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 erythematosus, 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...
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 erythematosus (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, CABI 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*, anti-rheumatic*, 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 anti-rheumatic drug (DMARD), DMARD, anakinra, natalizumab, tofacitinib, belimumab) AND (SLE, IBD, Crohn's disease, ulcerative colitis, RA, ankylosing spondylitis [AS], psoriasis*) 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 adjudicate 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 comitant 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-Haenszel 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, 20136 patients were included in the RCTs and 810939 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
| Study, Year          | Total Subjects | Disease State | Mean Age (years) | Gender (%Female) | Follow-up Duration (Weeks) | Herpes Zoster Definition | Treatment Group(s) | N⁰ | Comparator Group(s) | N⁰ |
|---------------------|----------------|---------------|------------------|------------------|----------------------------|--------------------------|---------------------|-----|---------------------|-----|
| 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 |
| Bachelez 2015       | 1106           | P             | 44               | 30               | 12                         | AE                       | D/ Tofacitinib 5 or 10 mg BID B/ ETA 50 mg BIW | 662 | Placebo            | 108 |
| 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  |
| Braun 2011          | 566            | AS            | 41               | 26               | 16                         | AE                       | B/ ETA 50 mg/wk | 379 | D/ Sulfasalazine 2.8 g/d | 187 |
| Bresnihan 1998      | 472            | RA            | 53               | 75               | 24                         | SAE                      | B/ IL1Ra (anakinra) 30 mg, 75 mg, or 150 mg × 1 | 351 | Placebo            | 121 |
| Cardiel 2008        | 317            | SLE           | –                | –                | 94                         | AE                       | B/ Abetimus 100 mg/wk | 158 | Placebo            | 159 |
| Chen 2013           | 396            | RA            | 48               | 87               | 24                         | AE                       | B/ ETA (Anbainuo) 25 mg BV + D/ MTX 15 mg/wk B/ ETA (Anbainuo) 25 mg BIW | 132 | D/ MTX 15 mg/wk     | 132 |
| 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 |
| Emery 2015          | 351            | RA            | 47               | 78               | 52                         | SAE                      | B/ ABA 125 mg/wk SC + D/ MTX 75 mg/wk titrated to 15–20 mg/wk after 6–8 wks B/ ABA 125 mg/wk SC | 119 | D/ MTX 7.5 mg/wk titrated to 15–20 mg/wk after 6–8 wk | 116 |
| Fleischmann 2012    | 384            | RA            | 53               | 48               | 24                         | AE                       | D/ Tofacitinib 1, 3, 5, 10, 15 mg BID B/ ADA 40 mg/qow until wk 12, then add tofacitinib 5 mg BID until wk 24 | 272 | Placebo            | 59  |
| 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 |
| 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, 253, 281, 309, and 337; or 10 mg/kg on all infusion days + D/ MMF + C/ | 198 | Placebo + D/ MMF + C/ | 100 |
| Furst 2003          | 636            | RA            | 55               | 79               | 24                         | SAE                      | B/ ADA 40 mg q2wk | 318 | Placebo            | 318 |
| Genovese 2008       | 1216           | RA            | 53               | 82               | 24                         | SAE                      | B/ Tocilizumab 8 mg/kg q4wk | 802 | Placebo            | 414 |
| Kameda 2011         | 147            | RA            | 57               | 84               | 52                         | SAE                      | B/ ETA 25 mg BIW + D/ MTX 74 mg/wk | 76  | B/ ETA 25 mg BIW    | 71  |
| Keystone 2004       | 619            | RA            | 57               | 75               | 52                         | SAE                      | B/ ADA 20 mg q2wk or 40 mg q2wk + D/ MTX 16.5 mg/wk | 419 | Placebo + D/ MTX 16.7 mg/wk | 200 |
| Study, Year | Total Subjects | Disease State | Mean Age (years) | Gender (% Female) | Follow-up Duration (Weeks) | Herpes Zoster Definition | Treatment Group(s) | N | Comparator Group(s) | N |
|-------------|----------------|---------------|------------------|-------------------|---------------------------|--------------------------|---------------------|---|---------------------|---|
| 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/ Siilkimimumab 0.3, 1, 3, 10 or 30 mg/kg x 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 |
| 24 Nishimoto 2007 | 302 | RA | 53 | 81 | 52 | SAE | B/ Tocilizumab 8 mg/kg q4wk | 157 | D/ MTX (85%) 71 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 | 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 Subjectsa | Disease Stateb | Mean Age (years) | Gender (% Female) | Follow-up Duration (Weeksec) | Herpes Zoster Definitiond | Treatment Groupf,g | Comparator Groups,h,i | N° | N° |
|------------------------|-----------------|----------------|------------------|-------------------|-----------------------------|--------------------------|---------------------|-----------------------|-----|-----|
| 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 | Placebo + D/ MTX 16.6 mg/wk | 156 | 110 |
|                        |                 |                |                  |                   |                             |                          | B/ INX 3 mg/kg on days 1, 15, 43, 85 and q56d thereafter + D/ MTX 16.3 mg/wk |                         | 165 |       |
| Schreiber 2005         | 292             | IBD (CD)       | 36               | 63                | 12                          | AE                       | B/ CZP 100 mg or 200 mg or 400 mg at wk 0, 4, 8 | Placebo                | 219 | 73  |
| Smolen 2009            | 461             | RA             | 55               | 80                | 14                          | SAE                      | B/ Golimumab 50 mg or 100 mg q4wk | Placebo                | 306 | 155 |
| Smolen 2013            | 604             | RA             | 48               | 81                | 52                          | SAE                      | B/ ETA 25 or 50 mg qwk + D/ MTX 10–25 mg qwk | Placebo + D/ MTX 10–25 mg/wk | 404 | 200 |
| Takeuchi 2013          | 308             | RA             | 52               | 82                | 16                          | SAE                      | B/ Golimumab 50 mg or 100 mg q4wk | Placebo + D/ MTX 6–8 mg/wk | 203 | 105 |
| Tanaka 2012            | 261             | RA             | 51               | 75                | 16                          | AE                       | B/ Golimumab 50 mg or 100 mg q4wk + D/ MTX 6–8 mg/wk | Placebo + D/ MTX 6-8 mg/wk | 173 | 88  |
| Tanaka 2015            | 317             | RA             | 53               | 83                | 12                          | AE                       | D/Tofacitinib 1, 3, 5, 10 or 15 mg BID | Placebo                | 265 | 52  |
| van der Heijde 2013    | 797             | RA             | 53               | 85                | 24                          | AE                       | D/Tofacitinib 5 or 10 BID | Placebo                | 716 | 81  |
| van Vollenhoven 2012   | 717             | RA             | 53               | 80                | 52                          | AE                       | D/Tofacitinib 5 or 10 BID | Placebo 0-26 wk | 454 | 59  |
|                        |                 |                |                  |                   |                             |                          | B/ ADA 40 mg q2wk 0–52 wk | Placebo 0-26 wk | 513 |       |
|                        |                 |                |                  |                   |                             |                          | B/ CZP 400 mg at wk 0, 2, 4 then 200 mg q2wk |                         | 116 | 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.

aTotal number of individuals randomized into one of the study arms.

bIBD unspecified or all types; IBD (CD + UC), both Crohn’s and Ulcerative Colitis in study.

cMaximum follow-up period (in weeks) for each subject.

dHerpes zoster was defined in the study as SAE and AE (or severity not specified).

eTypes of immunosuppressive agent(s) given to each subject.

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

gTotal number of individuals randomized into each arm.
Table 2. Characteristics of Observational Studies Included in the Meta-Analyses

| Study | Study Design | Total Subjects | Disease State | Mean Age (Years) | Gender (% Female) | Mean Duration on Drug (Weeks) | HZ Definition | Comparator Groups | N |
|-------|--------------|----------------|---------------|-----------------|------------------|-------------------------------|----------------|-------------------|----|
| 1     | Dreier 2012  | RC             | 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     | PC             | 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 |
|       | 2013          |                |               |                 |                  |                               |                 | B/ ETA           | 4139 |
|       |              |                |               |                 |                  |                               |                 | B/ INX           | 3475 |
|       |              |                |               |                 |                  |                               |                 | B/ ADA           | 4267 |
|       |              |                |               |                 |                  |                               |                 | D/ (unspecified) | 3673 |
| 3     | McDonald     | RC             | RA            | 63              | 9                | 165                           | Record of diagnosis (ICD-9-CM code) | C/               | 13 407 |
|       | 2009          |                |               |                 |                  |                               |                 | B/ (Mild) Hydroxychloroquine, sulfasalazine, auranofin, injectable gold, and penicillinamide | 9673 |
|       |              |                |               |                 |                  |                               |                 | B/ (Moderate) MTX, LEF, AZA, CYC, cyclosporine, and anakinra | 12 888 |
|       |              |                |               |                 |                  |                               |                 | B/ (Severe) TNFi (ETA, INX, and ADA) | 3661 |
| 4     | Nakajima     | PC             | RA            | 58              | 83               | 286                           | Patient report through a survey every 6 months and then confirmed with medical chart record | B               | 240  |
|       | 2015          |                |               |                 |                  |                               |                 | D/All            | 6945 |
|       |              |                |               |                 |                  |                               |                 | D/MTX           | 4392 |
|       |              |                |               |                 |                  |                               |                 | D/TAC           | 80   |
|       |              |                |               |                 |                  |                               |                 | C (11–5 mg/d, >5 mg/d) | 3801 |
| 5     | Pappas 2015  | PC             | RA            | 58              | 76               | 172                           | Rheumatologist diagnosis of HZ | B/ All TNFi (ETA, ADA, INX, golimumumb, and CZP) | 9888 |
|       |              |                |               |                 |                  |                               |                 | 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             | 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  |
| Study          | Study Design | Total Subjects* | Disease State | Mean Age (Years) | Gender (% Female) | Mean Duration on Drug (Weeks)* | HZ Definition                                                                 | Comparator Groups** | N* |
|---------------|--------------|-----------------|---------------|------------------|-------------------|------------------------------|--------------------------------------------------------------------------------|---------------------|-----|
| 7  Segan 2015 | RC           | 1870            | RA            | 56               | 75                | 204                         | Patient report through mailed survey every 6 months                           | B/ ETA              | 733 |
|               |              |                 |               |                  |                   |                              |                                                                                  | B/ ADA              |     |
|               |              |                 |               |                  |                   |                              |                                                                                  | 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              |     |
|               |              |                 |               |                  |                   |                              |                                                                                  | B/ INX              |     |
|               |              |                 |               |                  |                   |                              |                                                                                  | B/Ustekinumab       | 63  |
|               |              |                 |               |                  |                   |                              |                                                                                  | D/ CYC              | 148 |
|               |              |                 |               |                  |                   |                              |                                                                                  | D/MTX               | 4320|
|               |              |                 |               |                  |                   |                              |                                                                                  | B/Any TNFi + D/MTX  | 739 |
|               |              |                 |               |                  |                   |                              |                                                                                  | Control             | 94  |
| 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      |     |
|               |              |                 |               |                  |                   |                              |                                                                                  | B/TNF (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/                 |     |
|               |              |                 |               |                  |                   |                              |                                                                                  | DJ/ MTX            |     |
|               |              |                 |               |                  |                   |                              |                                                                                  | DJ/ HC             |     |
|               |              |                 |               |                  |                   |                              |                                                                                  | D/ Other nonbiologic DMARDs |     |
|               |              |                 |               |                  |                   |                              |                                                                                  | C/                 |     |
| 12 Winthrop 2013 | RC      | 59066           | RA, IBD, P/PA/AS | 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/TNF (INX, ETA, and ADA) | 33  |
|               |              |                 |               |                  |                   |                              |                                                                                  | D/                 | 25  |
|               |              |                 |               |                  |                   |                              |                                                                                  | C/ 0 mg/d          | 28  |
|               |              |                 |               |                  |                   |                              |                                                                                  | C/ 0 to <5 mg/d    | 14  |
|               |              |                 |               |                  |                   |                              |                                                                                  | C/ 5 to <10 mg/d   | 87  |
|               |              |                 |               |                  |                   |                              |                                                                                  | C/ 10 mg/d or above | 6869|
| 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, B/ ETA, B/ ADA, D/ LEF, D/ AZA, D/ HC, D/ MTX, D/ Sulfasalazine, D/ CYC | 3694  |
|               |              |                   |               |                 |                  |                                   |                                                                             | C/ <7.5 mg/d, COX II NSAID                                           |                 |
| 14 Yun 2015   | RC           | 29129             | RA            | 64              | 85               | 38                                | Record of diagnosis (ICD-9 code) + claim for antiviral within 30 days        | B/ ABA, B/ Rituximab, B/ Tocilizumab, B/ ADA, B/ CZP, B/ ETA, B/ Golimumab | 8389  |
|               |              |                   |               |                 |                  |                                   |                                                                             | D/ MTX, No MTX, No Corticosteroids                                      |                 |
|               |              |                   |               |                 |                  |                                   |                                                                             | C/ <7.5 mg/d, COX II NSAID                                           |                 |
| 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 | RC           | 3128              | RA            | 50              | 54               | 221                               | Record of diagnosis (ICD-9 code) + acyclovir IV/oral 5 days                 | B/ ETA + D/ No D/and no B/                                            | 158   |
|               |              |                   |               |                 |                  |                                   |                                                                             | Cases Controls                                                     | 1066  |
| Study | Disease State | Study Design | Total Subjects | Mean Age (Years) | Gender (% Female) | Mean Duration on Drug (Weeks) | HZ Definition | Comparator Groups | N  |
|-------|---------------|--------------|----------------|-----------------|------------------|-----------------------------|----------------|-----------------|-----|
| Gupta 2006 | IBD | RCC | 2238 | 55 | 51 | 234 | Record of diagnosis (Oxford Medical Information System and Read codes) | D/ Aza and 6-MP | 22 |
|         |     |     |     |     |     |     |                      | D/ Mesalamine       | 96 |
|         |     |     |     |     |     |     |                      | D/ MTX              | 1  |
|         |     |     |     |     |     |     |                      | C/                  | 48 |
| Long 2013 | IBD | RCC | 13129 | 43 | 55 | 130 | Record of diagnosis (ICD-9 code) | B/ INX, ADA, or CZP | 196 |
|         |     |     |     |     |     |     |                      | C/                  | 425 |
|         |     |     |     |     |     |     |                      | D/Aza or 6-MP       | 419 |
|         |     |     |     |     |     |     |                      | B/ INX, ADA, or CZP + D/ Aza | –  |
|         |     |     |     |     |     |     |                      | or 6-MP             |     |
|         |     |     |     |     |     |     |                      | D/ Sasa             | 744 |
| Smitten 2007 | RA | RCC | 12888 (Phar-Metrics) | 52 | 73 | 54 | Record of diagnosis (ICD-9 code) | B/ (INX, ETA, anakinra) | 32 |
|         |     |     |     |     |     |     |                      | D/ (MTX, AZA, TAC, LEF, CyA, CYC, HC, SZ, gold thiomalate, aurothioglucone, auranofin, and penicillamine) | 306 |
|         |     |     |     |     |     |     |                      | C/                  | 166 |
|         |     |     |     |     |     |     |                      | B/ + D/             | 19  |
|         |     |     |     |     |     |     |                      | B/ + C/             | 12  |
|         |     |     |     |     |     |     |                      | C/ + D/             | 188 |
|         |     |     |     |     |     |     |                      | B/, C/ and D/ MTX, AZA, TAC, LEF, CyA, CYC, HC, SZ, gold thiomalate, aurothioglucone, auranofin, and penicillamine | 11  |
|         |     |     |     |     |     |     |                      | No DMARD or corticosteroid | 877 |
|         |     |     |     |     |     |     |                      | D/ DMARD (GPRD) (MTX, AZA, TAC, LEF, CyA, CYC, HC, SZ, gold thiomalate, aurothioglucone, auranofin, and penicillamine) | 273 |
|         |     |     |     |     |     |     |                      | C/                  | 240 |
|         |     |     |     |     |     |     |                      | C/ + D/ MTX, AZA, TAC, LEF, CyA, CYC, HC, SZ, gold thiomalate, aurothioglucone, auranofin, and penicillamine | 122 |
|         |     |     |     |     |     |     |                      | No DMARD or oral corticosteroid | 1084 |

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; TNF, tumor necrosis factor-α inhibitor.

aTotal number of individuals included in the study.
bMean time on immunosuppressive agent (in weeks) for each subject.
cTypes of immunosuppressive agents (not mutually exclusive categories).
dTotal number of individuals taking the medication (not mutually exclusive categories).
eOnly 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 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 (Figure 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.
Table 1. Pooled Risk of Herpes Zoster in Individuals on Biologics, DMARDS, and/or Corticosteroids for Autoimmune Diseases

| Source                  | Drug                        | OR (95% CI)          | Weight |
|-------------------------|-----------------------------|----------------------|--------|
| Fleischmann 2012        | Azathioprine/Cyclophosphamide | 1.12 (0.84–1.50)    | 0.00   |
| Moutsopoulos 1978       | MTX                         | 1.10 (0.88–1.38)    | 0.00   |
| Chen 2013                | Azathioprine/Cyclophosphamide | 1.12 (0.84–1.50)    | 0.00   |
| Chen 2013                | MTX                         | 1.10 (0.88–1.38)    | 0.00   |
| Fleischmann 2012        | Azathioprine/Cyclophosphamide | 1.12 (0.84–1.50)    | 0.00   |
| Moutsopoulos 1978       | MTX                         | 1.10 (0.88–1.38)    | 0.00   |
| Fleischmann 2012        | Azathioprine/Cyclophosphamide | 1.12 (0.84–1.50)    | 0.00   |
| Moutsopoulos 1978       | MTX                         | 1.10 (0.88–1.38)    | 0.00   |
| Fleischmann 2012        | Azathioprine/Cyclophosphamide | 1.12 (0.84–1.50)    | 0.00   |
| Moutsopoulos 1978       | MTX                         | 1.10 (0.88–1.38)    | 0.00   |

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.
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.

![Table and Figure](https://academic.oup.com/ofid/article-abstract/3/4/ofw205/2649125/122340)

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

Disclaimer. The funder of this study, Merck Canada Inc., had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Financial support. This work was partially supported by Merck Canada Inc. Funds were used to cover expenses related to the data extraction and statistical analysis of the meta-analysis. Merck Canada provided funding as an unrestricted grant and, as part of the University policy, was not involved with any aspect of the study, such as the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Potential conflicts of interest. F. M. has received unrestricted grants from Merck Canada that may have influenced the submitted work.

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.

References

1. Cohen JI. Clinical practice: herpes zoster. N Engl J Med 2013; 369:255–63.
2. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. Mayo Clin Proc 2009; 84:274–80.
3. Kost RG, Strauss SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. N Engl J Med 1996; 335:32–42.
4. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology 2013; 81:928–30.
5. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open 2014; 4:e004833.
6. Yawn BP, Izler RE, Wollan PC, et al. Health care utilization and cost burden of herpes zoster in a community population. Mayo Clin Proc 2009; 84:787–94.
7. Hayward AR, Herberger M. Lymphocyte responses to varicella zoster virus in the elderly. J Clin Immunol 1987; 7:174–8.
8. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006; 295:2275–85.
9. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339:b2535.
10. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000; 283:2088–12.
11. Zorrela L, Golder S, Liu Y, et al. Quality of reporting in systematic reviews of adverse events: systematic review. BMJ 2014; 348:f6668.
12. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. BMJ 2013; 346:f2304.
13. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011; 343:d5928.
14. Wells GA, Shea B, O’Connell D, et al. (2011) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Available at: www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 4 October 2016.
15. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004; 23:1351–75.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557–60.
17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–34.
18. Spittal MJ, Piriski J, Gurrin LC. Meta-analysis of incidence rate data in the presence of zero events. BMC Med Res Methodol 2015; 15:42.
19. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977; 35:1–39.
20. Alarcón-Segovia D, Tulmin JA, Furie RA, et al. LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus: results from a randomized, double-blind, placebo-controlled study. Arthritis Rheum 2003; 48:442–54.
21. Bachelez H, van der Kerkhof PC, Strohal R, et al. Takotsubo versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet Lond Engl 2015; 386:552–61.
22. Bejarano V, Quinn M, Conaghan PG, et al. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum 2008; 59:1467–74.
23. Braun J, van der Horst-Bruinsema IE, Huang F, et al. Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomised, double-blind trial. Arthritis Rheum 2011; 63:1543–51.
24. Bresnihan B, Alvaro-Gracia JM, Cobly M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998; 41:2196–204.
25. Cardiel MH, Tulmin JA, Furie RA, et al. Abetimus sodium for renal flare in systemic lupus erythematosus: results of a randomized, controlled phase III trial. Arthritis Rheum 2008; 58:2470–80.
26. Chen XX, Dai Q, Huang AB, et al. A multicenter, randomized, double-blind clinical trial of combination therapy with Anbainuo, a novel recombinant human TNFRII:Fc fusion protein, plus methotrexate versus methotrexate alone or Anbainuo alone in Chinese patients with moderate to severe rheumatoid arthritis. Clin Rheumatol 2013; 32:99–108.
27. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008; 372:375–82.
28. Emery P, Burmester GR, Bykerk VP, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015; 74:19–26.
29. Fleischmann R, Catolito M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012; 64:617–29.
30. Fleischmann RM, Halland AM, Brzosko M, et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis.
arthritis and inadequate responses to methotrexate: LITHE study 2-year results. J Rheumatol 2013; 40:113–28.
31. Furie R, Nicholls K, Cheng TT, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Rheumatology 2014; 66:379–89.
32. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR Safety Trial of Adalimumab in Rheumatoid Arthritis. J Rheumatol 2003; 30:2563–71.
33. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocolizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 2009; 60:1895–905.
34. Kameda H, Kanbe K, Sato E, et al. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumatol 2011; 38:1585–92.
35. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004; 50:1400–11.
36. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIA trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum 2009; 60:1895–905.
37. Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum 2010; 62:917–28.
38. Kremer JM, Cohen S, Wilkinson BE, et al. A Phase Ib dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum 2012; 64:970–81.
39. Kremer J, Li ZG, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013; 159:253–61.
40. Leonardi CI, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX I). Lancet 2008; 371:1665–74.
41. Merrill JT, Wallace DJ, Petri M, et al. Safety profile and clinical activity of sifalimumab, a human anti-interferon-a monoclonal antibody, in systemic lupus erythematosus: a phase I, multicentre, double-blind randomised study. Ann Rheum Dis 2011; 70:1905–13.
42. Moutsopoulos HM, Gallagher JD, Decker JL, Steinberg AD. Herpes zoster in patients with systemic lupus erythematosus. Arthritis Rheum 1978; 21:798–802.
43. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy with tocilizumab in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomised radiographic study. Arthritis Rheum 2013; 65:559–70.
44. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012; 367:508–19.
45. Yamamoto K, Takeuchi T, Yamana H, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. Mod Rheumatol 2014; 24:552–60.
46. Dreher J, Kreshc FS, Comaneshter D, Cohen AD. Risk of herpes zoster in patients with psoriasis treated with biologic drugs. J Eur Acad Dermatol Venereol 2012; 26:1127–32.
47. Galloway JB, Mercer IK, Moseley A, et al. Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2013; 72:229–34.
48. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis 2009; 48:1364–71.
49. Nakajima A, Urano W, Inoue E, et al. Incidence of herpes zoster in Japanese patients with rheumatoid arthritis from 2005 to 2010. Mod Rheumatol Jpn Rheum Assoc 2015; 25:558–61.
50. Pappas DA, Hooper MM, Kremer JM, et al. Herpes zoster reactivation in patients with rheumatoid arthritis: analysis of disease characteristics and disease-modifying antirheumatic drugs. Arthritis Care Res (Hoboken) 2015; 67:1671–8.
51. Osterman MT, Haynes K, Delzell E, et al. Effectiveness and safety of immunomodulators with anti-tumor necrosis factor therapy in Crohn’s disease. Clin Gastroenterol Hepatol 2015; 13:293–301.e5; quiz e70, e72.
52. Segan J, Staples MP, March L, et al. Risk factors for herpes zoster in rheumatoid arthritis patients: the role of tumour necrosis factor-a inhibitors. Intern Med J 2015; 45:310–8.
53. Shah M, Chaudhari S, McLaughlin TP, et al. Cumulative burden of oral corticosteroid adverse effects and the economic implications of corticosteroid use in patients with systemic lupus erythematosus. Clin Ther 2013; 35:486–97.
54. Topozoglou G, Bolicher D, Nair R, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012; 366:1671–81.
55. Yamanaka H, Takeuchi T, Harigai M, et al. Golimumab monotherapy in Japanese patients with active rheumatoid arthritis: 12-week, randomized, phase 2 study. Mod Rheumatol 2015; 25:514–21.
56. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013; 65:559–70.
57. Yamamoto K, Takeuchi T, Yamana H, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. Mod Rheumatol 2014; 24:552–60.
77. Che H, Lukas C, Morel J, Combe B. Risk of herpes/herpes zoster during anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Systematic review and meta-analysis. Joint Bone Spine 2014; 81:215–21.
78. Singh JA, Cameron C, Noorbaloochi S, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet Lond Engl 2015; 386:258–65.
79. Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015; 74:2107–16.
80. Dixon WG. Rheumatoid arthritis: biological drugs and risk of infection. Lancet 2015; 386:224–5.
81. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001; 344:907–16.
82. Brenner D, Blaser H, Mak TW. Regulation of tumour necrosis factor signalling: live or let die. Nat Rev Immunol 2015; 15:362–74.
83. Moreland L, Bate G, Kirkpatrick P. Abatacept. Nat Rev Drug Discov 2006; 5:185–6.
84. Weiner GJ. Rituximab: mechanism of action. Semin Hematol 2010; 47:115–23.
85. Winthrop KL, Park SH, Gul A, et al. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016; 75:1133–8.
86. Genovese MC, Krermer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 2016; 374:1243–52.
87. Gupta V, Harrison C, Hexner EO, et al. The impact of anemia on overall survival in patients with myelofibrosis treated with ruxolitinib in the COMFORT studies. Haematologica. doi: 10.3324/haematol.2016.151449.
88. Cutolo M, Seriolo B, Pizzorni C, et al. Use of glucocorticoids and risk of infections. Autoimmun Rev 2008; 8:153–5.
89. Dixon WG, Sussa S, Hudson M. The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: systematic review and meta-analyses. Arthritis Res Ther 2011; 13:R139.
90. Hoets N, Jacobs JW, Poers M, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2007; 66:1560–7.
91. Youssef J, Novosad SA, Winthrop KL. Infection risk and safety of corticosteroid use. Rheum Dis Clin North Am 2016; 42:157–76, ix–x.
92. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352:2271–84.
93. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 2015; 372:2087–96.
94. Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57:1–30; quiz CE2–4.
95. Oxman MN, Schmader KE. Editorial commentary: zoster vaccine in immuno-compromised patients: time to reconsider current recommendations. Clin Infect Dis 2014; 59:920–2.