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MAJOR ARTICLE

Risk of Herpes Zoster in Individuals on Biologics, Disease-Modifying Antirheumatic Drugs, and/or Corticosteroids for Autoimmune Diseases: A Systematic Review and Meta-Analysis

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Background. Studies examining the risk of herpes zoster (HZ) associated with immunosuppressants, such as biologics, nonbiological disease-modifying antirheumatic drugs (nbDMARDs), or corticosteroids, have generated conflicting results.

Methods. We conducted a systematic literature search from January 1946 to February 2016. Search terms related to HZ, rheumatoid arthritis, psoriasis, psoriatic arthritis, systemic lupus erythematous, or inflammatory bowel disease, biologics, nbDMARDS, and corticosteroids were used. We included randomized controlled trials (RCTs) and observational studies reporting associations between immunosuppressants and HZ outcomes in adults. For RCTs, we used the Mantel-Haenszel fixed-effects model to estimate pooled odds ratios (ORs) and 95% confidence intervals (CIs) for HZ risk. For observational studies, adjusted ORs were pooled separately using random-effects inverse variance models.

Results. Data were pooled from 40 eligible RCTs (20 136 patients) and 19 observational studies (810 939 patients). Biologics were associated with a greater risk of HZ than control (RCTs: OR = 1.71, 95% CI = 1.11–2.64; observational studies: OR = 1.58, 95% CI = 1.39–1.81). In RCTs, the OR of non-tumor necrosis factor (TNF) blockers was 2.19 (95% CI 1.20–4.02), but that of TNF blockers was not significantly different from control. Increased risks of HZ with nbDMARDs (OR = 1.21; 95% CI = 1.15–1.28) and corticosteroids (OR = 1.73; 95% CI = 1.57–1.89) were observed in observational studies, but few RCTs examined these comparisons.

Conclusions. Immunocompromised patients receiving biologics were associated with an increased risk of HZ. The risk is also increased with corticosteroids and nbDMARDs. These findings raise the issue of prophylaxis with zoster vaccine in patients initiating immunosuppressive therapy for autoimmune diseases.

Keywords. biologics; DMARDs; herpes zoster; immunocompromised; rheumatoid arthritis.

Infection with varicella zoster virus, usually during childhood, leads to the virus seeding sensory ganglia and remaining dormant [1]. Reactivation of the virus later in life leads to herpes zoster (HZ) or shingles infection [1], which is characterized by a unilateral vesicular and painful rash, usually in a single dermatome [2]. Herpes zoster causes much morbidity including pain, depression, and long-term disability in the form of postherpetic neuralgia (PHN), pain that continues after the rash has subsided [2, 3]. More than 90% of the population has serologic evidence of varicella infection, and approximately 1 in 3 persons will develop HZ during their lifetime, leading to approximately 1 million HZ cases per year in the United States [1, 4]. However, the majority of treatment for HZ and PHN takes place on an outpatient basis with reported rates of HZ-related hospitalization ranging widely from 2 to 25 per 100 000 person-years [5]. The medical cost of treating HZ in the United States has been estimated to be approximately $1.1 billion US dollars per annum [6].

Rates of HZ infection in the general population are approximately 3 to 5 per 1000 person years, and interestingly these rates are increasing over time [4, 5]. The risk of HZ seems to increase with decreasing cellular immunity, which is responsible for holding the varicella virus in check [7]. Thus, the most important risk factors for developing HZ are age and decreasing immune status [1, 5]. For example, studies have shown that rates of HZ infection in those 60 years of age and over is 6–8 per 1000 person years, and rise to 8–12 per 1000 person years in persons 80 years of age [1, 5]. Herpes zoster risk is also higher in individuals who are immunocompromised due to autoimmune diseases, solid organ or stem cell transplants, human immunodeficiency virus (HIV), and/or immunosuppressive medications that impair T-cell immunity [8]. These medications include corticosteroids, biologics, such as tumor necrosis factor (TNF)-α blockers, or nonbiologic disease-modifying antirheumatic drugs (nbDMARDs), that is, conventional synthetic DMARDs, such as methotrexate, and

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targeted synthetic DMARDs, such as tofacitinib [8]. Not only are elderly and immunocompromised individuals at higher risk for HZ, but they are also more likely to develop HZ-related complications. As such, studies have found the medical costs of treating HZ for immunocompromised patients to be nearly twice as high as other HZ patients, due to the higher rates of PHN and other complications in this group [5, 6].

There are multiple studies reporting the risk of HZ associated with individual immunosuppressants in patients with autoimmune diseases such as rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, systemic lupus erythematous (SLE), and inflammatory bowel disease (IBD). However, the results are conflicting and statistical significance is often not detected due to the low incidence of HZ. We therefore conducted a systematic review and meta-analysis of published studies to assess the association of biologics, nbDMARDs, corticosteroids, or combinations and risk of HZ in adults with autoimmune diseases.

METHODS

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9] statement for randomized controlled trials (RCTs) and guidelines for the reporting of observational studies (OBS) and adverse events (AEs) [10, 11]. A prespecified study protocol was developed before the literature review and followed but was not registered.

Literature Search

We conducted a systematic literature search using MEDLINE, EMBASE, Google, Google Scholar, Cochrane, CAB Direct, CINAHL, Web of Knowledge, and PubMed for articles reporting on herpes infection in immunocompromised patients published between January 1946 and February 2016. Search terms, as both keywords and subject headings, included (*Immunosuppress*, antirheumatic*, methotrexate, azathioprine, 6-mercaptopurine, cyclophosphamide, cyclosporine, prednisone, corticosteroids, steroids, leflunomide, mycophenolate, tacrolimus, sirolimus, infliximab, adalimumab, etanercept, abatacept, rituximab, golimumab, certolizumab, tocilizumab, apremilast, ustekinumab, vedolizumab, biologics, mono-clonal antibodies, tumour necrosis factor (TNF) antibody, TNF, disease modifying agent, disease modifying antirheumatic drug (DMARD), DMARD, anakinra, natalizumab, tofacitinib, belimumab*) AND *(SLE, IBD, Crohn's disease, ulcerative colitis, RA, ankylosing spondylitis [AS], psoria*)* AND *(HZ, herpes virus, shingles*). We also conducted a manual search by reviewing the reference lists of included studies. The literature search was performed by 2 authors (E. L. and V. K.). Uncertainty and revisions were discussed with another author (F. M.).

Inclusion and Exclusion Criteria

We included studies if they compared the incidence of HZ between biologics, nbDMARDs, corticosteroids, or placebo in adults with RA, psoriasis, psoriatic arthritis, SLE, or IBD. We only included the biologicals that have been approved by the US Food and Drug Association and/or European Medicines Agency. Only RCTs and OBS, consisting of cohort studies and case-control studies, were eligible. We excluded SLE and non-SLE RCTs with fewer than 15 and 50 patients in each arm, respectively, because they were unlikely to be able to detect sufficient HZ events [12]. Due to the lack of randomization in OBS, eligible studies were those providing adjusted or propensity score-matched associations. We excluded non-English, nonhuman, nonadult (ie, juvenile disease), and unpublished studies. Finally, although individuals with HIV, solid organ transplant, and cancer may also receive treatment with biologicals, nbDMARDS, and/or corticosteroids, we excluded these individuals because the mechanisms of the immunosuppression is distinct in each of these diseases and thus it is very likely that the background risk of HZ is very different in each of these diseases.

Data Extraction, Study Verification, and Quality Assessment

Data were extracted independently by 2 authors (E. L. and V. K.) using a standardized abstraction form. Discrepancies were resolved through discussion with 2 other authors (F. M. and K. R.). Data extracted from the studies included the author, date of the study, baseline characteristics of patients (underlying autoimmune disease, age, sex), total number of subjects, study duration, treatment, number of patients in each medication group, duration of treatment, person-years, HZ definition, and incidence of HZ within the different medication groups.

For RCTs, where possible, we included all AEs reporting of HZ. If not recorded as such, we examined serious AEs (SAEs) of HZ, which were generally defined as HZ that is either life-threatening, causing hospitalization, or significant disability or incapacity. For the OBS, we included outcome definitions of HZ from either diagnostic records and/or adjunctive use of antiviral medications, patient or physician report. Although the primary data source was published data, for the RCT data, we searched the US National Institutes of Health trial registry and results database (https://clinicaltrials.gov) and contacted all principal investigators to verify the HZ definition used, whether SAE or not, and the reported numbers. We also contacted authors of OBS if any clarification was needed.

Two authors (E. L. and V. K.) independently conducted the quality assessment of the studies using the Cochrane Risk of Bias tool [13] and the Newcastle-Ottawa quality assessment scale [14] for RCTs and cohort/case-control studies, respectively. Points were awarded to OBS for comparability if they controlled or adjusted for age and concomitant medications because both are considered important risk factors for HZ [1, 8]. Discrepancies were resolved through discussion with another author (F. M. or K. R.).

Statistical Analysis

Because HZ is a rare event, we used the Mantel-Haenszel fixed-effects model to calculate pooled odds ratios (ORs) and

95% confidence intervals (CIs) for the risk of HZ associated with various immunosuppressants from the RCT data [15]. Due to imbalances in patient numbers across some study arms, we applied a continuity correction that was inversely proportional to the relative size of the opposite arm of the study [16]. For OBS, adjusted ORs were pooled separately using the inverse variance method. Random-effects models were used due to expected heterogeneity.

Primary analyses compared the risk of HZ of biologics (categorized by anti-TNF and non-TNF), nbDMARDs, and corticosteroids to control/placebo. For the RCTs, we either compared biologics to placebo or biologic + control therapy to control therapy. Secondary analyses compared the risk of HZ in biologics to the nbDMARDS and in combination treatments (biologics and nbDMARDS) compared with control/placebo.

We measured heterogeneity across studies using the I^2 statistic, with higher values reflecting increasing heterogeneity [16]. Sources of heterogeneity were assessed by subgroup analysis and by meta-regression. Specifically, subgroups were examined by disease, mean age, gender ratio, and RCT outcomes categorized both according to general AE/SAE and high risk of bias or not. We assessed publication bias by examining funnel plots and performing the Egger test for asymmetry [17]. Pooling RCT data with many zero events can lead to mathematical instability, and although the Mantel-Haeszel fixed-effect method has been shown to perform well for this situation [15], as a sensitivity analysis we also estimated the pooled RCT estimates using a fixed-effects Peto method and random-effects Poisson regression, which also allow for baseline study variability and any between-study heterogeneity [18, 19]. Stata version 12.1 (StataCorp, College Station, TX) was used for analysis. Statistical tests were 2 sided with $P < .05$ defining statistical significance.

RESULTS

Search Results and Trial Characteristics

The literature search and the manual search of reference lists identified 4225 studies (Figure 1). Of these, the majority were excluded after reviewing the title and/or abstract. Two hundred eighty-one studies were included for a full article review and 57 studies were included after detailed assessment, corresponding to 40 RCTs (2 studies reported results of 2 RCTs in 1 paper) [20–57], 16 cohort studies [58–72], and 3 case-control studies [73–75]. Reasons for exclusion were mainly irrelevance, study design, duplication, and lack of quantitative data about the incidence of HZ associated with individual medication or medication class.

The baseline characteristics of the patients included for analysis are summarized in Tables 1 and 2. In total, 20 136 patients were included in the RCTs and 810 939 in the OBS. The mean age of patients ranged from 25 to 75 years, and the percentage of women ranged from 9% to 87%. Study follow-up duration ranged from 6 to 104 weeks in the RCTs and 37–600 weeks in the OBS. Most studies focused on RA patients (25 of 40 RCTs and 14 of 19 observational), whereas a smaller number evaluated other autoimmune diseases. A wide variety of biologic agents, nbDMARDs, corticosteroids, and various combinations of these agents were evaluated.

Included Studies and the Risk of Bias

Assessment of study validity revealed a potential risk of bias amongst some RCT studies (eTable 1), with 21 of 40 being

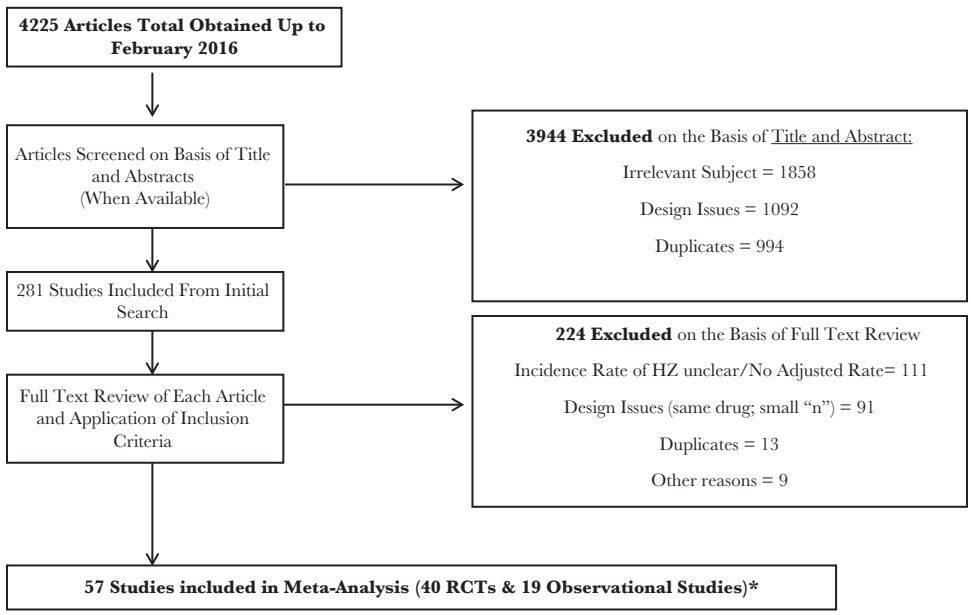


Figure 1. Study selection and included studies. *Two papers reported results of 2 randomized control trials in 1 article. HZ, herpes zoster.

Table 1. Characteristics of Randomized Controlled Trials Included in the Meta-Analyses

	Study, Year	Total Subjects[a]	Disease State[b]	Mean Age (years)	Gender (% Female)	Follow-up Duration (Weeks)[c]	Herpes Zoster Definition[d]	Treatment Group[e,f]	N[g]	Comparator Group(s)[e,f]	N[g]
1	Alarcon-Segovia 2003	230	SLE	36	90	76	AE	B/ Abetimus 100 mg q16 wk, then alternating 8-week drug holidays and 12 weekly treatments with 50 mg	114	Placebo	116
2	Bachelez 2015	1106	P	44	30	12	AE	D/Tofacitinib 5 or 10 mg BID	662	Placebo	108
								B/ ETA 50 mg BIW	336		
3	Bejarano 2008	148	RA	47	56	56	SAE	B/ ADA + D/ MTX 15.5 mg/wk	75	Placebo + D/ MTX 16.2 mg/wk	73
4	Braun 2011	566	AS	41	26	16	AE	B/ ETA 50 mg/wk	379	D/ Sulfasalazine 2.8 g/d	187
5	Bresnihan 1998	472	RA	53	75	24	SAE	B/ IL-1Ra (anakinra) 30 mg, 75 mg, or 150 mg × 1	351	Placebo	121
6	Cardiel 2008	317	SLE	–	–	94	AE	B/ Abetimus 100 mg/wk	158	Placebo	159
7	Chen 2013	396	RA	48	87	24	AE	B/ ETA (Anbainuo) 25 mg BIW + D/ MTX 15 mg/wk	132	D/ MTX 15 mg/wk	132
								B/ ETA (Anbainuo) 25 mg BIW	132		
8	Emery 2008	542	RA	51	73	52	SAE	B/ ETA 50 mg/wk + D/ MTX 7.5 mg/wk	274	D/ MTX 7.5 mg/wk	268
9	Emery 2015	351	RA	47	78	52	SAE	B/ ABA 125 mg/wk SC + D/ MTX 7.5 mg/wk titrated to 15–20 mg/wk after 6–8 wks	119	D/ MTX 7.5 mg/wk titrated to 15–20 mg/wk after 6–8 wk	116
								B/ ABA 125 mg/wk SC	116		
10	Fleischmann 2012	384	RA	53	48	24	AE	D/Tofacitinib 1, 3, 5, 10, 15 mg BID	272	Placebo	59
								B/ ADA 40 mg/qow until wk 12, then add tofacitinib 5 mg BID until wk 24	53		
11	Fleischmann 2013	1190	RA	52	83	104	SAE	B/Tocilizumab 4 mg/kg or 8 mg/kg + D/ MTX 10–25 mg/wk	798	Placebo + D/ MTX 10–25 mg/wk	392
12	Furie 2014	298	SLE	31	84	52	SAE	B/ ABA 30 mg/kg on days 1, 15, 29, and 57, followed by ABA 10 mg/kg on days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337; or 10 mg/kg on all infusion days + D/ MMF + C/	198	Placebo + D/ MMF + C/	100
13	Furst 2003	636	RA	55	79	24	SAE	B/ ADA 40 mg q2wk	318	Placebo	318
14	Genovese 2008	1216	RA	53	82	24	SAE	B/Tocilizumab 8 mg/kg q4wk	802	Placebo	414
15	Kameda 2011	147	RA	57	84	52	SAE	B/ ETA 25 mg BIW + D/ MTX 7.4 mg/wk	76	B/ ETA 25 mg BIW	71
16	Keystone 2004	619	RA	57	75	52	SAE	B/ ADA 20 mg qwk or 40 mg q2wk + D/ MTX 16.5 mg/wk	419	Placebo + D/ MTX 16.7 mg/wk	200

Table 1 Continued.

	Study, Year	Total Subjects[a]	Disease State[b]	Mean Age (years)	Gender (%Female)	Follow-up Duration (Weeks)[c]	Herpes Zoster Definition[d]	Treatment Group[e,f]	N[g]	Comparator Group(s)[e,f]	N[g]
17	Kremer 2009	264	RA	51	86	6	AE	D/Tofacitinib 5 mg, 15 mg, or 30 mg BID	199	Placebo	65
18	Kremer 2010	609	RA	50	80	48	SAE	B/ Golimumab 2 mg/kg or 4 mg/kg q12wk + D/ MTX qwk	462	B/ Golimumab 2 mg/kg or 4 mg/kg q12wk	147
19	Kremer 2012	507	RA	53	81	24	AE	D/ Tofacitinib 1, 3, 5 mg, 10, 15 mg or 20 mg BID	456	Placebo	51
20	Kremer 2013	795	RA	52	82	52	AE	D/Tofacitinib 5 mg or 10 mg BID	636	Placebo - Advanced to Tofacitinib at month 3; placebos that didn't respond were put on 5 mg BID Tofacitinib; at month 6, anyone not on Tofacitinib was randomly assigned to on 5 mg or 10 mg BID	159
21	Leonardi 2008	765	P	45	31	12	SAE	B/ Ustekinumab 45 mg or 90 mg at wk 0, 4 then q12wk	510	Placebo	255
22	Merrill 2011	50	SLE	45	94	12	AE	B/ Sifalimumab 0.3, 1, 3, 10 or 30 mg/kg × 1	33	Placebo	17
23	Moutsopoulos 1978	65	SLE	25	81	≥26	AE	D/ CYC 0.5–3 mg/kg per day + C/ Pred <0.5 mg/kg per day	18	C/ Pred 0.5–1.5 mg/kg per day	18
								D/ CYC IV 0.5 g/m^2 q3m + C/ Pred <0.5 mg/kg per day	11		
								D/ AZA 1–3 mg/kg per day + C/ Pred <0.5 mg/kg per day	18		
24	Nishimoto 2007	302	RA	53	81	52	SAE	B/Tocilizumab 8 mg/kg q4wk	157	D/ MTX(85%) 7.1 mg/wk + other DMARDs	145
25	Papp 2015a	900	P	46	29	16	AE	D/Tofacitinib 5 or 10 BID	723	Placebo	177
26	Papp 2015b	959	P	45	33	16	AE	D/Tofacitinib 5 or 10 BID	763	Placebo	196
27	Rutgeerts 2005	364 (ACT1)	IBD (UC)	42	39	54	AE	B/ INX 5 mg/kg or 10 mg/kg at wk 0, 2, 6 then q8wk + C/	243	Placebo	121
28		364 (ACT2)		40	40	30		B/ INX 5 mg/kg or 10 mg/kg at week 0, 2, 6 then q8wk	241	Placebo	123
29	Sandborn 2005 (ENACT 2)	428	IBD (CD)	37	33	48	AE	B/ Natalizumab 300 mg q4wk	214	Placebo	214
30	Sandborn 2009	728	IBD (UC)	41	40	54	AE	B/ INX 5 mg/kg or 10 mg/kg at wk 0, 2, 6 then q8wk	484	Placebo	244

Table 1 Continued.

	Study, Year	Total Subjects[a]	Disease State[b]	Mean Age (years)	Gender (% Female)	Follow-up Duration (Weeks)[c]	Herpes Zoster Definition[d]	Treatment Group[e,f]	N[g]	Comparator Group(s)[e,f]	N[g]
31	Schiff 2008	431	RA	49	84	52	SAE	B/ ABA 10 mg/kg on days 1, 15, 29, then q28d up to and including day 337 + D/ MTX 16.5 mg/wk	156	Placebo + D/ MTX 16.6 mg/wk	110
								B/ INX 3 mg/kg on days 1, 15, 43, 85 and q56d thereafter + D/ MTX 16.3 mg/wk	165		
32	Schreiber 2005	292	IBD (CD)	36	63	12	AE	B/ CZP 100 mg or 200 mg or 400 mg at wk 0, 4, 8	219	Placebo	73
33	Smolen 2009	461	RA	55	80	14	SAE	B/ Golimumab 50 mg or 100 mg q4wk	306	Placebo	155
34	Smolen 2013	604	RA	48	81	52	SAE	B/ ETA 25 or 50 mg qwk + D/ MTX 10–25 mg qwk	404	Placebo + D/ MTX 10–25 mg/wk	200
35	Takeuchi 2013	308	RA	52	82	16	SAE	B/ Golimumab 50 mg or 100 mg q4wk	203	Placebo	105
36	Tanaka 2012	261	RA	51	75	16	AE	B/ Golimumab 50 mg or 100 mg q4wk + D/ MTX 6–8 mg/wk	173	Placebo + D/ MTX 6–8 mg/wk	88
37	Tanaka 2015	317	RA	53	83	12	AE	D/ Tofacitinib 1, 3, 5, 10 or 15 mg BID	265	Placebo	52
38	van der Heijde 2013	797	RA	53	85	24	AE	D/ Tofacitinib 5 or 10 BID	716	Placebo	81
39	van Vollenhoven 2012	717	RA	53	80	52	AE	D/ Tofacitinib 5 or 10 BID	454 0–26 wk, 513 27–52 wk	Placebo 0–26 wk	59
								B/ ADA 40 mg q2wk 0–52 wk	204		
40	Yamamoto 2014	230	RA	56	74	24	SAE	B/ CZP 400 mg at wk 0, 2, 4 then 200 mg q2wk	116	Placebo	114

Abbreviations: ABA, abatacept; ADA, adalimumab; AE, adverse event; AS, ankylosing spondylitis; AZA, azathioprine; B, biologics; BID, twice daily; BIW, twice weekly; C, corticosteroid; CD, Crohn's disease; CYC, cyclophosphamide; CZP, certolizumab; D, nonbiologics disease-modifying antirheumatic drug; ETA, etanercept; IBD, inflammatory bowel disease; IL, interleukin; INX, infliximab; IV, intravenous; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; P, psoriasis; Pred, prednisone; q, every; qow, every other week; RA, rheumatoid arthritis; SAE, serious adverse event; SC, subcutaneous; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; UC, ulcerative colitis.

[a]Total number of individuals randomized into one of the study arms.

[b]IBD unspecified or all types; IBD (CD + UC), both Crohn's and Ulcerative Colitis in study.

[c]Maximum follow-up period (in weeks) for each subject.

[d]Herpes zoster was defined in the study as SAE and AE (or severity not specified).

[e]Types of immunosuppressive agent(s) given to each subject.

[f]Classification of agents as TNF-α inhibitors (adalimumab, etanercept, infliximab, certolizumab, golimumab) and non-TNF-α inhibitors (abetimus, anakinra, abatacept, tocilizumab, ustekinumab, sifalimumab, natalizumab).

[g]Total number of individuals randomized into each arm.

Table 2. Characteristics of Observational Studies Included in the Meta-Analyses

	Study	Study Design	Total Subjects[a]	Disease State	Mean Age (Years)	Gender (% Female)	Mean Duration on Drug (Weeks)[b]	HZ Definition	Comparator Groups[c]	N[d]
1	Dreiher 2012	RC	22330	P	49	53	506	Record of diagnosis or prescription of antiviral	B/ Alefacept	71
									B/ Efalizumab	41
									B/ ETA	271
									B/ INX	112
									B/ ADA	129
									D/ Cyclosporine	94
									D/ MTX	1382
									C/	4126
									Control period	14 746
2	Galloway 2013	PC	15554	RA	57	75	156	Patient or rheumatologist report through mailed survey every 6 months or patient diary of hospital attendances and prescriptions	B/ TNFi (ETA, INX, and ADA)	11 881
									B/ ETA	4139
									B/ INX	3475
									B/ ADA	4267
									D/(unspecified)	3673
3	McDonald 2009	RC	20357	RA	63	9	165	Record of diagnosis (ICD-9-CM code)	C/	13 407
									D/ (Mild) Hydroxycholoroquine, sulfasalazine, auranofin, injectable gold, and penicillamine	9673
									BD/ (Moderate) MTX, LEF, AZA, CYC, cyclosporine, and anakinra	12 888
									B/ (Severe) TNFi (ETA, INX, and ADA)	3661
4	Nakajima 2015	PC	7986	RA	58	83	286	Patient report through a survey every 6 months and then confirmed with medical chart record	B	240
									D/All	6945
									D/MTX	4392
									D/TAC	80
									C (1–5 mg/d, ≥5 mg/d)	3801
5	Pappas 2015	PC	28852	RA	58	76	172	Rheumalogist diagnosis of HZ	B/ All TNFi (ETA, ADA, INX, golimumab, and CZP)	9889
									Non-TNFi	1387
									D/MTX	8864
									D/Other	2795
									C/ 0 mg	18 042
									C/ 1–7.4 mg/d	5305
									C/ >7.5 mg/d	1.496
6	Osterman 2015	RC	1994	IBD	54	63	73	Record of diagnosis (ICD-9-CM code)	B/ INX	912
									B/ ADA	505
									B/ INX + D/MTX or thiopurine	381
									B/ ADA + D/MTX or thiopurine	196

Table 2 Continued.

	Study	Study Design	Total Subjects[a]	Disease State	Mean Age (Years)	Gender (% Female)	Mean Duration on Drug (Weeks)[b]	HZ Definition	Comparator Groups[c]	N[d]
7	Segan 2015	RC	1870	RA	56	75	204	Patient report through mailed survey every 6 months	B/ ETA	733
									B/ ADA	522
									B/ INX	88
									B/ All TNFi (ETA, ADA, INX, golimumab, and CZP)	1365
									No TNFi use	297
8	Shah 2013	RC	2717	SLE	49	87	103	Record of diagnosis (ICD-9-CM code) or prescription (not specified)	C/ (Oral and injectable)	989
									No Corticosteroids	1728
9	Shalom 2015	RC	95941	P	46	51	600	Record of diagnosis and antiviral prescription	B/ ETA	1030
									B/ ADA	719
									B/ INX	392
									B/Ustekinumab	63
									D/ CYC	148
									D/MTX	4320
									B/Any TNFi + D/MTX	739
									Control	94 073
10	Strangfeld 2009	PC	5040	RA	55	78	108	Adverse event (serious or nonserious) of HZ as recorded by the rheumatologist	B/ ETA	1252
									B/ ADA and INX	2014
									B/TNFi (All 3 above)	3266
									D/ (Control)	1774
									C/ 0 mg	961
									C/ 1–9 mg/d	2663
									C/ >10 mg/d	1416
11	Veetil 2013	RC	813	RA	56	68%	533	Record of diagnosis (ICD-9 code) confirmed by reviewing medical record	B/	–
									D/ MTX	–
									D/ HC	–
									D/ Other nonbiologic DMARDs	–
									C/	–
12	Winthrop 2013	RC	59066	RA, IBD, P/PA/AS	RA 58.5, IBD 40.4, P/PA/AS 52.2	RA 86.3%, IBD 63.1%, P/PA/AS 61.4%	37	Record of diagnosis (ICD-9 code) + antiviral prescription within 30 days	B/TNFi (INX, ETA, and ADA)	33 324
									D/	25 742
									C/ 0 mg/d	28 797
									C/ 0 to <5 mg/d	14 646
									C/ 5 to <10 mg/d	8759
									C/ 10 mg/d or above	6869

Table 2 Continued.

	Study	Study Design	Total Subjects[a]	Disease State	Mean Age (Years)	Gender (% Female)	Mean Duration on Drug (Weeks)[b]	HZ Definition	Comparator Groups[c]	N[d]	
13	Wolfe 2006	PC	10614	RA, MSK	61	78	142	Patient report through survey every 6 months	B/ INX	3694	
									B/ ETA	2006	
									B/ ADA	467	
									D/ LEF	212	
									D/ AZA	329	
									D/ HC	2664	
									D/ MTX	6018	
									D/ Sulfasalazine	701	
									D/ CYC	21	
									C/	4362	
									COX-II NSAID	3587	
									Non-COX II-NSAID	4819	
14	Yun 2015	RC	29129	RA	64	85	38	Record of diagnosis (ICD-9 code) + claim for antiviral within 30 days	B/ ABA	8389	
									B/ Rituximab	4311	
									B/ Tocilizumab	1777	
									B/ ADA	4486	
									B/ CZP	1689	
									B/ ETA	3554	
									B/ Golimumab	1282	
									B/ INX	3612	
									D/ MTX	16 516	
									No MTX	12 613	
									No Corticosteroids	11 622	
									C/ <7.5 mg/d	12 962	
									C/ >7.5 mg/d	4544	
15	Zhang 2012	RC	463541	RA + P + IBD + PA + AS	75	72	104	Record of diagnosis (ICD-9 code) + claim for antiviral within 7 days	B/ TNFi (INX, ETA, ADA, and others)	–	
									B/ non-TNFi (ABA, rituximab)	–	
									D/ MTX, HC, sulfasalazine, AZA, LEF, cyclosporine, and 6-MP	–	
									No B/ nor D/	–	
									With C/	–	
									Without C/	–	
16	Zisman 2014[e]	RC	3128	RA	50	54	221	Record of diagnosis (ICD-9 code) + acyclovir IV/oral 5 days	B/ ETA + D/	158	
									No D/and no B/	1066	
										Cases	Controls

Table 2 Continued.

	Study	Study Design	Total Subjects[a]	Disease State	Mean Age (Years)	Gender (% Female)	Mean Duration on Drug (Weeks)[b]	HZ Definition	Comparator Groups[c]	N[d]	
17	Gupta 2006	RCC	2238	IBD	55	51	234	Record of diagnosis (Oxford Medical Information System and Read codes)	D/ AZA and 6-MP	22	26
									D/ Mesalamine	96	374
									D/ MTX	1	1
									C/	48	118
18	Long 2013	RCC	13129	IBD	43	55	130	Record of diagnosis (ICD-9 code)	B/ INX, ADA, or CZP	196	327
									C/	425	728
									D/ AZA or 6MP	419	806
									B/ INX, ADA, or CZP + D/ AZA or 6MP	–	–
									D/ 5ASA	744	2563
19	Smitten 2007	RCC	12888 (PharMetrics)	RA	52	73	54	Record of diagnosis (ICD-9 code)	B/ (INX, ETA, anakinra)	32	185
									D/ (MTX, AZA, TAC, LEF, CyA, CYC, HC, SZ, gold thiomalate, aurothioglucose, auranofin, and penicillamine)	306	2018
									C/	166	503
									B/ + D/	19	129
									B/ + C/	12	43
									C/ + D/	188	660
									B/, C/ and D/ MTX, AZA, TAC, LEF, CyA, CYC, HC, SZ, gold thiomalate, aurothioglucose, auranofin, and penicillamine)	11	49
									No DMARD or corticosteroid	877	7690
			13752 (GPRD)	RA	61	73	168	Record of diagnosis (Oxford Medical Information System and Read codes)	D/ DMARD (GPRD) (MTX, AZA, TAC, LEF, CyA, CYC, HC, SZ, gold thiomalate, aurothioglucose, auranofin, and penicillamine)	273	1633
									C/	240	1061
									C/ + D/ MTX, AZA, TAC, LEF, CyA, CYC, HC, SZ, gold thiomalate, aurothioglucose, auranofin, and penicillamine)	122	470
									No DMARD or oral corticosteroid	1084	8869

Abbreviations: 6-MP, 6-mercaptopurine; ABA, abatacept; ADA, adalimumab; AS, ankylosing spondylitis; AZA, azathioprine; B, biologics; C, corticosteroid; COX-II NSAID, cyclooxygenase II nonsteroidal anti-inflammatory drug; CYC, cyclophosphamide; CyA, cyclosporine A; CZP, certolizumab; D, nonbiologics disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HC, hydroxychloroquine; HZ, herpes zoster; IBD, inflammatory bowel disease; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; INX, infliximab; IV, intravenous; LEF, leflunomide; MSK, musculoskeletal disease; MTX, methotrexate; P, psoriasis; PA, psoriatic arthritis; PC, prospective cohort; Pred, prednisone (corticosteroid dose was quoted as prednisone equivalents); RA, rheumatoid arthritis; RC, retrospective cohort; RCC, retrospective case control; SLE, systemic lupus erythematosus; SZ, sulfasalazine; TAC, tacrolimus; TNFi, tumor necrosis factor-α inhibitor.

[a]Total number of individuals included in the study.

[b]Mean time on immunosuppressive agent (in weeks) for each subject

[c]Types of immunosuppressive agent(s) given to each subject.

[d]Total number of individuals taking the medication (not mutually exclusive categories).

[e]Only medication groups listed compared due to overlap with the Shalom 2015 study.

graded as having a "high" risk of bias in any domain and only 6 RCTs rated with a low risk of bias across all domains. "Unclear" was graded for most studies due to a lack of description of the details of sequence generation and allocation concealment. Although many of the studies claimed a "double-blind" design, few of them explicitly described the parties that were blinded. The risk for incomplete outcome data was graded as high for 18 of 40 RCTs because their dropout rates exceeded 20%. In contrast, the included OBS were found at low risk of bias with scores ranging from 7 of 9 to 9 of 9, as a consequence of our inclusion criteria (eTable 2 and 3).

Risk of Herpes Zoster With Biologics

Twenty-eight RCTs (n = 12 272) and 6 OBS (n = 132 647) reported the risk of HZ associated with biologics compared with control or no therapy (Figure 2). Biologics were associated with an increased risk of HZ than control in the RCT data (OR, 1.71; 95% CI, 1.11–2.64; I^2 = 0%) (Figure 2a) and in the OBS (OR, 1.58; 95% CI, 1.39–1.81; I^2 = 0%) (Figure 2b). Stratified analysis of the RCT data, according to TNF-α inhibitors, demonstrated a greater risk of HZ for the non-TNF-α inhibitors compared with placebo (OR, 2.19; 95% CI, 1.20–4.02; I^2 = 0%) and no statistically significant difference for the TNF-α inhibitors (OR, 1.28; 95% CI, 0.69–2.40; I^2 = 0%) (Figure 2a).

Risk of Herpes Zoster With Nonbiological Disease-Modifying Agents

The pooled OR for HZ with nbDMARDS compared with control across 16 RCTs was 1.61 (95% CI, 0.84–3.10, I^2 = 0%) (Figure 3a), and across 6 OBS the pooled OR was 1.21 (95% CI, 1.15–1.28; I^2 = 15%) (Figure 3b). Only the 10 RCTs studying tofacitinib examined the impact of nbDMARD dose on HZ risk. The pooled ORs (95% CI) for 1–3 mg, 5 mg, 10 mg, and 15–30 mg twice daily (BID) of tofacitinib were 0.34 (95% CI, 0.05–2.27), 2.10 (95% CI, 0.83–5.34), 3.01 (95% CI, 1.15–7.87), and 0.63 (95% CI, 0.16–2.52), respectively (eFigure 1). However, this analysis is limited by few RCTs examining tofacitinib at 1–3 or 15–30 mg BID.

Risk of Herpes Zoster With Corticosteroids

No RCTs and 15 OBS evaluated corticosteroids. The risk of HZ associated with corticosteroid use was increased significantly (OR, 1.73; 95% CI, 1.57–1.89), although there was considerable heterogeneity (I^2 = 76%) (Figure 4). Study characteristics did not explain the heterogeneity. Only 6 studies reported associations for HZ risk by corticosteroid dose. Two studies found no difference in HZ risk across dose, whereas 4 studies demonstrated increasing HZ risk with greater dose, in particular with greater than 10 mg per day (eTable 4). Because the risk of reporting bias cannot be ruled out, further analysis of corticosteroid dose was not performed.

Secondary Analyses

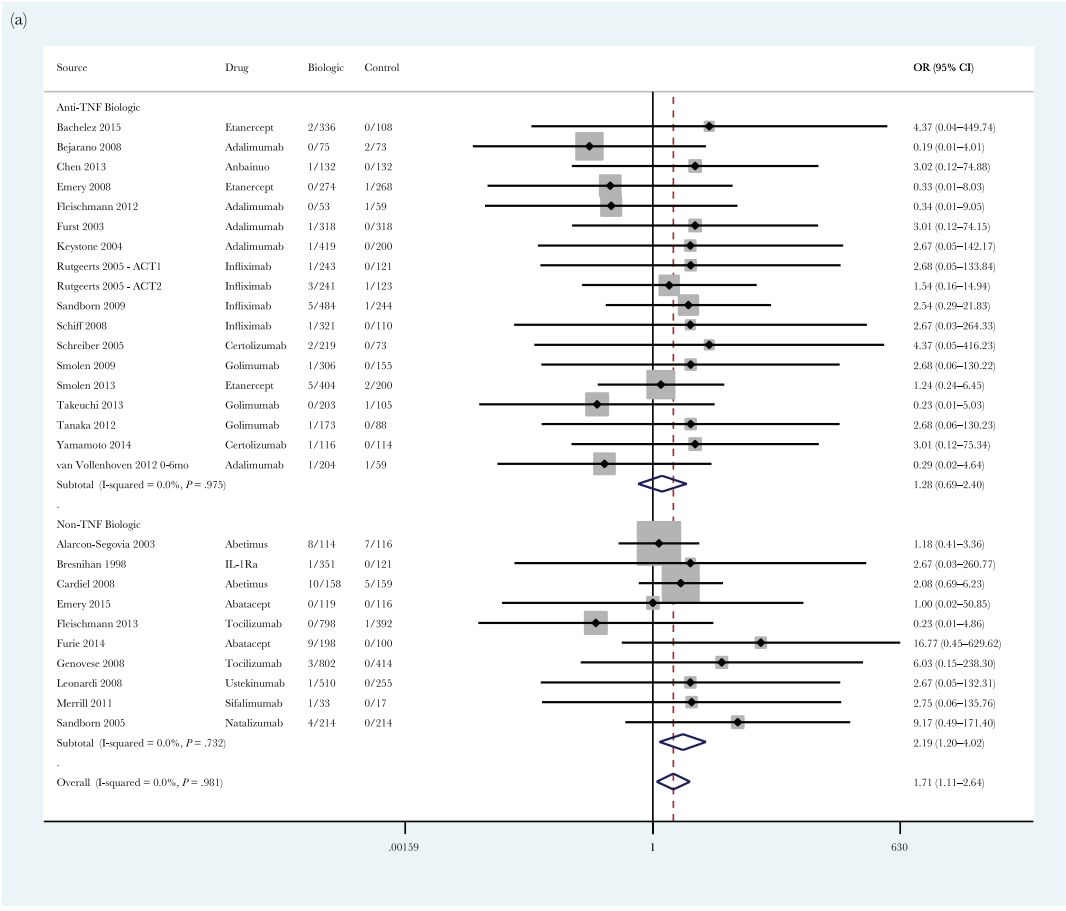
Pooled data from 7 RCTs (OR, 0.82; 95% CI, 0.40–1.67; I^2 = 0%) and 5 OBS (OR, 1.06; 95% CI, 0.69–1.61; I^2 = 71%) failed to show a significantly greater HZ risk with biologics compared with nbDMARDs (eFigure 2). Combination treatment of biologics and nbDMARD was compared with no use in 3 OBS and was associated with a greater risk of HZ (OR, 2.25; 95% CI, 1.32–3.66; I^2 = 74%), although there was considerable heterogeneity (eFigure 3).

None of the findings varied significantly by age or sex, nor by high risk of bias or reporting of AE vs SAE for the RCT data. When evaluating the risk by disease state, there was the suggestion of reduced risks in RA patients compared with the other diseases in the RCTs but not in the OBS (eTable 5). There was also no evidence of publication bias (eFigure 4 displays the funnel plot for the RCT data comparing biologics to control therapy). Pooled effect sizes for the RCT data were generally similar when we used either the fixed-effects Peto method or random-effects Poisson regression (eTable 6).

DISCUSSION

This is the first review to systematically examine the risks of HZ associated with immunosuppressants across various autoimmune disease states while including evidence from RCTs. Our meta-analysis indicates an elevated risk of HZ in immunosuppressed patients treated with biologics in both RCT and OBS. It is interesting to note that elevated risk of HZ was observed with non-TNF-α blocking agents but not TNF-α inhibitors. There was also evidence that treatment with corticosteroids or nbDMARDs increases the risk of HZ.

Two meta-analyses have evaluated HZ risk with immunosuppressive medications in RA patients specifically [76, 77]. Kourbeti et al [76] examined opportunistic infections due to biologics from 70 RCTs (N = 21 916). As a secondary analysis including 11 RCTs, they also examined varicella-zoster infection, and they found similar findings to our study, albeit not reaching statistical significance (OR, 1.51; 95% CI, 0.71–3.22). Che et al [77] compared TNF-α blockers (N = 73 510) with nbDMARDs (N = 89 567) from crude numbers obtained from OBS and found an elevated risk of HZ (OR, 1.61; 95% CI, 1.16–2.23). This association is probably greater than our pooled estimates because confounding factors such as age and disease severity were not accounted for. Numerous meta-analyses have evaluated the general risk of serious infections or opportunistic infections, defined as development of a mycobacterial, fungal, or viral infection, during treatment with biologics and/or nbDMARDs. These studies have shown a clear risk of granulomatous infections, such as tuberculosis with biologics, but not necessarily for viral infections, although this may be related to lack of standardized reporting in RCTs [8, 76, 78, 79]. There were insufficient RCT data to enable us to examine HZ risk according to specific biological agents, but we did stratify our analysis according to the type of biologic and found evidence of a greater risk of HZ with non-TNF biologics. However, this finding needs to be corroborated by other investigators. Contrary to our findings, in their



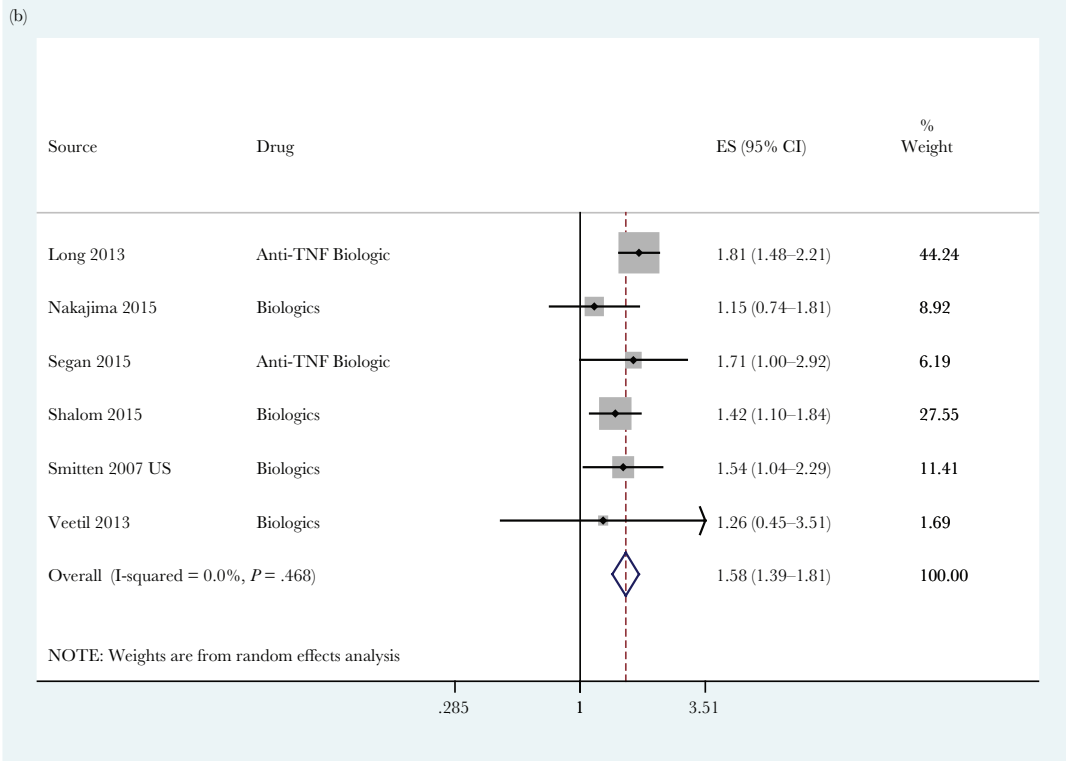
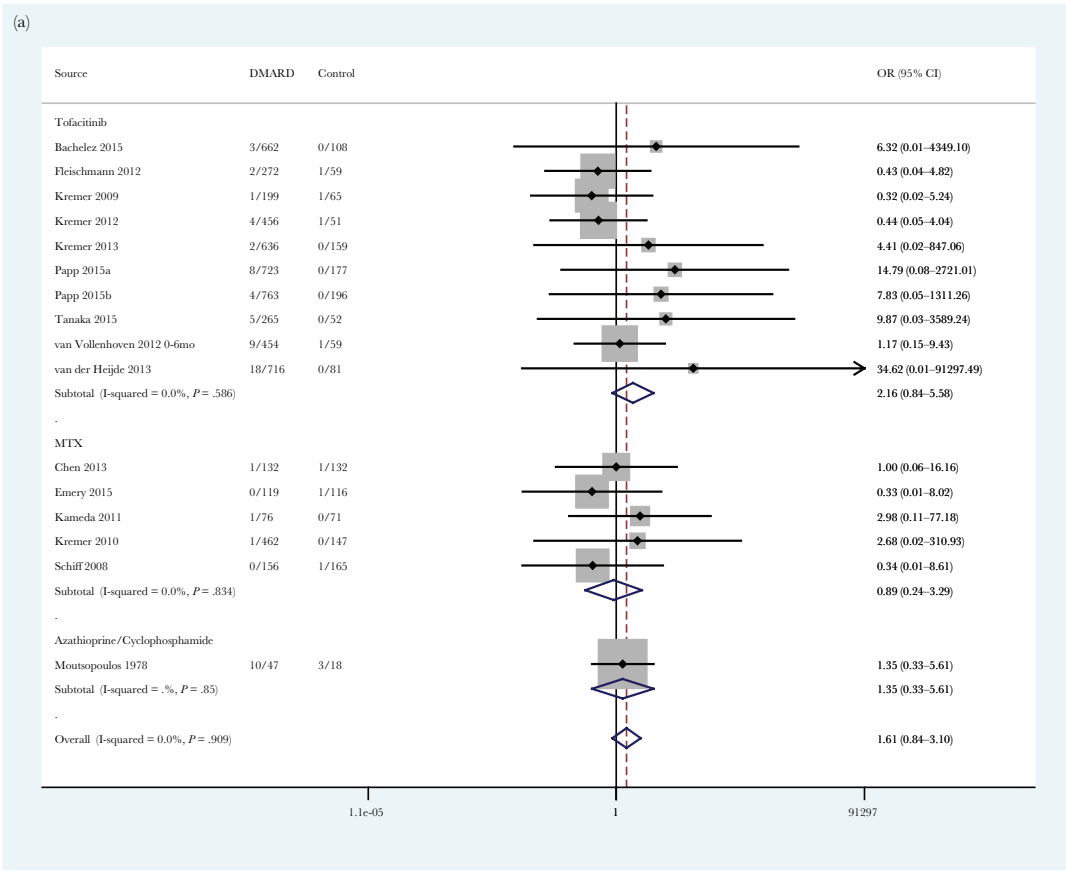


Figure 2. Risk of herpes zoster with biologics compared with control, pooled analysis of (a) randomized control trials and (b) observational studies. CI, confidence interval; ES, effect size; OR, odds ratio; TNF, tumor necrosis factor.



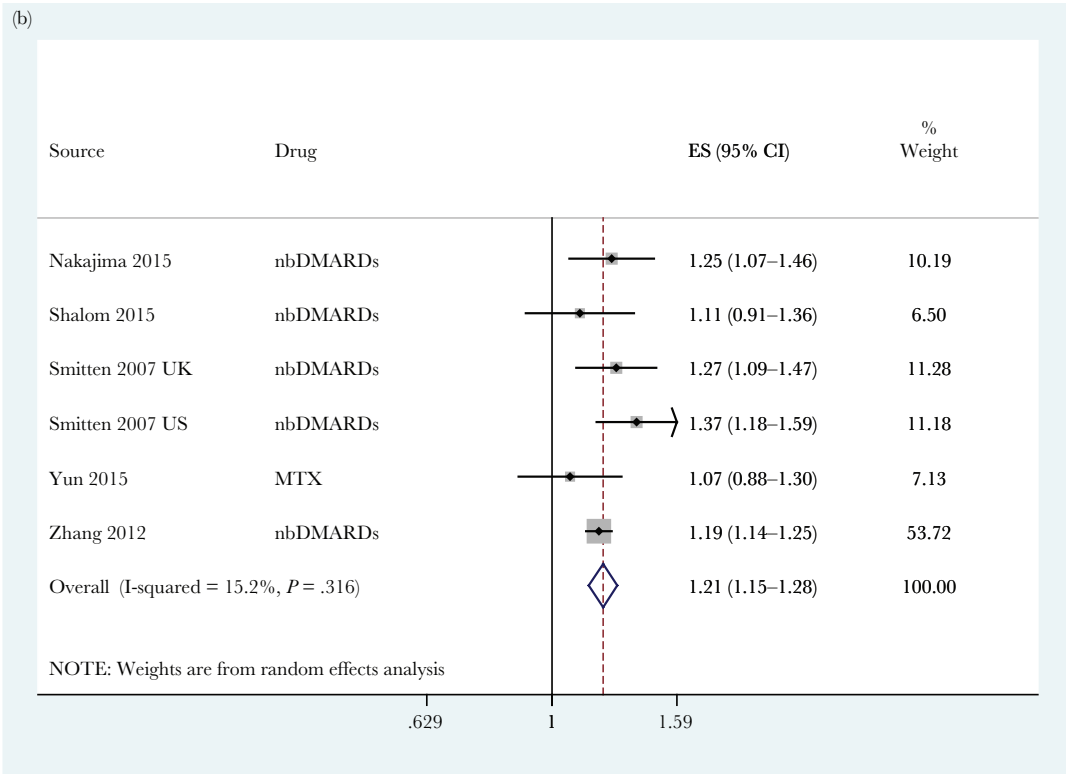


Figure 3. Risk of herpes zoster with nonbiological disease-modifying agents compared with control, pooled analysis of (a) randomized control trials and (b) observational studies. CI, confidence interval; ES, effect size; TNF, tumor necrosis factor.

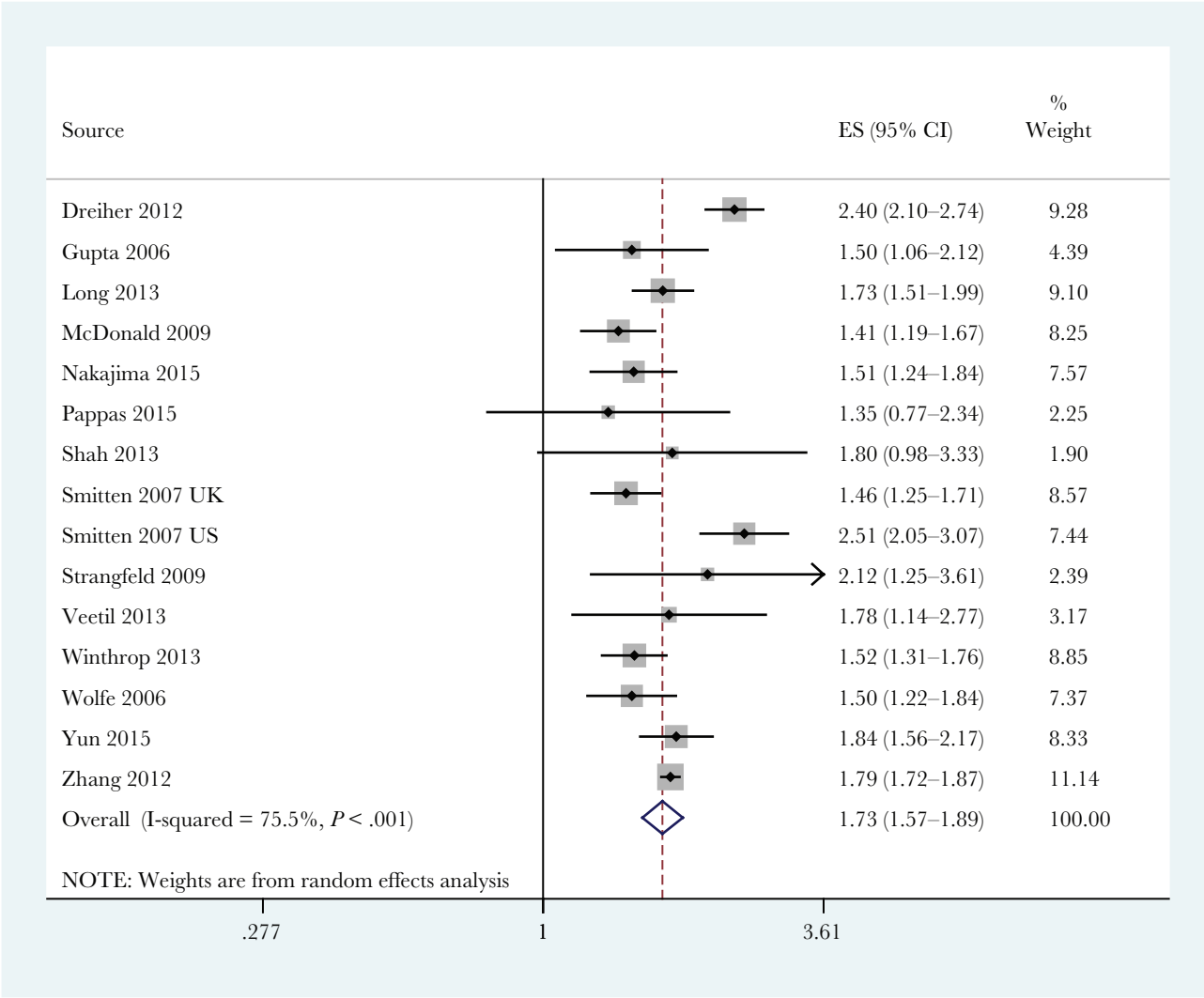


Figure 4. Risk of herpes zoster with corticosteroids compared with control, pooled analysis of observational studies. CI, confidence interval; ES, effect size.

secondary analysis, Kourbeti et al [76] found anti-TNF blocking agents, but not non-TNF-α blocking agents, to be associated with a significant risk of opportunistic infections (OR, 2.10; 95% CI, 1.27–3.45). The authors suggested that this may be due to heightened awareness of infectious complications in recent trials or that newer non-TNF-α blocking agents have a lower risk for opportunistic infections.

The conflicting data seen in the various reviews are likely related to whether the endpoint is risk of opportunistic infections or HZ specifically, the disease stage of the patients, given that some studies have shown a higher risk earlier on in their treatment course, as well as which particular immunosuppressive agents are being assessed [78]. Biologics, nbDMARDs, and corticosteroids impair B-cell and T-cell immunity through different mechanisms; therefore, one can expect different degrees of immunosuppression and different effects depending on whether the pathogen is bacterial, fungal, or viral. Furthermore, all biologics do not have the same mechanism of action. For example, those considered monoclonal antibodies, such as infliximab, golimumab, adalimumab, and certolizumab, bind to both free-floating and membrane-bound TNF-α receptors [80–82]; etanercept also inhibits TNF-α but is not a monoclonal antibody and binds to free TNF-α receptors only [81]. In addition, the monoclonal antibodies can lyse other cells involved in the inflammatory process, whereas the receptor fusion protein, etanercept, lacks this capability [81]. Non-TNF-α blocking agents are more of a mixed bag, exploiting different targets, such as antigen presenting cells (abatacept) [83], proinflammatory cytokines, and B-cell-depleting monoclonal antibodies binding CD20 (rituximab) [84], and therefore may have very different risk for the various microbes compared with the monoclonal TNF-α inhibitors. These differential mechanisms may be contributing to the differential risk with respect to serious infections, and further studies are needed to elucidate the specific infectious risk associated with specific agents.

Our meta-analysis found an increased HZ risk of approximately 21%–61% with nbDMARD treatment, but this only reached statistical significance in the pooled OBS. This may be due to the RCTs being underpowered to detect differences in rare AEs such as HZ [79]. The types of nbDMARD used in the trials and clinical practice vary considerably, and our meta-analysis studies included 8 different nbDMARDs, because such we were not able to stratify results by drug, other than tofacitinib, which had enough RCTs for us to pool the results. We found that much of the increased risk associated with the nbDMARDs was related to the newer Janus kinase (JAK) inhibitor, tofacitinib, rather than the conventional DMARDs. Increased HZ with tofacitinib was also seen in Winthrop et al's [85] meta-analysis, which evaluated data from Phase II and III studies and showed a crude incident rate of 4.4/100 person-years (95% CI, 3.8–4.9), almost 3 times the rate for TNF-α inhibitors; the risk occurred early in the treatment course rather than later. When evaluating the data according to the tofacitinib dose, we generally observed that higher doses posed an increased risk of HZ. Our literature search was completed in February 2016, and therefore we did not include 2 further studies published recently evaluating the JAK inhibitors baricitinib [86] and ruxolitinib [87]; however, both appear to cause an increased risk of zoster infection.

Our meta-analysis of OBS also showed an increased HZ risk with corticosteroid use. Corticosteroids impact almost all immune cells through transcriptional regulation of gene targets and inhibition of cellular proliferative responses by impairing phagocyte function and suppressing cell-mediated immunity, thereby plausibly increasing the risk of infection [88]. A meta-analysis of 21 RCTs and 42 OBS showed that steroid therapy was not associated with a risk of infection (relative risk [RR], 0.97; 95% CI, 0.69–1.36) when data were pooled from the RCTs, but the OBS generated a RR of 1.67 (95% CI, 1.49–1.87), although significant heterogeneity was present [89]. The authors concluded that the small number of events in the RCTs likely precluded seeing a clinically important increased or decreased risk. Our results also showed considerable heterogeneity and should be interpreted with caution. The heterogeneity could be due to a combination of differences in study design (eg, the inclusion of new users vs prevalent users), the ability to account for disease severity, or definitions of the control group and of HZ; however, we were not able to identify any consistent predictors. Most included studies did not examine the association between corticosteroid use and HZ as a primary hypothesis, and this could have contributed to the varying results. The dose-related increases in zoster risk reported by included studies is in keeping with guideline development reviews, which have identified that higher doses and longer treatment duration confer a greater risk of serious infection [90, 91].

Our study is not without limitations. We were limited by the reporting of HZ. In the RCTs, HZ was either reported as a SAE or an AE, and rather than being reported as a separate entity, it was often reported under other categories such as skin infection. We may have missed smaller studies that did not report their HZ events, and we excluded unpublished and non-English studies; however, we saw no evidence of publication bias. The studies that reported on HZ events were usually of better quality because they were larger and had structured protocols to capture rare AEs. We verified the number of HZ events in 83% of RCTs. Restricting our analysis of biologics to those verified did not affect our findings.

The minority of RCTs with substantial attrition rates are a concern. In general, they experienced greater numbers discontinuing the placebo arms due to lack of efficacy, which could have resulted in lower HZ events in the placebo arm. In contrast, studies have noted discontinuation of corticosteroid use amongst patients in biologics arms [20, 41, 45], suggesting reduced HZ risk in those arms. Hence, we do not believe HZ was consistently differentially under- or overreported in treatment arms. In addition, our findings were consistent when restricted to the studies without a high risk of bias. Our pooled estimates from the RCT data were potentially mathematical unstable because they were based on few events [8]. However, we used appropriate methods for pooling rare event data, and our estimates were very similar when other statistical approaches were applied. Unfortunately, we were unable to examine the effect of biologic dose on HZ risk because the majority of RCTs used recommended doses. We found no significant differences in HZ risk when comparing those using recommended to those using the higher end of recommended doses for biologics (results not shown). However, both the nbDMARD tofacitinib and the corticosteroids showed evidence of dose-response relationships.

Our RCT meta-analysis is strengthened by the consistent parallel evidence observed from pooled OBS that were also of high quality due to their adjustment for relevant confounders. The OBS all adjusted for age, sex, and concomitant medications, and the majority adjusted for at least a proxy for disease severity, and as such there can be considered to be limited remaining residual confounding.

Other than prompt diagnosis and initiation of antiviral therapy, prophylaxis with vaccination is an effective strategy against zoster infection. Zostavax has been demonstrated in largely healthy elderly patients of 60 years and above to decrease the risk of HZ by 51% in the 3 years postvaccination, with rates of SAE similar with placebo group [92]; a new adjuvanted, nonlive varicella-zoster vaccine was recently tested in a Phase III clinical trial in adults 50 years or above and found to have an overall efficacy of 97% [93]. Unfortunately, zoster vaccine is a live vaccine and is therefore not recommended to be administered to immunocompromised individuals, although a US study in which immunocompromised individuals who inadvertently received HZ vaccine did not have increased risk of HZ infection compared with controls [71]. Given the numerous findings on the risk of HZ with biologics, and the trend seen in our study with respect to nbDMARDS and corticosteroids, we recommend

following the Advisory Committee on Immunization Practices-issued guidance and offering the vaccine to patients before starting therapy [94, 95]. To better determine its safety profile, further efficacy trials of the nonlive HZ vaccine in patients with autoimmune disorders are also needed.

CONCLUSIONS

We demonstrated an increased risk of HZ in immunocompromized patients receiving biologics, especially non-TNF-α blockers. Increased HZ risk from corticosteroid and nbDMARD use was also observed in OBS. The use of biologics and DMARDS is now commonplace, not only in RA patients but a host of other autoimmune diseases. Our findings raise the issue of appropriate medical history and screening of patients before treatment before initiating immunosuppressants. Finally, not all biological agents are equal with respect to their potential for opportunistic infections, and postmarketing surveillance of these newer agents with different mechanisms of action than the traditional TNF-α inhibitors is vital.

Supplementary Data

Supplementary material is available at *Open Forum Infectious Diseases* online.

Acknowledgments

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. F. M. contributed to study conception and design. E. L. and V. K. performed literature search. F. M., V. K., and E. L. acquired data. K. R. performed data analysis. F. M., V. K., E. L., and K. R. interpreted the data. F. M. provided the first draft of the article. F. M., V. K., E. L., and K. R. critically revised the article for important intellectual content. F. M., V. K., E. L., and K. R. provided final approval for the manuscript.

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All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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