Risk of Herpes Zoster in Patients With Rheumatoid Arthritis Treated With Anti–TNF-α Agents

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Context The risk of bacterial infection is increased in patients treated with drugs that inhibit tumor necrosis factor α (TNF-α). Little is known about the reactivation of latent viral infections during treatment with TNF-α inhibitors.

Objective To investigate whether TNF-α inhibitors together as a class, or separately as either monoclonal anti–TNF-α antibodies (adalimumab, infliximab) or a fusion protein (etanercept), are related to higher rates of herpes zoster in patients with rheumatoid arthritis.

Design, Setting, and Patients Patients were enrolled in the German biologics register RABBIT, a prospective cohort, between May 2001 and December 2006 at the initiation of treatment with infliximab, etanercept, adalimumab, or anakinra, or when they changed conventional disease-modifying antirheumatic drug (DMARD). Treatment, clinical status, and adverse events were assessed by rheumatologists at fixed points during follow-up.

Main Outcome Measures Hazard ratio (HR) of herpes zoster episodes following anti–TNF-α treatment. Study aims were to detect a clinically significant difference (HR, 2.0) between TNF-α inhibitors as a class compared with DMARDs and to detect an HR of at least 2.5 for each of 2 types of TNF-α inhibitors, the monoclonal antibodies or the fusion protein, compared with conventional DMARDs.

Results Among 5040 patients receiving TNF-α inhibitors or conventional DMARDs, 86 episodes of herpes zoster occurred in 82 patients. Thirty-nine occurrences could be attributed to treatment with anti–TNF-α antibodies, 23 to etanercept, and 24 to conventional DMARDs. The crude incidence rate per 1000 patient-years was 11.1 (95% confidence interval [CI], 7.9-15.1) for the monoclonal antibodies, 8.9 (95% CI, 5.6-13.3) for etanercept, and 5.6 (95% CI, 3.6-8.3) for conventional DMARDs. Adjusted for age, rheumatoid arthritis severity, and glucocorticoid use, a significantly increased risk was observed for treatment with the monoclonal antibodies (HR, 1.82 [95% CI, 1.05-3.15]), although this risk was lower than the threshold for clinical significance. No significant associations were found for etanercept use (HR, 1.36 [95% CI, 0.73-2.55]) or for anti–TNF-α treatment (HR, 1.63 [95% CI, 0.97-2.74]) as a class.

Conclusion Treatment with monoclonal anti–TNF-α antibodies may be associated with increased risk of herpes zoster, but this requires further study.

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INHIBITION OF TUMOR NECROSIS FACTOR α (TNF-α) has been shown effective in the treatment of patients with active rheumatoid arthritis. For patients in whom the disease activity cannot be sufficiently controlled with conventional disease-modifying antirheumatic drugs (DMARDs), drugs targeting TNF-α have become indispensable. Increased use of anti–TNF-α agents for routine care of rheumatoid arthritis, as well as their use to treat an increasing number of other diseases such as ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease, has led to the need to better understand their safety profiles. Obtaining such knowledge is a primary aim of the biologics registers established in several countries at the time these new agents were introduced.

There is evidence from randomized controlled trials (RCTs)[1,2] as well as observational cohort studies[3-5] and claims data[6] that patients treated with anti–TNF-α agents are at increased risk of bacterial infections. Furthermore, opportunistic infections of all etiologies have been reported in such patients. These data suggest that patients should be carefully monitored and that specific attention be paid to atypical sites or symptoms of infection.

Compared with bacterial infection, little is known about the risk of viral infections in patients with rheumatoid arthritis undergoing anti–TNF-α treatment.

For editorial comment see p 774.

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Herpes zoster, a neurocutaneous disease characterized by a painful vesicular dermatomal rash resulting from reactivation of the varicella zoster virus (VZV), is one of the most common adverse events reported in clinical trials of anti–TNF-α agents. Complications include bacterial superinfection and, more frequently, postherpetic neuralgia, which can cause substantial morbidity. Declining cellular immunity due to increasing age or immunosuppression is known to trigger reactivation of herpes zoster.[7] Immunodeficiency in any form was shown to strongly increase the risk of developing herpes zoster in studies of children with leukemia,[8,9] recipients of bone marrow transplants,[10] and individuals infected with human immunodeficiency virus.[11]

Patients with rheumatoid arthritis, systemic lupus erythematosus, or noninflammatory musculoskeletal disorders are at increased risk of herpes zoster compared with the general population.[12,13] In a retrospective study, Smitten et al analyzed a US claims database and the UK general practitioner database and found adjusted hazard ratios (HRs) of 1.91 (95% confidence interval [CI], 1.80-2.03) and 1.65 (95% CI, 1.57-1.75), respectively, for herpes zoster in patients with rheumatoid arthritis compared with patients without rheumatoid arthritis.[14] We analyzed data from the German biologics register RABBIT to investigate the contribution of various rheumatoid arthritis treatments, especially anti–TNF-α therapy, to the risk of VZV reactivation.

METHODS

RABBIT is an ongoing nationwide prospective cohort study initiated in 2001 with the purpose of investigating the long-term safety and effectiveness of biologic agents in treatment of rheumatoid arthritis. The study includes patients from more than 150 outpatient clinics and private practices specializing in rheumatology.[15] From May 1, 2001, to December 31, 2006, all patients with rheumatoid arthritis starting new treatment with either infliximab, etanercept, adalimumab, or anakinra and patients who were changing their DMARD treatment after at least 1 DMARD failure (control group) were asked by their rheumatologist to participate in the register. Once enrolled, data collection from the patients would continue until the end of 2011. The study protocol was approved in 2001 by the ethics committee of the Charité University School of Medicine, Berlin, Germany. Every patient participating in the study provided written informed consent before study entry.

At baseline and during fixed points of follow-up at 3, 6, 12, 18, 24, 30, and 36 months, data regarding treatment, disease activity (tender and swollen joint count, erythrocyte sedimentation rate, C-reactive protein level, and morning stiffness), comorbid conditions, and adverse events were recorded by the treating rheumatologist. Treatment information included the start and stop dates of DMARD therapy, as well as biologic therapies, reasons for treatment termination, and concomitant therapy with glucocorticoids, nonsteroidal anti-inflammatory drugs, or cyclooxygenase 2 selective inhibitors. The data recorded by the rheumatologist were complemented by patient questionnaires that also assessed functional capacity (measured by the Hannover Functional Status Questionnaire as percentage of full function[16]], global health status, pain, current disease activity, and adverse effects of the prescribed medications.

Adverse events were recorded and classified by the rheumatologist as serious or nonserious according to the International Conference on Harmonization E2A guidelines.[17] In addition, these events were graded as mild, moderate, or severe.[18] All adverse events were coded using the Medical Dictionary for Regulatory Affairs[19] by the study physician (A.S.).

All events reported from the treating rheumatologist prior to November 1, 2007, and coded as herpes zoster, herpes zoster multidermatomal, herpes zoster disseminated, herpes zoster oticus, herpes zoster ophthalmic, herpes zoster iridocyclitis, and herpes zoster infection neurological were included in the analysis. All patient reports of adverse effects were additionally screened to check the completeness of the physician reports. This procedure revealed 2 additional cases of herpes zoster treated with etanercept; these were included in the analysis after confirmation with the treating physician.

We considered a patient as receiving anti–TNF-α treatment at the time of the event if treatment was ongoing or was terminated 1 month or less prior to the event. The remaining treatment periods were regarded as periods under control conditions. Because of the low number of patient-years contributed to the data set, we excluded all events and observation periods after start of treatment with anakinra (76 patient-years) or rituximab (60 patient-years). Furthermore, we excluded 152 patients (2.9%) who did not have follow-up data.

Main Study Questions

The statistical analysis plan prespecified 2 hypotheses. First, that anti–TNF-α treatment is associated with an increased risk of herpes zoster. Second, that owing to different modes of action, the risk associated with treatment with the monoclonal antibodies (adalimumab or infliximab) differs from that conferred by the receptor fusion protein etanercept when compared with conventional DMARD treatment. This second hypothesis was suggested by data regarding the biology of granulomatous infections[20] and by our previous findings regarding all herpes infections.[3] The first hypothesis of a class effect may be inappropriate if the second hypothesis of a subclass effect is true. We did not adjust for multiple testing, because in a safety analysis it is more important to detect a possible risk (low β error) than to avoid an erroneous rejection of the null hypothesis (no association).

Statistical Analysis

Crude incidence rates were calculated as the number of herpes zoster infections per 1000 patient-years of follow-up (under specific treatment). Survival analysis methods (Cox regression,

Andersen-Gill models[21]) were applied to identify risk factors for herpes zoster and to estimate the contribution of anti–TNF-α treatment to that risk. By Cox regression, the contribution of time-independent and time-dependent covariates to the first development of herpes zoster was investigated. The follow-up time following this event was not considered in this analysis. Patient characteristics at baseline (age, sex, comorbid conditions, and disease activity measured by the Disease Activity Score based on 28 joint counts [DAS28]) and parameters that varied with time during follow-up (treatment with glucocorticoids, treatment with anti–TNF-α agents, DAS28 at follow-up) were taken into account as possible risk factors.

To deal with confounding by indication, a propensity score (likelihood of being treated with anti–TNF-α agents) approach was applied. The propensity score was estimated by means of logistic regression with the covariates age, sex, number of previous DMARDs, DAS28, erythrocyte sedimentation rate, Hannover Functional Status Questionnaire score, and as additional markers of disease severity: osteoporosis (yes/no) and previous treatment with cyclosporine A (yes/no).[22] The tertiles of this score were used for stratification of the patients into 3 groups of equal size and increasing propensity score. These groups were then included as covariates in Cox and Andersen-Gill regression analyses for adjustment. This type of analysis allows showing the influence of the propensity score as a "severity indicator." We used tertiles instead of quintiles to increase the robustness of the model. Nevertheless, in a sensitivity analysis we also performed stratified regression analyses with quintiles, as proposed originally by D'Agostino.[23] Since the HRs of both analyses (stratified or with covariates) were very similar, we report only the results of the covariate adjustment. In a primary analysis, we analyzed the factors associated with the occurrence of herpes zoster in the total sample by means of Cox regression.

Based on our previous findings, we aimed to detect a 2-fold increase (HR, 2.0) in the hazard risk of developing herpes zoster in patients treated with anti–TNF-α agents. In the case of different risk profiles of anti–TNF-α agents, we aimed to detect at least a 2.5-fold increase in the hazard risk of patients treated with the monoclonal antibodies or with etanercept. To achieve 80% power for both hypotheses it was necessary to have observed 80 cases of herpes zoster, which occurred in November 2007. At that point we merged the data from the adverse events database with the clinical and treatment database and performed the current analysis.

In a secondary analysis, we selected a subsample of patients who switched treatments and had episodes while receiving anti–TNF-α therapy, as well as "control episodes" of more than 1 month of treatment with a traditional DMARD, glucocorticoids, or both. Applying Andersen-Gill models, we considered the complete follow-up time of these patients and investigated whether the first or second occurrence of herpes zoster was observed within an anti–TNF-α treatment episode or within a control episode.

Calculations were performed using the PHREG procedure in SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). Furthermore, the invariance of the herpes zoster over time was investigated by means of a test developed by Thernau and Grambsch.[24] To check for possible incompleteness in our multivariate models, standard errors and CIs of the HRs were calculated by means of robust sandwich estimates.[25] These data are not shown, since they differed only slightly from the estimates calculated using the standard methods. All statistical tests performed were 2-sided; $P < .05$ was considered statistically significant.

RESULTS

A total of 5040 patients were included in the analysis. Baseline characteristics are shown in TABLE 1. Patients receiving anti–TNF-α treatment differed significantly from controls in regard to age, disease duration, rheu-

Table 1. Baseline Characteristics

Characteristic	Anti–TNF-α Agents				Controls (n = 1774)	*P* Value[a]
	Etanercept (n = 1252)	Infliximab (n = 591)	Adalimumab (n = 1423)	Total (n = 3266)		
Age, mean (SD), y	53.8 (12.5)	52.9 (12.7)	54.2 (12.0)	53.8 (12.3)	56.2 (11.4)	<.001
Women, No. (%)	975 (77.8)	433 (73.3)	1141 (80.2)	2549 (78.0)	1394 (78.6)	.66
Rheumatoid factor–positive, No. (%)	1008 (80.5)	469 (79.4)	1143 (80.4)	2620 (80.3)	1271 (71.7)	<.001
FFbH score, mean (SD)[b]	56.0 (22.9)	55.3 (21.6)	58.6 (23.4)	57.0 (22.9)	66.6 (21.5)	<.001
Disease duration, median (IQR), y	9 (4-16)	8.5 (4-14)	10 (5-17)	9 (5-16)	6 (3-12)	<.001
DAS28, mean (SD)	5.8 (1.3)	5.9 (1.2)	5.7 (1.3)	5.8 (1.3)	5.0 (1.3)	<.001
CRP, median (IQR), mg/L	16 (5-37)	17 (7-41)	13 (5-30)	17 (8-38)	8 (3-22)	<.001
Previous DMARD therapies, No. (%)	3.6 (1.4)	3.7 (1.5)	3.5 (1.4)	3.5 (1.4)	1.8 (1.1)	<.001
Glucocorticoids, No. (%)	1073 (86.1)	498 (84.4)	1154 (81.6)	2725 (83.8)	1354 (76.5)	<.001
Prednisolone ≥10 mg/d, No. (%)	440 (35.1)	217 (36.7)	416 (29.2)	1073 (32.9)	343 (19.3)	<.001

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joint counts; DMARD, disease-modifying antirheumatic drugs; FFbH, Hannover Functional Status Questionnaire; IQR, interquartile range; TNF, tumor necrosis factor.
SI conversion factor: To convert CRP values to nmol/L, multiply by 9.524.
[a] For comparison of anti–TNF-α agents total with controls.
[b] Functional capacity in percentage of full function.

Table 2. Crude Incidence Rates of Herpes Zoster Events per 1000 Patient-years

	Anti–TNF-α Agent			
	Etanercept	Infliximab/ Adalimumab	Total	Controls
Observed patient-years	2588	3524	6112	4291
Herpes zoster				
No.	23	39	62	24
Incidence rate (95% CI)	8.9 (5.6-13.3)	11.1 (7.9-15.1)[a]	10.1 (7.8-13.0)[a]	5.6 (3.6-8.3)
Multidermatomal and ophthalmic zoster only				
No.	2	13	15	4
Incidence rate (95% CI)	0.8 (0.009-2.8)	3.7 (2.0-6.3)	2.5 (1.4-4.0)	0.9 (0.3-2.4)

Abbreviations: CI, confidence interval; TNF, tumor necrosis factor.
[a]Significantly different ($P<.05$) compared with controls.

matoid factor positivity, functional status, and number of previous DMARD failures. In addition, they had higher disease activity (as measured by the DAS28) at the time of inclusion in the study. No differences in demographic or clinical characteristics were found between patients treated with the 3 individual anti–TNF-α agents.

There were 86 cases of herpes zoster among 82 patients. Fifteen patients had multidermatomal zoster, and 4 had herpes zoster ophthalmicus. Eighteen events were serious, 12 of which required hospitalization due to either severe multidermatomal disease (n=8), eye involvement (n=1), or other reasons (n=3). Complications were reported in 3 patients. Postherpetic neuralgia occurred in 2 patients (1 while receiving etanercept and 1 while receiving adalimumab), and multidermatomal zoster with esophagitis and pulmonary involvement occurred in 1 patient (while receiving infliximab).

Compared with the control group, we found significantly higher crude incidence rates of herpes zoster in the patients receiving anti–TNF-α-treatment ($P=.01$), especially in those treated with the monoclonal antibodies (TABLE 2). Among the cases of multidermatomal herpes zoster, the crude incidence rate was highest for patients treated with the monoclonal antibodies (3.8 [95% CI, 1.0-9.7] per 1000 patient-years for patients treated with infliximab and 3.6 [95% CI, 1.7-6.9] per 1000 patient-years for patients treated with adalimumab). Five patients experienced recurrent episodes of herpes zoster that were not always located at the site of the primary occurrence. Two occurred in the control group, 2 in patients receiving etanercept, and 1 in a patient receiving unknown therapy. This last patient had been enrolled in an RCT after several years of observation in RABBIT and was excluded from our analyses because the exact treatment at the time of the herpes zoster epsiode was unknown.

Univariate Cox regression analysis (TABLE 3) showed a significantly increased risk of herpes zoster with increasing age (HR, 1.23 [95% CI, 1.02-1.49] per 10 years) and higher disease activity at baseline, as measured by the DAS28 (HR, 1.36 per unit increase [95% CI, 1.14-1.63]). An insignificant association was found for longer disease duration as a risk factor. We found a nonlinear increase in the risk of herpes zoster with increasing likelihood of being treated with biologics (propensity score tertiles). Patients with a high likelihood of being treated with biologics (patients with a propensity score >0.86, constituting the upper one-third of the propensity score tertiles) had a nearly 2-fold risk of herpes zoster compared with the remaining patients (10.9 [95% CI, 7.8-14.9] per 1000 patient-years vs 6.5 [95% CI, 4.7-8.7] per 1000 patient-years). Similar results were found by stratification of patients into quintiles of the propensity score, as proposed by D'Agostino.[23] Using this strategy, patients from the fourth and fifth quintiles had a 1.9-fold significantly higher risk for herpes zoster than the remaining patients, whereas patients from the first, second, and third quintiles did not differ significantly in their risk.

Baseline features that were not significantly associated with herpes zoster were female sex, positive rheumatoid factor, and functional capacity (as measured using the Hannover Functional Status Questionnaire) at study entry. No associations ($P>.90$) were found for specific comorbid conditions (eg, diabetes, renal insufficiency, and pulmonary disease; data not shown).

Treatment factors associated with an increased risk of herpes zoster were glucocorticoid use and treatment with anti–TNF-α agents, compared with conventional DMARD treatment. The corresponding incidence rates for episodes of herpes zoster during anti–TNF-α treatment and DMARD treatment were 9.8 (95% CI, 7.5-12.6) per 1000 patient-years and 5.1 (95% CI, 3.2-7.8) per 1000 patient-years. For the monoclonal antibodies and etanercept, the rates were 11.1 (95% CI, 7.9-15.1) per 1000 patient-years and 8.1 (95% CI, 5.0-12.4) per 1000 patient-years, respectively. There was no significant trend in HR over time; therefore, the application of Cox regression analysis was appropriate. We observed a greater risk of herpes zoster associated with increasing doses of glucocorticoids (Table 3). No significant associations were found for treatment with MTX ($P=.87$), leflunomide ($P=.12$), or azathioprine ($P=.13$). The corresponding incidence rates per 1000 patient-years were 7.8 (95% CI, 5.7-10.3), 5.5 (95% CI, 2.9-9.4), and 18.4 (95% CI, 3.8-53.8), respectively.

In the multivariate Cox regression analysis, anti–TNF-α treatment as a class was not significantly associated with an increased risk of herpes zoster (HR, 1.63 [95% CI, 0.97-2.74]). In subgroup analysis, we found no significantly increased risk of herpes zoster for patients treated with etanercept, whereas patients treated with either infliximab or adalimumab had a significantly increased risk (HR, 1.82 [95% CI, 1.05-3.15]) (Table 3), although this risk was lower than the study's predefined HR threshold of 2.5

for clinical significance. The association for glucocorticoid use of 10 mg or more per day remained significant, even when the data were adjusted for age and disease severity using the propensity score (Table 3). Because of the high correlation of the DAS28 with both the propensity score and glucocorticoids use, it was not included in the multivariate model.

Subsample Analyses of Patients Who Switched Treatments

To investigate whether the adjustment by propensity score modeling was sufficient or whether selection bias resulting in higher risk for use of anti–TNF-α agents remained, we examined a subsample of 1344 patients who switched treatment at least once and therefore contributed data to the cohort while receiving anti–TNF-α treatment, as well as while receiving conventional DMARD treatment alone. On average, a patient from this subsample was treated for 15.8 months with anti–TNF-α therapy and 11.3 months with conventional DMARDs alone (TABLE 4). This subgroup of patients who had switched treatments had a higher risk of herpes zoster than the remaining sample (adjusted HR, 2.4 [95% CI, 1.5-3.9]).

We then considered the complete follow-up period of these patients and investigated whether herpes zoster was observed during control episodes or during episodes of treatment with anti–TNF-α agents. We observed incidence rates of 23.8 (95% CI, 15.5-34.8) per 1000 patient-years for treatment with monoclonal antibodies, 7.8 (95% CI, 2.5-18.2) per 1000 patient-years for treatment with etanercept, 17.9 (95% CI, 12.1-25.3) per 1000 patient-years for anti–TNF-α treatment as a class, and 6.9 (95% CI, 3.2-13.1) per 1000 patient-years for the control episodes. After adjustment for age and propensity score, treatment with anti–TNF-α agents was associated with a significantly increased risk of herpes zoster (TABLE 5). The association was highly significant for treatment with monoclonal antibodies (HR for adalimumab/infliximab vs controls, 2.91 [95% CI, 1.35-6.30]) and not significant for etanercept (HR, 1.09 [95% CI, 0.39-3.06]). Age remained a significant predictor in this analysis, whereas no association was found for treatment with glucocorticoids ($P > .70$ for any dosage).

Table 3. Risk of Herpes Zoster

Characteristic	Patients With Herpes Zoster, No.	Patient-years	Univariate Cox Regression		Multivariate Analysis	
			HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Characteristics at study entry						
Age, y[a]			1.23 (1.02-1.49)	.03	1.28 (1.05-1.55)	.01
Sex						
Men	17	2221	1 [Reference]			
Women	65	8260	1.04 (0.61-1.77)	.90		
Disease duration, y[b]			1.09 (0.98-1.22)	.10		
Rheumatoid factor						
Negative	20	2312	1 [Reference]			
Positive	62	8168	0.89 (0.54-1.48)	.66		
CRP[a]			1.04 (0.99-1.09)	.11		
DAS28			1.36 (1.14-1.63)	<.001		
FFbH[a]			0.96 (0.88-1.06)	.41		
Propensity score						
Tertile 1 (low)	19	3176	1 [Reference]			
Tertile 2 (moderate)	23	3324	1.26 (0.69-2.30)	.45		
Tertile 3 (high)	39	3571	2.06 (1.20-3.54)	.008		
High vs moderate/low	39	3571	1.84 (1.19-2.83)	.006	1.59 (1.00-2.52)	.05
Characteristics at follow-up						
Glucocorticoids, mg						
0	9	2317	1 [Reference]			
1-9	54	6681	2.06 (1.02-4.18)	.04	1.86 (0.92-3.78)	.09
≥10	19	1482	2.90 (1.30-6.47)	.01	2.52 (1.12-5.65)	.03
DAS28			1.21 (1.02-1.43)	.03		
DMARDs	22	4291	1 [Reference]			
Anti–TNF-α agents	60	6112	1.84 (1.13-3.00)	.02	1.63 (0.97-2.74)	.07
Etanercept	21	2588	1.55 (0.85-2.82)	.14	1.36 (0.73-2.55)	.33
Adalimumab/infliximab	39	3524	2.05 (1.22-3.45)	.007	1.82 (1.05-3.15)	.03

Abbreviations: CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joint counts; DMARD, disease-modifying antirheumatic drug; FFbH, Hannover Functional Status Questionnaire; HR, hazard ratio; TNF, tumor necrosis factor.
[a] In steps of 10 units or years.
[b] In steps of 5 years.

COMMENT

Although herpes zoster is a common disorder and is often reported as an adverse event during clinical trials, the association of various rheumatoid arthritis treatments with herpes zoster has been limited to a few published reports, mainly case reports. Serious herpes zoster episodes have been observed in RCTs and their open-label follow-up studies in patients with rheumatoid arthritis receiving the anti–TNF-α agents infliximab or adalimumab[26-29] but had not been reported from RCTs of patients with rheumatoid arthritis using etanercept.[30] However, it is not possible to generalize these findings, because sample sizes and follow-up times are too low. We investigated a hypothesis derived from these case reports and found a significant association between herpes zoster and treatment with the monoclonal anti–TNF-α antibodies infliximab and adalimumab; we found no significant association between herpes zoster and treatment with etanercept.

Patients with highly active rheumatoid arthritis and a history of more than 3 DMARD failures on average (and therefore a high likelihood of being treated with biologics [>85% in our data]) had a significantly increased risk of developing herpes zoster. Furthermore, a significantly higher risk was found for older age and, at least in the total sample, for treatment with glucocorticoids. The use of glucocorticoids is a known risk factor for several infections and has been shown to be associated with herpes zoster in other inflammatory diseases such as Crohn disease and ulcerative colitis.[31,32] In the present study we were not able to distinguish between the risk of herpes zoster due to the inflammatory activity of the disease itself as opposed to that due to the treatment with immunosuppressive drugs. If such an effect were present, it would be strongly confounded by treatment with glucocorticoids, which decrease cell-mediated immunity.

Our findings of an increased risk of VZV reactivation associated with anti–TNF-α antibody treatment are supported by the results of Smitten et al, who analyzed 2 large databases in the United States and United Kingdom[14] and reported an increased risk of herpes zoster in patients receiving biologic agents (odds ratio compared with patients with rheumatoid arthritis but not receiving DMARDs or glucocorticoids, 1.54) as well as for patients receiving DMARDs alone or glucocorticoids. Because Smitten et al were not able to adjust for the severity of rheumatoid arthritis, their comparator group might not be fully comparable.

In contrast, Wolfe et al[13] did not find an increased risk for infliximab, etanercept, or adalimumab in the National Data Bank for Rheumatic Diseases. The authors based their analysis on patient answers to a herpes zoster–specific question in the National Data Bank questionnaire; these answers were validated in a subsample by physician confirmation. We used physician diag-

Table 4. Baseline Characteristics of Patients Who Changed Treatment From Biologics to DMARDs or Vice Versa

Characteristic	Etanercept	Infliximab/ Adalimumab	Controls	Total
No.	361	677	306	1344
Age, mean (SD), y	55.2 (12.9)	54.5 (12.3)	53.7 (11.2)	54.5 (12.2)
Women, No. (%)	282 (78.1)	525 (77.6)	231 (75.5)	1038 (77.2)
Rheumatoid factor–positive, No. (%)	299 (82.8)	545 (80.5)	227 (74.2)	1071 (79.7)
DAS28, mean (SD)	5.8 (1.2)	5.9 (1.2)	5.5 (1.2)	5.8 (1.2)
CRP, median (IQR), mg/L	19 (9-38)	17 (7-40)	14 (6-33)	16 (7-37)
Previous DMARDs, No. (%)	3.7 (1.6)	3.7 (1.4)	2.2 (1.3)	3.4 (1.6)
Glucocorticoids, No. (%)	314 (87.0)	557 (82.5)	250 (82.0)	1121 (83.6)
Duration of treatment episodes, mean (SD), mo				
1st episode	9.4 (7.7)	8.8 (7.4)	15.8 (12.9)	9.8 (7.9)
2nd episode	8.2 (9.6)	7.6 (8.5)	14.5 (13.5)	8.6 (9.0)
With biologics per episode	16.9 (10.7)	16.2 (10.8)	13.8 (9.1)	15.8 (10.5)
Control periods, No. (%)	11.1 (9.7)	9.7 (8.8)	15.0 (9.2)	11.3 (9.4)

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joint counts; DMARD, disease-modifying antirheumatic drug; IQR, interquartile range.

Table 5. Risk of Herpes Zoster: Andersen-Gill Model[a]

	Herpes Zoster Episodes, No.	Patient-years	Adjusted HR (95% CI)[b]	*P* Value
Characteristics at study entry				
Age, y[c]			1.50 (1.12-2.01)	.006
Propensity score				
Tertiles 1 and 2 (moderate/low)	18	1727	1 [Reference]	
Tertile 3 (high)	22	1342	1.53 (0.82-2.83)	.18
Characteristics at follow-up				
DMARDs	9	1301	1 [Reference]	
Anti–TNF-α	31	1736	2.24 (1.05-4.75)	.04
Etanercept	5	642	1.12 (0.39-3.17)	.84
Adalimumab/infliximab	26	1094	2.91 (1.35-6.30)	.007
Analyses for single agents				
Etanercept	5	642	1.09 (0.39-3.06)	.87
Adalimumab	18	717	3.01 (1.36-6.64)	.007
Infliximab	8	377	2.43 (0.94-6.26)	.07

Abbreviations: CI, confidence interval; DMARD, disease-modifying antirheumatic drug; HR, hazard ratio.
[a] Includes only patients who changed treatment from biologics to DMARDs or vice versa. Four of the patients experienced 2 episodes.
[b] Adjusted for age and disease severity (propensity score).
[c] In steps of 10 years.

noses for our analysis and checked them with the patient reports for completeness. Patients reported herpes simplex more frequently than physicians, but we found only 2 additional patient reports of herpes zoster.

Herpes zoster cases published in RCTs have been serious events[28] or associated with severe complications, including 1 case of encephalitis[28] and 1 death after secondary streptococcal A superinfection (necrotizing fasciitis).[29] In our data, only 20% of the herpes zoster epsiodes were classified as serious events, which could explain our higher rates in comparison to the RCTs. Recently it was reported that the risk of serious infections observed in patients with rheumatoid arthritis who are receiving biologics decreases with longer treatment duration.[4,5] However, we did not find a decrease in HRs for herpes zoster events with longer duration of anti–TNF-α treatment.

Our study has several limitations. First, though our results indicate a significant difference between monoclonal antibodies and conventional DMARD treatment, the HR of 1.8 did not reach our predefined threshold for clinical significance. Second, we cannot completely rule out a type I error greater than 5%, because we decided not adjust for multiple testing in order to be more sensitive in the detection of a possible risk. Third, our analyses are based on a limited number of herpes zoster episodes. Fourth, the observational character of the study may account for a possible residual confounding by indication.

To improve control of confounding factors, we applied Cox regression analyses in a robust way and, more importantly, examined a subsample of patients who experienced a change in therapy and therefore had been observed under different treatment regimens. The strength of this analysis was that each patient served as his or her own control, thus carrying his or her own risk factors while receiving different treatments. Furthermore, second occurrences of herpes zoster in the same patients could be taken into account. Compared with the multivariate Cox regression analysis, this analysis showed a stronger relationship between VZV reactivations and treatment with anti–TNF-α agents and supports the finding of different risk profiles of the individual anti–TNF-α agents.

It is possible that the observed effect of the different drugs on risk of herpes zoster is the consequence of their different molecular mechanisms of action. A similar difference has been observed in risk of tuberculosis reactivation, for which substantial differences have been found regarding treatment with the monoclonal antibodies compared with the soluble receptor fusion protein.[33,34] This idea is plausible, considering that etanercept is not effective to treat inflammatory bowel diseases such as Crohn disease, whereas infliximab and adalimumab are successful therapeutic options. These differing treatment effects could correspond with differing safety profiles.

Varicella and its reactivation as herpes zoster are vaccine-preventable diseases. The Shingle Prevention Study showed that vaccination of adults 60 years or older reduced the incidence of herpes zoster from 11.1 to 5.4 cases per 1000 person-years.[35] Additionally, the severity of herpes zoster and the number of complications were reduced significantly in those for whom the disease developed despite vaccination. Vaccination is therefore recommended for seronegative patients for whom immunosuppressive therapy is planned. The situation is less clear for patients with active rheumatoid arthritis who are in need of treatment with anti–TNF-α agents. The varicella vaccine contains live, attenuated virus. There have been reports of disseminated disease with fatal outcome caused by use of live vaccines in immunocompromised patients.[36,37] As a result, live vaccines are contraindicated during treatment with anti–TNF-α drugs. If immunization with live vaccine is indispensable, it should be given at least 3 weeks[38] before anti–TNF-α treatment is started or after anti–TNF-α treatment has been stopped for at least 5 half-lives.[39]

In contrast to the herpes zoster episodes reported in RCTs, our findings regarding serious complications such as bacterial superinfections, long-lasting postherpetic neuralgia, or ocular complications are reassuring; despite sometimes highly suppressed immunity and high disease activity, major complications were rare for all of the treatments. We believe that the efficient antiviral treatments currently available are mainly responsible for preventing the development of these complications.

Aside from age and disease severity, glucocorticoid use and treatment with the monoclonal anti–TNF-α antibodies adalimumab and infliximab appears to be associated with an increased risk of herpes zoster. Our data suggest that risk is not increased with the receptor fusion protein etanercept. Based on our data, we recommend careful monitoring of patients treated with monoclonal anti–TNF-α antibodies for early signs and symptoms of herpes zoster.

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Study concept and design: Strangfeld, Listing, Zink.
Acquisition of data: Strangfeld, Herzer, Liebhaber, Rockwitz, Richter.
Analysis and interpretation of data: Strangfeld, Listing, Zink.
Drafting of the manuscript: Strangfeld, Listing.
Critical revision of the manuscript for important intellectual content: Herzer, Liebhaber, Rockwitz, Richter, Zink.
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