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

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Word Count: 3498, abstract 249, Tables 2, Figures 4, References 91

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Role of Funding Source 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.

Abstract

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

Methods We conducted a systematic literature search from Jan 1946 to Feb 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 (OR) and 95% confidence intervals (CI) for HZ risk. For observational studies, adjusted ORs were pooled separately using random-effects inverse variance models.

Findings 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 OR 1.58, 95% CI 1.39-1.81). In RCTs, the OR of non-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 Immunocompromized 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: Herpes zoster, meta-analysis, DMARDS, biologics, autoimmune diseases, rheumatoid arthritis, immunocompromised

Introduction

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] HZ 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 ninety percent 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 around $1.1 billion US dollars per annum.[6]

Rates of HZ infection in the general population are around 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] HZ risk is also higher in individuals who are immunocompromised due to autoimmune diseases, solid organ

or stem cell transplants, HIV and/or immunosuppressive medications that impair T-cell immunity.[8] These medications include corticosteroids, biologics, such as TNF-alpha blockers, or non-biologic disease modifying anti-rheumatic drugs (nbDMARDs), that is, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), such as methotrexate and targeted synthetic disease modifying anti-rheumatic drugs (tsDMARDs) 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 RCTs and guidelines for the reporting of observational studies and adverse events. [10,11] A pre-specified study protocol was developed prior to 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 two authors (EL/VK). Uncertainty and revisions were discussed with another author (FM).

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 FDA and/or EMA. Only randomized controlled trials (RCTs) and observational studies (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 randomisation in observational studies, eligible studies were those providing adjusted or propensity score matched associations. We excluded non-English, non-human, non-adult (i.e., 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 as 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 was extracted independently by two authors (EL/VK) using a standardised abstraction form. Discrepancies were resolved through discussion with two other authors (FM/KR). 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 adverse events reporting of HZ. If not recorded as such, we examined serious adverse events (SAE) of HZ, which were generally defined as HZ that is either life-threatening, causing hospitalization, or significant disability or incapacity. For the observational studies 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 U.S. 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 observational studies if any clarification was needed.

Two authors (EL/VK) 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 observational studies for comparability if they controlled or adjusted for age and concomitant medications as both are considered important risk factors for HZ.[1,8] Discrepancies were resolved through discussion with another author (FM/KR).

Statistical Analysis

As HZ is a rare event, we used the Mantel-Haenszel fixed-effects model to calculate pooled odds-ratios and 95% confidence intervals (CI) 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 observational studies, 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 (categorised 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 to 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 two sided with $p<0.05$ 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 and 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 one 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 observational studies. 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 6-104 weeks in the RCTs and 37-600 weeks in the observational studies. Most studies focused on RA patients (25 of 40 RCTs and 14 of 19 observational) while 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 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. While 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 as their drop-out rates exceeded 20%. In contrast, the included observational studies were found at low risk of bias with scores ranging from 7/9 to 9/9, 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 observational studies (n=132,647) reported the risk of HZ associated with biologics compared to 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 observational

studies (OR 1.58, 95% CI 1.39-1.81; I^2=0%) (Figure 2b). Stratified analysis of the RCT data according to TNF-alpha inhibitors, demonstrated a greater risk of HZ for the non-TNF-alpha inhibitors compared to placebo (OR 2.19, 95% CI 1.20-4.02; I^2=0%) and no statistically significant difference for the TNF-alpha inhibitors (OR 1.28, 95% CI 0.69-2.40; I^2=0%) (Figure 2a).

Risk of Herpes Zoster with Non-Biologic DMARDS

The pooled odds ratio for HZ with nbDMARDS compared to control across 16 RCTs was 1.61 (95% CI: 0.84-3.10, I^2=0%) (Figure 3a) and across 6 observational studies 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 1-3mg, 5mg, 10mg, and 15-30mg 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 15-30mg BID.

Risk of Herpes Zoster with Corticosteroids

No RCTs and 15 observational studies 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 10mg per day (eTable 4). Since 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 observational studies (OR 1.06, 95% CI: 0.69-1.61, I^2=71%) failed to show a significantly greater HZ risk with biologics compared to nbDMARDs (eFigure 2). Combination treatment of biologics and nbDMARD was compared to no use in 3 observational studies, 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 rheumatoid arthritis patients compared to the other diseases in the RCTs, but not in the observational studies (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 whilst including evidence from RCTs. Our meta-analysis indicates an elevated risk of HZ in immunosuppressed patients treated with biologics in both RCT and observational studies. Interestingly, elevated risk of HZ was observed with non-TNF-alpha blocking agents but not TNF-alpha 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 examined opportunistic infections due to biologics from 70 RCTs (N=21,916).[76] As a secondary analysis including 11 RCTs, they also examined varicella-zoster infection, and found similar findings to our study, albeit not reaching statistical significance (OR 1.51, 95%CI 0.71-3.22). Che et al compared TNF-alpha blockers (N=73,510) with nbDMARDs (N=89,567) from crude numbers obtained from observational studies and found an elevated risk of HZ (OR 1.61, 95%CI 1.16-2.23).[77] This association is probably greater than our pooled estimates as 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 secondary analysis, Kourbeti and colleagues found anti-TNF blocking agents, but not non-TNF-alpha blocking agents, to be associated with a significant risk of opportunistic infections (OR 2.10; 95%CI 1.27-3.45).[76] The authors suggested this may be due to heightened awareness of infectious complications in recent trials or that newer non-TNF-alpha blocking agents have a lower risk for opportunistic infections.

The conflicting data seen in the various reviews is 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; and 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-alpha receptors;[80–82] etanercept also inhibits TNF-alpha but is not a monoclonal antibody and binds to free TNF-alpha receptors only.[81] Additionally, the monoclonal antibodies can lyse other cells involved in the

inflammatory process, whereas the receptor fusion protein, etanercept, lacks this capability.[81] Non-TNF alpha blocking agents are more of a mixed bag, exploiting different targets, like-antigen presenting cells (abatacept),[83] pro-inflammatory cytokines, B cell depleting monoclonal antibodies binding CD20 (rituximab),[84] and therefore may have very different risk for the various microbes compared to the monoclonal TNF-alpha 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 around 21-61% with nbDMARD treatment, but this only reached statistical significance in the pooled observational studies. This may be due to the RCTs being under-powered to detect differences in rare adverse events like HZ.[79] The types of nbDMARD used in the trials and clinical practice vary considerably and our meta-analysis studies included 8 different nbDMARDs, as 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 JAK inhibitor, tofacitinib, rather than the conventional DMARDs. Increased HZ with tofacitinib was also seen in Winthrop et al's meta-analysis, which evaluated data from Phase II and III studies and showed a crude IR of 4.4/100 person-years (95% CI: 3.8-4.9), almost 3 times the rate for TNF-alpha inhibitors; the risk occurred early in the treatment course rather than later.[85] When evaluating the data according to

the tofacitinib dose, we generally observed higher doses posing an increased risk of HZ. Our literature search was completed in February 2016 and therefore we did not include two further studies published recently evaluating the JAK inhibitors baricitinib[86] and ruxolitinib[87], both appear to cause an increased risk of zoster infection.

Our meta-analysis of observational studies 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 observational studies showed that steroid therapy was not associated with a risk of infection (RR 0.97, 95% CI 0.69-1.36) when data was pooled from the RCTs, but the observational studies 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 (e.g. 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, 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 as they were larger and they had structured protocols to capture rare adverse events. 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. Generally 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. Conversely, 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 over-reported in treatment arms. Additionally, 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 as 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 as 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 observational studies that were also of high quality due to their adjustment for relevant confounders. The observational studies all adjusted for age, sex, 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 post vaccination, with rates of SAE similar with placebo group;[92] a new adjuvanted, non-live varicella-zoster vaccine was recently tested in a phase 3 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 to 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 ACIP issued guidance and offering the vaccine to patients before starting therapy.[94,95] To better determine its safety profile, further efficacy trials of the non-live herpes zoster 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-alpha blockers. Increased HZ risk from corticosteroid and nbDMARD use was also observed in observational studies. The use of biologics and DMARDS is now commonplace, not only in rheumatoid arthritis patients but a host of other autoimmune diseases. Our findings raise the issue of appropriate medical history and screening of patients before treatment prior to initiating immunosuppressants. Finally, not all biological agents are equal with respect to their potential for opportunistic infections and post-marketing surveillance of these newer agents with different mechanisms of action than the traditional TNF-alpha inhibitors is vital.

Key Messages

Herpes zoster is increased in patients receiving biologics, especially non-TNF-alpha blockers, although all biologics do not pose the same risk. Patients are also at risk for zoster infection if placed on corticosteroids or non-biologic DMARDS.

Conflict of Interest Statement

All authors, except Dr. Marra, declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work except the corresponding author. Dr. Marra has received unrestricted grants from Merck Canada that may have influenced the submitted work.

Funding Sources

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.

Contributors Statement

The contribution of the authors to the study are as follows: Conception and design of the study (FM), literature search (EL, VK), acquisition of data (FM, VK, EL), data analysis (KR), interpretation of data (FM, VK, EL, KR), first draft of the article (FM), revised it critically for important intellectual content (FM, VK, EL, KR), and final approval of the version to be published (FM, VK, EL, KR).

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