0.47–1.0)	0.85 (0.58–1.3)	1.5 (0.90–2.5)
aIRR* (95% CI)	Ref.	1.4 (1.0–1.9)	1.6 (1.1–2.5)	1.2 (0.82–1.8)	1.4 (0.96–2.1)	2.1 (1.3–3.4)
aIRR** (95% CI)	Ref.	0.9 (0.6–1.4)	1.2 (0.63–2.3)	0.84 (0.53–1.3)	0.98 (0.60–1.6)	1.1 (0.59–1.9)
IRR (95% CI)	—	Ref.	—	—	—	1.9 (1.2–3.1)
aIRR* (95% CI)	—	Ref.	—	—	—	1.6 (1.0–2.6)
aIRR*** (95% CI)	—	Ref.	—	—	—	1.4 (0.78–2.6)

* Age and sex. ** Full model. *** Full model and prior biologic treatments. cDMARD: conventional disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitors; IFX: infliximab; ETN: etanercept; ADA: adalimumab; RTX: rituximab; IR: incidence rates; aIRR: adjusted incidence rate ratios; Ref.: reference group.

overall IR of hospitalizations because of all and unique infections were 31 (95% CI 28–34) and 25 (95% CI 23–29) per 1000 patient-years, respectively. The most frequent infections requiring hospitalization were erysipelas (n = 59), infectious gastroenteritis and colitis (n = 38), bronchitis (n = 31), TB (n = 27), and sepsis (n = 22). There were 6 hospitalizations because of TB in the cDMARD group while no patient treated with RTX was hospitalized for TB.

The counts and crude rates of hospitalizations because of an infection were 106 (IR 34, 95% CI 28–41), 198 (IR 28, 95% CI 24–32), 53 (IR 31, 95% CI 23–41), 68 (IR 24, 95% CI 19–30), 77 (IR 29, 95% CI 23–37), and 37 (IR 52, 95% CI 37–72) among the users of cDMARD, pooled TNFi, IFX, ETN, ADA, and RTX, respectively. The mean length of hospital stay was 7.4 days (SD 5.9) with no statistically significant differences between the treatment regimens. In comparison to cDMARD, results adjusted for age and sex showed a statistically significant increase in the incidence for hospital admission because of infection for IFX, ADA, and RTX. The full model did not, however, recognize any single biologic more harmful than cDMARD. No statistically significant differences were observed in direct comparison between TNFi and other RTX after adjusting for all observed confounders. Sensitivity analysis excluding subsequent hospitalizations because of the same infections did not statistically significantly alter the results (results not shown). From the potential confounders, age, history of previous hospitalizations because of infections, Health Assessment Questionnaire score, and use of cortisone predicted increased risk for hospitalization because of an infection. Meanwhile, the use of MTX and SSZ was associated with a reduced infection risk. In the comparison between TNFi and RTX, prior biologic drug use was not associated with increased or decreased incidence of serious infections.

Malignancies. The number of malignancies during the followup was 92, of which 83 were solid cancers and 9 were hematologic or lymphatic malignancies. The IR of all malignancies was 8.4 (95% CI 6.7–10) while the rates of solid cancers and hematologic/lymphatic malignancies were 7.6 (95% CI 6.0–9.4) and 0.80 (95% CI 0.37–1.6), respectively. Four malignancies occurred in patients with prior malignancy and the IR of completely new and recurrent malignancies were 8.0 (95% CI 6.4–9.9) and 0.36 (95% CI 0.099–0.93) per 1000 patient-years, respectively.

The crude rates of malignancies were highest among the patients treated with cDMARD (IR 12, 95% CI 8.6–17) and RTX (IR 9.5, 95% CI 3.8–20), and lowest were among IFX-treated patients (IR 5.8, 95% CI 2.8–11). Analyses adjusted did not reveal any statistically significant differences in the IR of malignancies between the patients receiving cDMARD and biologics, or between different biologic agents (Table 3). In comparison to nonbiological medication, all biologicals but RTX were associated with decreased risk for malignancy. However, after adding age and sex into the statistical model, the effect disappeared. With a full set of confounders, only age was a significant predictor of malignancy.

DISCUSSION

A comparison to patients treated with cDMARD revealed a lower IRR for hospital admissions because of infections among TNFi users and a higher IRR among RTX-treated patients. Adjustment for age and sex led to increased IRR among all biologics users and suggested that IFX and ADA users have a statistically significantly increased risk of being hospitalized because of an infection. After including the remaining confounders, however, the adjusted IRR showed no statistically significant difference between biologics users and DMARD-treated patients. The same pattern was observed previously by Dixon, *et al*[12]. ETN had the lowest estimate of IRR, and while the finding lacked statistical significance, it is in line with previous literature[19]. While the unadjusted IR for infections and malignancies were relatively high for RTX, the multivariate analyses disclosed confounding factors and revealed that RTX is at least as safe as other antirheumatic agents, which is in line with previous studies[15,20]. While previous infections and corticosteroid use were recognized as strong predictors of hospital admission because of infections, it could be hypothesized that corticosteroid-treated patients have higher off-medication disease activity, which would account for some of the explanatory effect.

The crude rate of malignancies was highest among patients treated with cDMARD and patients receiving RTX. Despite the highest crude IR of malignancies of biologics among RTX users, the adjusted results proved this to be due to confounding. In general, there were no statistically significant differences between the treatment alternatives in the incidence of malignancies. These findings are also in line with previous literature and provide a further reassurance of similar safety profiles of different antirheumatic biological therapies[21].

Patients treated with cDMARD differ significantly from biologics-treated patients in many respects at the study entry. The lower disease activity of cDMARD users may explain the absence of biologic treatment because the criteria for the initiation of biologic treatment in Finland include insufficient treatment response to cDMARD. While the users of different TNFi appear a homogeneous group, RTX users have numerous differences compared to TNFi-treated patients. In accordance with current national care guideline and the drug label, RTX is less commonly chosen than TNFi as the first biologic for the patient[1]. Consequently, patients receiving RTX are older and have a longer time since diagnosis as compared to TNFi users. RTX users have a greater percentage of prior malignancies and infections, suggesting that it may have been considered

Table 3. Rates of malignancies.

Characteristics	cDMARD	TNFi	IFX	ETN	ADA	RTX
Patient-yrs	3119	7162	1700	2842	2620	712
No. malignancies	39	47	10	21	16	6
IR/1000 patient-yrs (95% CI)	13 (8.9–17)	6.6 (4.8–8.7)	5.9 (2.8–11)	7.4 (4.6–11)	6.1 (3.5–9.9)	8.4 (3.1–18)
IRR	Ref.	0.52 (0.34–0.80)	0.46 (0.23–0.93)	0.59 (0.35–1.0)	0.49 (0.27–0.88)	0.68 (0.29–1.6)
aIRR* (95% CI)	Ref.	0.98 (0.61–1.57)	0.91 (0.44–1.9)	1.1 (0.63–2.0)	0.87 (0.47–1.6)	1.0 (0.42–2.4)
aIRR** (95% CI)	Ref.	1.2 (0.63–2.2)	1.2 (0.44–3.1)	1.3 (0.65–2.6)	1.1 (0.51–2.2)	1.2 (0.49–3.2)
IRR (95% CI)	—	Ref.	—	—	—	1.3 (0.56–3.0)
aIRR* (95% CI)	—	Ref.	—	—	—	1.0 (0.43–2.4)
aIRR*** (95% CI)	—	Ref.	—	—	—	1.1 (0.42–2.7)

* Age and sex. ** Full model. *** Full model and prior biologic treatments. cDMARD: conventional disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitors; IFX: infliximab; ETN: etanercept; ADA: adalimumab; RTX: rituximab; IR: incidence rates; aIRR: adjusted incidence rate ratios; Ref.: reference group.

a safer alternative in the presence of the aforementioned medical history. There were notable differences in the year of treatment onset between the treatment alternatives, but including it in the model did not identify it as a statistically significant confounder.

The ROB-FIN is a prospective cohort study, whose data collection is based on reports on routine care visits in specialized outpatient healthcare, submitted at least biannually by rheumatologists. All adult patients initiating a biologic drug for treatment of an inflammatory rheumatic disease are included and data collection is continued as long as the biologic treatment persists. Estimated coverage is 60% of biologic treatments of rheumatic diseases in Finland[22]. However, with the addition of biologic users from Central Finland, the coverage is probably elevated to 70%[23]. Patient data in Central Finland Central Hospital are collected using GoTreatIT, which facilitates more in-depth data collection compared to preexisting systems in Finnish Healthcare. Both the ROB-FIN and the Central Finland Central Hospital databases are composed of a wide range of patients' background, disease activity, and medication-related variables. Data on malignancies were retrieved from the Finnish Cancer Register, a national register maintained by the Institute for Statistical and Epidemiological Cancer Research, whereas the incidence of infections was based on the Finnish Hospital Discharge Register.

Reporting hospitalization and malignancy to the national registries is mandatory in Finland, thus providing an unbiased source for medical outcomes. The Finnish cancer registry estimates that it has 99%–100% coverage in malignant tumors and lymphomas[24]. However, because the data on infections were retrieved from hospital records, they represent only the most severe cases of infections. Serious infection is often in practice defined as one requiring hospitalization, whereas mild to moderate infections can usually be treated in the outpatient setting. While some infections, such as sepsis, are always likely to lead to hospitalization and the results might, therefore, represent their true incidence, the same cannot be said for bronchitis, for example, which is usually treated in community health centers by general practitioners. Postoperative infections were excluded because of dissimilar rates of arthroplasty surgery among DMARD and biologics users in Finland, which could have biased the results[25]. We included subsequent hospitalizations because of the same infection during the followup time. However, a sensitivity analysis excluding subsequent hospitals admissions because of the same infection did not change the results in a statistically significant way.

As usual, there were some missing data, particularly among the variables related to disease activity. Most of the data are gathered alongside daily clinical work where it is not always possible to write up information systematically. Medication data were considered complete, although the followup had to be censored in case the patient was lost to followup. The outcome data, however, is very likely to be complete and to cover all hospital episodes and malignancies during the study period.

Lag time in our present study was longer than that of other studies[11,12]. This was in part because of the instructed data reporting interval of 6 months for the ROB-FIN and in part the limitation of not being able to define the medication period more accurately than as the time between 2 visits while being treated with drugs. Had the lag time been shorter, possible adverse events could have led to a discontinuation of the treatment before the rheumatologist filed another report, thus introducing a protopathic bias. Further, the lag time of 6 months allowed calculations of meaningful followup times for patients treated with RTX infusions.

The IR of malignancies and hospitalization because of infection among users of biologics were first compared to cDMARD users and in the second step to pooled TNFi users. Despite including all recognized confounding factors in the multivariate analyses, it is possible that some residual confounding from unmeasured factors, such as comorbidities, have played a role in the decision whether to start a

biologic. Many of the cDMARD-treated comparators had been taking those drugs for a period of time unlike most of the biologic users in our study, which could lead to an overestimation of the IRR of infections among biologic users[26]. Therefore, comparing RTX to TNFi could have meant a lesser possibility of selection bias. Further, the between-biologics comparison also enables the inclusion of prior biologic treatment as a confounder.

Possible weaknesses of our study are limited or missing information on comorbidities and confounding factors such as smoking. However, a previous cross-sectional study did not find differences in smoking between biologics users and cDMARD users in general[2]. We did not have complete data on deaths and could not use them in analyses to truncate the lag time where applicable. Neither could we calculate the standardized incidence ratio for malignancies because of the lack of data on mortality. The levels of immunoglobulins and lymphocyte subsets were not available to us and could not be used in the model. Further, our study had limited statistical power that prevented us from studying various discrete types of infections and malignancies in regression analyses.

There were no statistically significant differences in the incidence of infections requiring hospitalization and malignancies between the users of cDMARD, IFX, ETN, ADA, and RTX. However, it is possible that our present study was statistically underpowered. The study population covers a major proportion of Finnish patients with RA ever exposed to biologic treatment, and thus is highly generalizable inside Finland. Generalization outside Finland, however, is not guaranteed because of the differences in treatment guidelines, population characteristics, and comorbidities such as latent TB.

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