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Conflict of interest

LR Harrold is an employee and shareholder of Corrona, LLC. She has been a consultant to AbbVie, BMS, and Roche and has a research grant from Pfizer. CJ Barr is an employee and shareholder of Corrona, LLC. HJ Litman is an employee of Corrona, LLC. B Gershenson is an employee of University of Massachusetts Medical School. J Griffith, SS Islam, D Guo, J Fay, and P Zueger are employees of AbbVie Inc. and own AbbVie stock. J Greenberg is an employee and shareholder of Corrona, LLC. He has been a consultant to Genentech, Janssen, Novartis, Pfizer and Eli Lilly.

ABSTRACT (249/250)

Objective

To assess long-term safety in a US cohort of rheumatoid arthritis (RA) patients treated with adalimumab in real-world clinical care settings.

Methods

This observational study analyzed the long-term incidence of safety outcomes among RA patients initiating adalimumab using data from the Corrona RA registry. Patients were adults (≥18 years) who initiated adalimumab treatment between January 2008 and June 2017, and who had at least 1 follow-up visit.

Results

In total, 2798 adalimumab initiators were available for analysis, with a mean age of 54.5 years, 77% female, and mean duration of disease of 8.3 years. Nearly half (48%) were biologic naïve, and 9% were using prednisone ≥10 mg at adalimumab initiation. The incidence rates per 100 person-years for serious infections, congestive heart failure requiring hospitalization, malignancy (excluding nonmelanoma skin cancer), and all-cause mortality were 1.86, 0.15, 0.64, and 0.33, respectively. The incidence of serious infections was higher in the first year of therapy (3.44 [95% confidence interval: 2.45–4.84]) than subsequent years, while other measured AEs did not vary substantially by duration of exposure. The median time to adalimumab discontinuation was 11 months, while the median time to first serious infection among those experiencing a serious infection event was 12 months.

Conclusion

Analysis of long-term data from this prospective real-world registry demonstrated a safety profile consistent with previous studies in patients with RA. This analysis did not identify any new safety signals associated with adalimumab treatment and provides valuable guidance for physicians prescribing adalimumab for extended periods of time.

Rheumatoid arthritis (RA) is a complex immune-mediated inflammatory disease, which, if not treated effectively, can cause significant pain and progressive joint damage leading to disability and a reduced quality of life (1,2). When compared with the general population, RA is associated with increased morbidity due to complications and comorbidities such as serious infections, cardiovascular (CV) disease and certain cancers (3-5). Higher mortality rates have also been reported (3,5). Inhibition of tumor necrosis factor (TNF), a key component of the inflammatory mechanism associated with many immune-mediated diseases, has been shown to reduce RA disease activity and improve clinical, radiographic, and functional outcomes (6,7).

TNF inhibitors (TNFi) have been associated with a reduced risk of CV disease in patients with RA (8,9); however, some uncertainty remains on the increased risk of infections and the increased potential for malignancy and other adverse events (AE) in patients treated with TNFi. Prior studies have reported an increased risk of serious infections and malignancies, particularly lymphoma, in psoriasis patients treated with TNFi, while other more recent studies have not identified similar significantly increased risks among patients treated with TNFi (10-18). As TNF is an important component of the human immune system and has a role in tumor growth mediation, the link between its inhibition and an increase in the frequency of serious infections or malignancies deserves more investigation (19).

To date, more than 20 years after the introduction of TNFis, the safety of biologics, such as adalimumab (ADA), has been established through both randomized controlled clinical trials and registry-based European observational studies (17,18,20-22). A large cross-indication (including

RA, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease) analysis of long-term safety based on almost 30,000 patients treated with ADA in global clinical trials and open-label extension studies did not identify any new safety signals, although individual differences between the disease populations did exist (17,18). Additionally, in these studies the mortality rate for most indications was below what would be expected in an age- and gender-adjusted population (17,18). However, the patient populations from randomized clinical trials and open-label extension studies may not be reflective of a real-world population of RA patients in the US. Comparisons between different registry-based studies are also challenging due to differences in design, follow-up assessments, and other variables assessed within each registry, which may result in heterogeneity between studies (23). For example, the percentage of patients with a high Disease Activity Score has been shown to vary between registries, with patients in the Corrona registry having lower disease activity and higher functional status (23,24). Differences in healthcare delivery systems and baseline patient characteristics between European and US populations may result in differences in the underlying risk of certain AEs, highlighting the need to establish the safety profile of TNFi in both of these populations.

The long-term incidence of AEs among ADA users in real-world clinical settings has not been well documented in the United States. In a recent US study, approximately half of biologic-naive RA patients stated their primary unwillingness to initiate treatment with a biologic was due to fear/concern about side effects, highlighting the need to clarify the safety of biologics, such as ADA, in US real-world practice (25). The objective of our study was therefore to build on the

existing knowledge base on the safety of TNFis through the evaluation of the risk of AEs in relation to duration of ADA exposure in a US-based population. This will complement ongoing long-term clinical trial safety analyses and further test the hypothesis that the real-world safety profile of ADA is consistent with that previously demonstrated by randomized controlled clinical trial analyses as well as ex-US RA registries.

MATERIALS AND METHODS

Study design

This was a retrospective analysis of the US Corrona RA Registry, a prospective observational cohort of RA patients initiated in 2001 (26), which contains data on nearly 50,000 patients across 40 states, covering approximately 373,000 visits and 173,000 patient-years of follow-up. Data are collected from both patients and their treating rheumatologists, who gather information on disease duration, prognosis, disease severity and activity, comorbidities, use of medications, and patient-reported outcome (PRO) data. Participating rheumatologists also actively assess for the occurrence of AEs at each registry follow-up visit. Follow-up assessments are requested as often as approximately every 6 months and completed during routine clinical encounters.

Study population

Patients were included in this analysis if they were adults (≥18 years of age), initiated ADA as therapy for a clinical diagnosis of RA between 01 January 2008 and 01 June 2017, and were enrolled in the US Corrona RA Registry. Patients were also required to have at least 1 follow-up

visit post drug initiation. Patients with RA onset prior to 16 years of age were excluded from the study.

Ethics

All patients provided written informed consent prior to registry participation. Institutional review board (IRB) approvals for this study were obtained from a central IRB (New England Independent Review Board, NEIRB No. 02-021) for private practice sites and local IRBs of participating academic sites.

Exposure

The date on which each patient initiated ADA therapy was defined as their "index date" and served as the starting point for the measurement of both the time to first AE and the incidence of the AE over time.

Outcomes and covariates

The safety outcomes assessed in this analysis were physician-reported serious infections (eg, infections requiring hospitalization or intravenous antibiotics), malignancies (excluding nonmelanoma skin cancer), congestive heart failure (CHF) that required hospitalization, tuberculosis (TB) with a focus on active TB, and drug-induced systemic lupus erythematosus (SLE). All-cause mortality was also assessed. Outcomes were assessed by both time from ADA initiation to the first occurrence of a specific AE, and the frequency, or "incidence," of each specific AE over time. Measurement of these outcomes continued until either the first

occurrence of the specific AE, or, for incidence of the specific AE over time, until 90 days following discontinuation of ADA or the patient's last Corrona visit (whichever occurred first), at which point the patient was censored. For malignancy and mortality, all events occurring during follow-up were included regardless of ADA continuation or discontinuation.

The Corrona registry uses an established system for the validation of physician-reported AEs. In brief, treating physicians complete "Targeted Adverse Event" questionnaires to record serious AEs. These questionnaires, alongside supporting documents appropriate to the event (eg, hospitalization records, pathology reports), are submitted to Corrona for validation. A subset of questionnaires is also triaged for expert adjudication. This methodology has been supported by previous validation studies, which found positive predictive values of Targeted Adverse Event forms to be 96% for CV events (27), 86% for malignancies (28), and 71% for serious infectious events (29).

Analysis

Demographic and disease characteristics, including prior treatment history, of all patients at the time of their ADA therapy initiation were recorded. Percentages were used to describe categorical variables while means and standard deviations (SD) were used to describe continuous variables. In cases of highly skewed distributions, medians and interquartile ranges were used to describe continuous variables.

The analysis of time from ADA initiation to the first occurrence of a specific AE was analyzed as 'incident events.' For each specific AE, only patients without a history of that AE prior to or at the time of ADA initiation were followed for the occurrence of the AE.

Incidence rates (IR) and 95% confidence intervals (CIs) are reported per 100 person-years, assuming a Poisson distribution. Time to the first event for particular events, including time to discontinuation, time to serious infection, and time to malignancy, was evaluated using Kaplan-Meier curves. Median (95% CIs) time to first event was calculated as well as the proportion of patients that did not have an event at 6, 12, 24, 36, 48, 60, 72 and 84 months after ADA initiation. The standardized mortality ratio (SMR) was calculated based on recent Centers for Disease Control and Prevention mortality data (30).

RESULTS

Study population at ADA initiation

In total, 2798 real-world patients who had initiated ADA therapy were available for analysis. Patient, disease, and prior treatment characteristics of these patients at time of ADA initiation are presented in **Table 1**. The mean age of these patients, who were predominantly female (77%), was 54.5 years (SD: 12.3 years), with a mean body mass index (BMI) of 30.4 (SD: 7.5) and approximately half of patients (52%) had never smoked. The mean (SD) duration of disease was 8.3 (9) years, and mean CDAI was 20.4 (14) with 39% of patients in the high disease activity category. Approximately half (48%) were biologic naïve, and 9% were treated with ≥10 mg prednisone daily. The majority of patients (60%) were receiving concomitant methotrexate at

ADA initiation.

Duration of ADA exposure during the assessment period

Overall, the majority of patients (84%) received ADA therapy for <3 years (**Table 1**). The median time from ADA initiation to last visit on ADA therapy was 11 (95% CI: 4–25) months. The proportion of patients remaining on ADA therapy at 6 and 12 months after initiation was 70% and 56%, respectively. In the subset of patients that were biologic-naïve at ADA initiation, the median time from ADA initiation to last visit on ADA therapy was 13 (95% CI: 6–29) months, with 78% and 62% remaining on ADA at 6 and 12 months, respectively.

The probability of patients within the analysis remaining on ADA over time is presented as a time to discontinuation from ADA in **Figure 1**. The 3 most commonly reported reasons for discontinuing ADA treatment among the overall population included failure to maintain initial response (27%), inadequate initial response (16%), and minor side effect (14%); serious side effects accounted for 6% of reported reasons for discontinuation (data not shown). Similar frequencies of reasons for discontinuation were observed among the bio-naïve population.

Incidence of events during ADA exposure

The IR per 100 person-years of ADA exposure was 1.86 (95% CI: 1.50–2.31) for serious infections, 0.15 (0.07–0.31) for CHF requiring hospitalization, 0.64 (0.50–0.84) for malignancy (excluding nonmelanoma skin cancers), and 0.33 (0.24–0.48) for all-cause mortality (**Table 2**). No cases of TB were reported during follow-up. The IR per 100 person-years of ADA exposure

for AEs included in this study (excluding malignancy and mortality) leading to ADA discontinuation was 0.73 (0.52–1.03).

The incidence of events by duration of ADA exposure categories (≤1 year, >1 to 3 years, >3 to 5 years, >5 years) are presented in **Figure 2**. The incidence of serious infections was higher in the first year of therapy (3.44 [95% CI: 2.45–4.84]) than subsequent years, while other AEs did not vary by duration of exposure.

Time to first occurrence of adverse events of interest

Median times to first serious infection and malignancy among those experiencing each respective event were 12 (95% CI: 7–26) months and 34 (16–56) months, respectively. The proportion of patients not having a first occurrence of serious infection and malignancy at 6 months was 98.4% and 99.7%, respectively. This remained largely unchanged at 12 months, at which 97.5% and 99.4% of patients had not had an occurrence of serious infection or malignancy. Throughout the remainder of the evaluation period, the large majority of patients did not have an occurrence of serious infection or malignancy at 24, 36, 48, 60, 72 or 84 months (Suppl Table 2). Kaplan-Meier curves for the probability of not having a serious infection or having a malignancy event are presented in **Figure 3** and **Figure 4**, respectively.

Standardized mortality ratio

The age-gender adjusted SMR comparing the observed and expected number of deaths was 0.50 ± 0.32. The SMR reveals that there were an expected 62 mortalities within the ADA

initiating population compared to only 31 deaths observed (data not shown).

DISCUSSION

With an increasing number of physicians prescribing disease modifying anti-rheumatic medications for long-term, chronic use, knowledge of the long-term safety profiles of such medications is critical in guiding providers in prescribing strategies which minimize the risk of serious AEs for their patients. This retrospective analysis of a real-world US database of RA patients treated with ADA immunotherapy is consistent with the previously established safety profile through RCTs, open-label extension studies and European RA registries.

A recent update of global long-term clinical trial safety data in adult patients treated with ADA for multiple indications (predominately RA studies), which included 29,987 patients with 56,951 patient-years of exposure, identified serious infections as the most frequent AE, with an IR of 4.6 events per 100 patient-years (18). Our study found a lower IR per 100 person-years for serious infections, which was higher during the first year of exposure (3.44 [95% CI: 2.45-4.84]) than subsequent years. Previous studies have also shown the risk of infection to be higher earlier in treatment compared with later in treatment (31). It may be the case that these AEs were more strictly reported in the clinical trials, as compared with the Corrona registry, although given the serious nature of these AEs, this seems unlikely. Patients in Corrona may have lower levels of disease activity compared to patients in the RCTs; previous studies have shown that increased RA disease activity is associated with an increased risk for serious infections (24,32,33). Differences in the methodology used for the calculation of AE IRs may

also help explain the differences in the observed rates; compared to the present study which captured AEs at the patient level, the global long-term clinical trials study captured AEs at the event level, with multiple AEs of the same type within an individual reflected in the IRs. The global clinical trial analysis reported a lower number of deaths in RA patients treated with ADA (SMR of 0.74) than would be expected in an age- and gender- adjusted population (18), which was directionally similar to the SMR observed in this real-world analysis. For both analyses, underlying explanations for this result are not immediately clear.

Comparison of the Corrona registry findings with those from other real-world databases also reveals variations in outcomes across these analyses. The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) reported that no TNFi was associated with a statistically higher risk of serious infection than any other TNFi among a total of 19,282 patients contributing 46,771 patient-years of follow-up. BSRBR-RA reported an IR for serious infection of 5.42 per 100 patient-years among 7,818 patients initiating ADA which was higher than the first year incidence rates of serious infection reported for ADA exposed patients in our study (IR=3.44) (22). The IR for malignancy during a median follow-up of 3.5 years per patient in a BSRBR-RA cohort exposed to TNFi was more similar, although still slightly higher, than that observed in the present study (0.77 vs. 0.64, respectively) (21). During a total of 3 years follow-up, the Anti-Rheumatic Therapy in Sweden (ARTIS) biologics register reported an IR for mortality of 1.4 per 100 person-years after exposure to ADA. In both studies, the IRs observed may be higher than that reported in our analysis due to differences in median follow-up time (20). Additionally, patients in Europe often have more restricted access to biologics and thus

have higher levels of disease activity, greater use of prednisone and higher levels of disability prior to biologic initiation, all of which influence the risk of infection (24,34). Prevalence of clinical characteristics (eg, smoking) and comorbidities (eg, obesity) also varies between US and European registries, which may reflect the way comorbidity data were captured as well as general cultural differences between countries; differences in comorbidity profiles could create differences in the incidence rates of AEs (23,24).

Comparing safety outcomes for ADA in US clinical practice using data from a large, nationwide cohort of patients with RA is a vital strength of this study. Due to payer and regulatory differences, patient characteristics and access to biologic drugs can vary substantially between countries. Therefore, it is essential to obtain representative clinical evidence directly relevant to practicing rheumatologists in the United States. A previous study showed that Medicare beneficiaries who were enrolled in Corrona share similar demographic and clinical characteristics with Medicare beneficiaries with claims for RA or visits to a rheumatology specialist who were not enrolled, thus suggesting that the results presented here may be generalizable to the broader RA population in the United States (35). The relative similarity of the AE findings of our analysis compared with prior clinical trials and other observational registry studies is reassuring, yet also highlights the importance of continuing to assess these outcomes over longer periods of time, and in more diverse populations.

This study also has several limitations. First, ADA exposure time was limited for some patients. In total, 50% of patients used ADA for 1 year or less and only 16% of patients were exposed for

3 years or more. While serious infection event rates tend to be highest during the first 6–12 months of TNFi exposure (36,37), the limited number of patients in our study with longer-term ADA exposure may not have allowed us to fully characterize the rates of serious infection as well as other AEs such as malignancies due to the relative infrequency and longer-term onset of these AEs. There is an inability to determine with certainty if ADA exposure had an impact on the development of the AEs measured, particularly, those AEs occurring after drug discontinuation or conditions which typically take many years to develop (eg, malignancy). We did not account for subsequent therapies initiated after adalimumab discontinuation and their potential impact on the occurrence of AEs observed in this study. The SMR among this population was low, which suggests the possibility of under-ascertainment of events within the Corrona registry; however, serious events are less likely to be underreported and a low SMR was also found in the ESPRIT study which evaluated the long-term safety and effectiveness of ADA in the treatment of psoriasis and in studies evaluating the long-term safety of ADA across multiple indications (15,17,18). Finally, the precision with which ADA discontinuation is measured in the Corrona registry may have resulted in misclassified exposure time. The date of discontinuation was recorded at the time of physician visit, however, there may be challenges with recall bias if the discontinuation is not well documented in the physician's clinical notes.

This analysis of targeted data from the prospective Corrona real-world RA registry demonstrated ADA to have a safety profile consistent with previous studies and did not identify any new safety signals with long-term ADA treatment. Therefore, with the addition of these real-world data in a large sample of US RA patients, the previously understood benefit-risk

profile of ADA for the treatment of RA remains unchanged. This confirmation of existing knowledge may reassure providers who are initiating and monitoring ADA in their patients.

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FIGURE LEGENDS

Figure 1. Probability of remaining on adalimumab treatment. CI, confidence interval.

Figure 2. Incidence of events by duration of adalimumab exposure. Error bars indicate 95% confidence intervals. [a]Serious infections included those that led to hospitalization or IV antibiotics. [b]Malignancy excluded nonmelanoma skin cancer. CHF, congestive heart failure; IV, intravenous.

Figure 3. Probability of not having a serious infection. CI, confidence interval.

Figure 4. Probability of not having a malignancy event. CI, confidence interval.

Table 1. Patient, disease, and prior treatment characteristics at ADA initiation

	ADA initiators (n=2798)
Patient characteristics	
Age in years, mean (SD)	54.5 (12.3)
Female	2167 (77)
Race, n (%)	
Indigenous American	19 (1)
White Caucasian	2477 (89)
African American	200 (7)
Asian	30 (1)
Other[a]	72 (3)
BMI, n	2784
Mean (SD)	30.4 (7.5)
BMI categorized, n (%)	
Underweight/normal (<25)	683 (25)
Overweight (25≤BMI≥30)	868 (31)
Obese (30<BMI≤35)	576 (21)
Extremely obese (<35)	657 (24)
Smoking status, n (%)	
Never smoker	1441 (52)
Previous smoker	767 (27)
Current smoker	568 (20)
Histories of comorbidities, n (%)	

Malignancy (excluding NMSC)	133 (5)
Congestive heart failure	17 (1)
Serious infections*	127 (5)
Cardiovascular disease**	959 (34)
Disease characteristics	
Duration of disease, mean (SD)	8.3 (9)
Swollen joint count (0–28) median (IQR)	4 (1, 8)
Tender joint count (0–28) median (IQR)	5 (1, 10)
Patient pain (0–100) median (IQR)	50 (24, 70)
Patient global assessment (0–100) median (IQR)	49 [20, 68)
Physician global assessment (0–100) median (IQR)	35 (17, 50)
CDAI, mean (SD)	20.4 (14)
HAQ, mean (SD)	0.50 (0.50)
DAS28, mean (SD)	4.2 (1.6)
Treatment characteristics	
ADA exposure time	
≤1 year	1398 (50)
>1–3 years	945 (34)
>3–5 years	290 (10)
>5–7 years	114 (4)
>7 years	51 (2)
Prednisone use, n (%)	
No prednisone use	2004 (72)
Prednisone dose <10 mg	525 (19)

Prednisone dose ≥10 mg	242 (9)
Prior biologics used (median IQR)	1 (0, 1)
Naïve	1337 (48)
1 previous biologic	992 (35)
2 previous biologics	321 (11)
3 or more previous biologics	148 (5)
Prior cDMARDs used (median IQR)	2 (1, 2)
Naïve	131 (5)
1 previous cDMARD	1254 (45)
2 or more previous cDMARD	1413 (51)
Concomitant MTX, alone or in combination, n (%)	1678 (60)

[a] "Other" category includes Pacific Islander, Unknown, Mixed Race, and (originally) Other. *History of serious infections include those infections that lead to hospitalization or intravenous antibiotics, including joint/bursa, cellulitis, sinusitis, diverticulitis, sepsis, pneumonia bronchitis, gastroenteritis, meningitis, urinary tract infection, upper respiratory infection, or other specified infections. **History of cardiovascular (CV) disease includes hypertension, coronary artery disease, cardiac revascularization procedure (coronary artery bypass grafting, stent, angioplasty), ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, congestive heart failure, unstable angina, stroke, transient ischemic attack (TIA), other CV events, deep vein thrombosis, peripheral artery disease, pulmonary embolism, peripheral arterial thrombosis, urgent peripheral revascularization, peripheral ischemia/gangrene, hyperlipidemia, and carotid artery disease. ADA, adalimumab; BMI, body mass index; CDAI, Clinical Disease Activity Index; cDMARD, conventional disease-modifying antirheumatic drug; DAS28, Disease Activity Score in 28 joints; HAQ, Health Assessment Questionnaire; IQR, interquartile range; MTX, methotrexate; NMSC, nonmelanoma skin cancer, SD, standard deviation.

Table 2. Incidence of AEs[a] among ADA initiators.

Variable	All ADA initiators		
	Patients with ≥1 event, n	Follow-up time, PYs	Rate, events/100 PYs (95% CI)
Serious infections[b]	83	4452	1.86 (1.50–2.31)
Tuberculosis	0	4751	0 (N/A–N/A)
CHF requiring hospitalization	7	4728	0.15 (0.07–0.31)
Drug-induced SLE	2	4750	0.04 (0.01–0.17)
Any AE listed above leading to discontinuation of ADA[c]	33	4494	0.73 (0.52–1.03)
Malignancy[d]	56[e]	8691	0.64 (0.50–0.84)
Mortality	31	9268	0.33 (0.24–0.48)

[a]Among patients without a history of and who were not experiencing the particular event at the time of ADA initiation. [b]Serious infections included those that led to hospitalization or intravenous antibiotics, including joint/bursa, cellulitis, sinusitis, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis, urinary tract infection, upper respiratory infection, or other specified infections. Among those with serious infections, we calculated the number of opportunistic infections, including histoplasmosis, coccidioidomycosis, pneumocystosis, listeria, herpes zoster/varicella-zoster virus and active tuberculosis. Aspergillosis, blastomycosis, legionella, and candidiasis information were not specifically collected. [c]Excludes malignancy as all person-time time was used to assess rate of malignancy, regardless of ADA continuation or discontinuation during follow-up. [d]Excluding nonmelanoma skin cancer. [e]Includes solid tumors (n=40), melanoma (n=8), lymphoma (n=6), and other blood cancers (n=2). ADA, adalimumab; AE, adverse event; CHF, congestive heart failure; CI, confidence interval; N/A, not applicable; PY, person-year; SLE, systemic lupus erythematosus.

Figure 1. Probability of remaining on adalimumab treatment

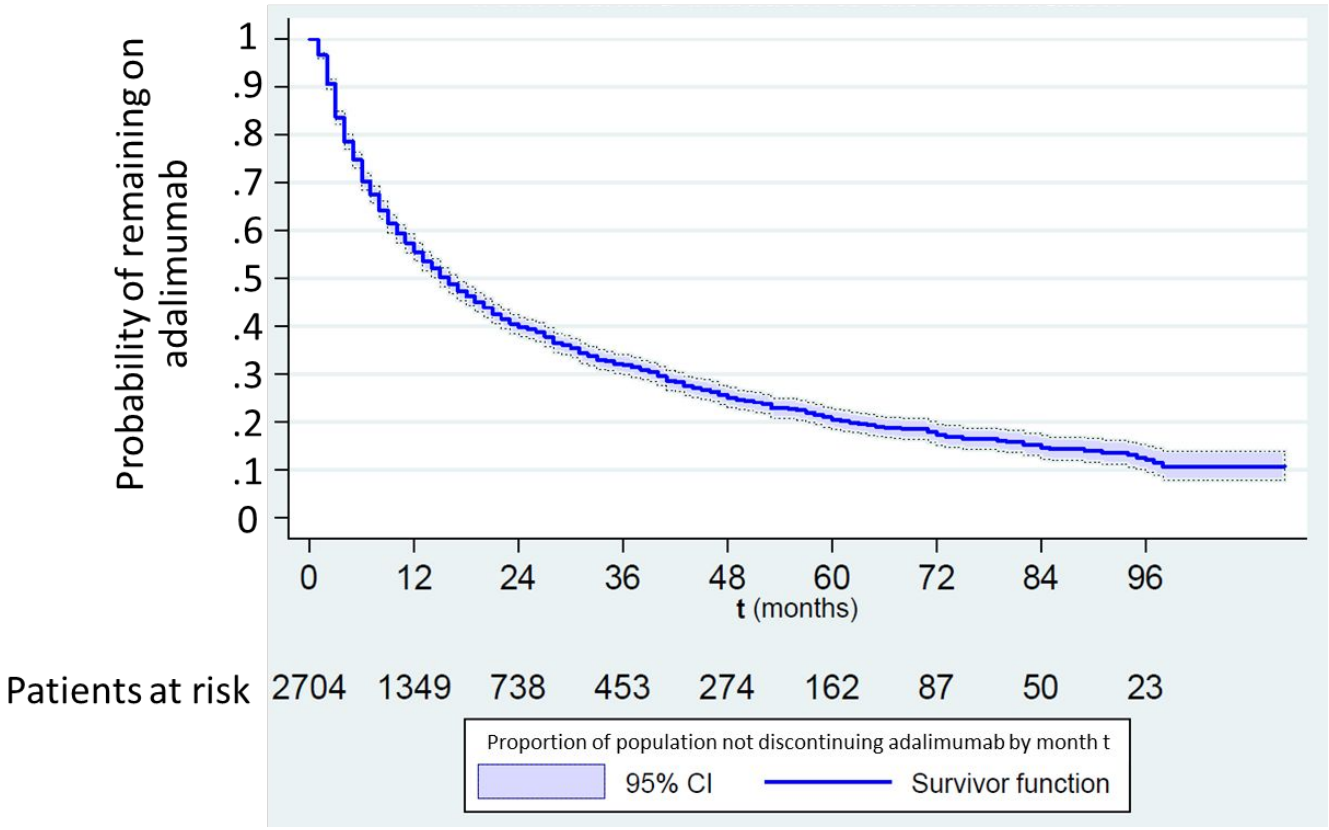
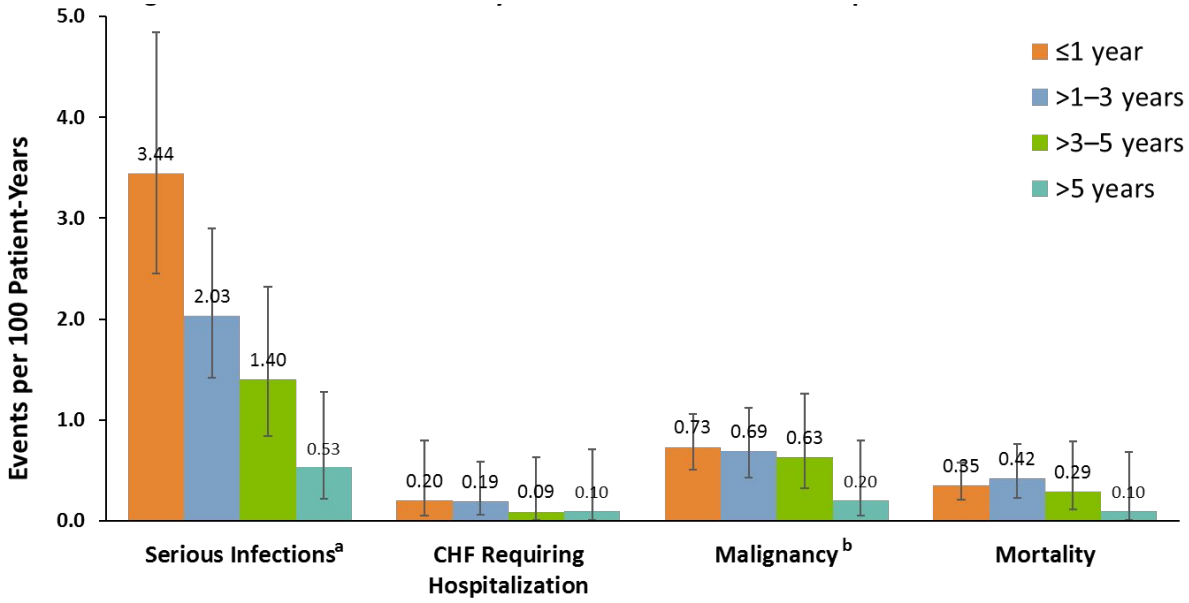


Figure 2. Incidence of events by duration of adalimumab exposure



Error bars indicate 95% confidence intervals.
CHF, congestive heart failure; IV, intravenous.
[a]Serious infections included those that led to hospitalization or IV antibiotics. [b]Malignancy excluded nonmelanoma skin cancer.

Figure 3. Probability of not having a serious infection.

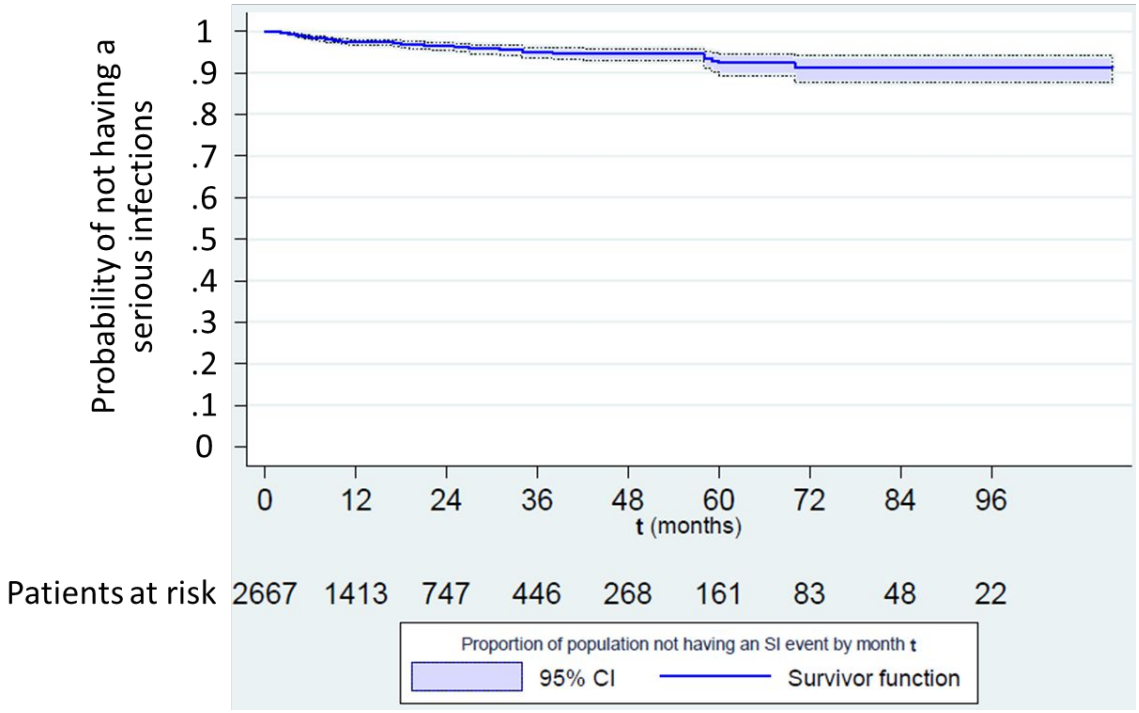


Figure 4. Probability of not having a malignancy event .