SYSTEMATIC REVIEW

Administering Shingles Vaccine Prior to the Initiation of Biologics Therapy: A Systematic Review

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Abstract

Background: Shingles, also known as herpes zoster, is a viral infection caused by the varicella-zoster virus. The classic feature is a painful dermatomal rash. Although the disease is often self-limiting, complications such as postherpetic neuralgia can cause long-lasting morbidity. Patients who are immunosuppressed are more susceptible to developing shingles. The purpose of this paper is to systematically review the evidence for prophylactic use of the shingles vaccine prior to initiating biological therapy.

Objectives: To evaluate the evidence for shingles vaccine prophylaxis prior to initiating biologics therapy.

Methods: We performed a comprehensive Boolean search of PubMed and EMBASE from January 2000 to October 2019 for the following terms: prophylaxis, prior, shingles vaccine, varicella-zoster, infliximab, biological therapy, and guidelines. Eligible studies met the following criteria: published in English since 2000, used any shingles vaccine type and dose; and involved both vaccine monotherapy and autoimmune disease biological therapy. Randomised controlled trials, meta-analyses, and systematic reviews were included. Duplicate studies were excluded, as well as non-English papers.

Results: 32 studies met the search criteria, of which 8 were selected for the literature review. All studies had generally differing conclusions as to whether shingles vaccination in autoimmune patients undertaking biologic therapy was safe and effective.

Conclusions: Patients with autoimmune diseases should be considered for the herpes zoster vaccine prior to initiating biological therapy. Our findings support the use of the live attenuated vaccine, *Zostavax*, or the non-live vaccine, *Shingrix*. However, further research is required to evaluate specific autoimmune conditions and specific biological agents with a view to the formulation of national clinical guidelines on the use of the herpes zoster vaccine in the immunocompromised.

Keywords: Shingles, Herpes zoster, Varicella-zoster virus, Vaccine prophylaxis, Biologics

Introduction

Herpes zoster (HZ), otherwise called shingles, is an infection of a nerve and surrounding skin caused by the varicella-zoster virus (VZV)[1]. Whilst occurring mostly during childhood, it can remain dormant and reactivate later in life. Characterised by a unilateral vesicular and painful rash, severe complications can also occur. These range from postherpetic neuralgia (PHN), long-term pain continuing after the rash has subsided, to potentially death[2].

Within the general population, shingles occurs approximately every 4 per 1000 person-years, though these rates are higher amongst elderly autoimmune patients, particularly those on immunosuppressive therapy[2]. This is worrying, given the increased use of immunosuppressive medications like biologics. Widely used for their minimal toxicity profile[3], higher efficacy, and target specificity; biological agents including tumour necrosis factor alpha (TNFα) inhibitors have become mainstream therapeutic options for autoimmune diseases[4]. Whilst directing their therapeutic effect by targeting abnormal immune activity, the mechanism of action can cause immunosuppression leading to VZV reactivation[5,6].

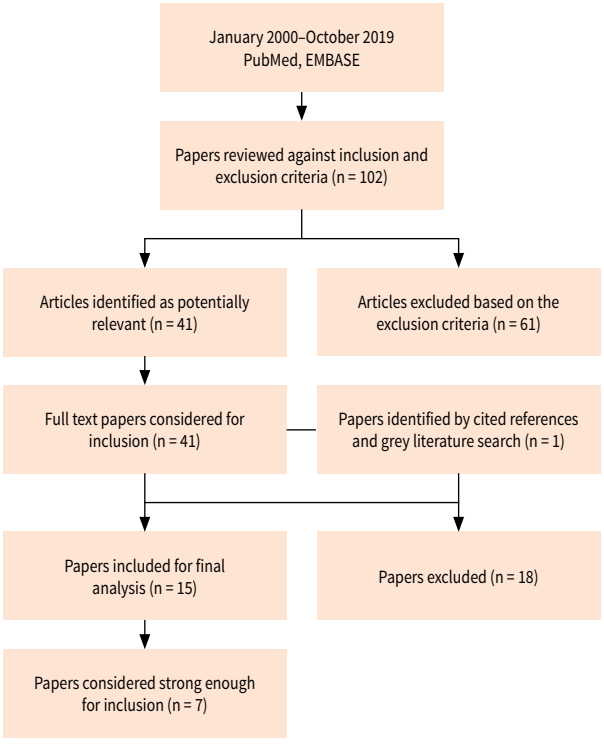
The use of a shingles vaccine is an avenue currently being explored to provide prophylaxis against VZV reactivation. Although the 2005 Shingles Prevention Study demonstrated the live-attenuated vaccine's efficacy and informs much of our current practice, HZ vaccination in immunocompromised cohorts remains poorly understood[7].

Thus, the objective of this systematic literature review is to evaluate the evidence surrounding prophylactic shingles vaccination in adult autoimmune patients prior to initiating biological therapy.

Methods

A literature search of PubMed and EMBASE databases was carried out. The databases were searched for titles and abstracts containing keywords to identify the risk of various infections among patients receiving biological

Figure 1. **PRISMA Chart Highlighting Inclusion of Articles for the Literature Review**



therapy for autoimmune diseases. The following Boolean search parameters were used: "Prophylaxis" OR "Primary Prevention" AND "Shingles Vaccine" OR "Varicella Zoster Vaccine" AND "Autoimmune Disease" AND "Adult Patients"' OR "Infliximab" OR "Biological Therapy" AND "Guidelines".

Search Strategy

The first live-attenuated vaccine for the prevention of HZ, *Zostavax*, was released by the Food and Drug Administration (FDA) in the USA in 2006[8]. However, the search was broadened to include data for when the first biological agent, Etanercept, was approved by the FDA in 1998 and started seeing clinical usage for rheumatoid arthritis (RA) in 2002[9]. This broadening of the time scale ensured we could account for the emergence of biological therapy in autoimmune diseases.

Initial results were recorded with the removal of duplicate results. Relevant articles were reviewed according to titles and abstracts for inclusion in the literature review.

Inclusion/Exclusion Criteria

Studies were included in the literature review if they were published in English, published from 2000-2022, and if studies involved (a) VZV vaccine monotherapy, (b) any patient over the age of 18 with autoimmune disease, and (c) any biologic therapy causing immunosuppression.

Studies were excluded if they remained unpublished or if the data was not specific to vaccination or biologics. This was supplemented by a grey literature search. The discrete number of papers retrieved, excluded, included, and analysed are displayed in a PRISMA diagram (**Figure 1**).

Results

Study Outcome

Study findings (as shown in **Tables 1–2**) were mixed, differing in whether patients with autoimmune disease on biologic therapies had a higher incidence of developing shingles. All, however, did not find a definitive link between HZ infection following biologic therapy. This led to mixed recommendations. Only one study recommended vaccination being acceptable with biologic therapy[10], with the rest either recommending vaccination with certain (conflicting) caveats or stopping short of recommending it.

Defining a stringent 'evidence-based conclusion' was difficult. Only seven studies were found, with many of them being reviews of current guidelines, which tended to homogenise biologics and autoimmune diseases and give non-clinically specific data. Primary research was lacking, and most examined populations were too small for a significant conclusion within their settings.

Only one study was deemed significantly relevant in study scope[11], but its findings were unclear. Another study demonstrated statistically significant VZV-specific immune markers following vaccination[12], though laboratory markers do not directly translate into being disease-free. Taking all this into account, any links between biologics and prophylactic vaccination remained probable at best.

Discussion

Biological Therapy

Most biologics reviewed were TNFα inhibitors; this makes sense, given that TNFα is key in many inflammatory diseases[13]. Aside from the etanercept study[14], all studies homogenised biologics under 'biological therapy' or failed to specify specific drugs under mono/dual therapy. Thus, except for finding that dual biologic-thiopurine therapy increased HZ risk[14], we could not gauge the different extent any biologics or therapy combination had on immunosuppression or opportunistic infection risk.

Reviewing external literature yielded mixed results. Whilst one study showed a higher HZ risk in non-TNFα biologics than other immunosuppressive therapies[15], an alternative study with IL-17 inhibitors found no HZ risk change in psoriasis patients[13]. Presumably important, it is also unclear what effect biologic dosage could have; one study mentioned 'low dose biologics' but did not evaluate whether the resulting small HZ risk was because of the low dose, or despite it[16].

It is also unclear if immunosuppressive therapy usage generally increased HZ risk. One study found no significant differences in RA patients for VZV-specific immune markers and cell-mediated immune responses following live VZV vaccination and subsequent tofacitinib treatment[17].

Demographics: Autoimmune Disease Cohorts

Used to treat over 80 different illnesses, most biologics are typically indicated for inflammatory bowel disease

Table 1. **Papers Deemed Fit for Inclusion in Final Analysis**

Reference	Objective	Design	Population	Study Population and Age	Intervention and Duration	Effect/Benefit	Recommendations	Other comments
Papadopoulou et al. (2013)	To compare existing recommendations on vaccination of adult patients with autoimmune rheumatic diseases (ARDs) in Europe, North America and Australia	Systematic Review	ARD patients in Europe, North America & Australia	N/A Age not explicitly mentioned; lowest age recommendations reviewed to were adults ≥ 50	Abatacept, rituximab, tocilizumab, others (but not specified). Duration of biologic therapy not mentioned either.	Not covered.	As of Feb 2014, EULAR and various European and Australian committees on immunisation practices recommend avoiding VZV vaccination in patients receiving any immunosuppressive therapy, due to a lack of literature on the subject.	General guidelines are not specific to the VZV vaccine. Paper notes that most recommendations are based on expert opinions.
Kopylov et al. (2012)	To determine the prevalence of seropositivity for VZV-IgG in immunomodulator-treated IBD patients (including anti-TNFs biologics)	Case-Control Study	IBD (CD & UC)	121; 86 of them were on anti-TNFs Study cohort mean age = 37 ±12.8	Infliximab, Adalimumab. Duration of therapy not mentioned; study only recorded whether biologics were used at time of serological testing.	Most (90.7%) patients using anti-TNF biologics were seropositive for the VZV IgG, suggesting that in this group, biologic therapy probably does not significantly interfere with VZV IgG production (thus, immunity). Negative history of VZV exposure was a poor predictor of VZV IgG seronegativity.	The authors recommend serological testing for HZV for all IBD patients regardless of exposure history prior to initiation of immunosuppressive therapy with subsequent vaccination of patients found to be seronegative. This questions the current European Crohn's and Colitis Organisation (ECCO) guidelines, which recommends VZV vaccine immunisation ≥3 weeks before immunomodulator therapy onset (preferably at IBD diagnosis), with a negative history of chickenpox, shingles, and VZV vaccination.	Prophylactic vaccination data not included, measured via self-questionnaire on prior exposure to VZV. This can include the VZV vaccine and/or history of VZV-related illnesses.
Furer et al. (2019)	To update the present EULAR recommendations for vaccination in patients with autoimmune inflammatory rheumatoid disease (AIIRD); including information on the incidence/prevalence of vaccine preventable infections and the efficacy, immunogenicity, and safety of vaccines provided to AIIRD patients undergoing immunosuppressive therapies	Systematic review	AIIRD patients (adults & paediatrics) on immunosuppressive therapy (glucocorticoids, conventional synthetic / biological / targeted synthetic DMARDs)	N/A	Includes, but not limited to: Infliximab, etanercept, adalimumab, certolizumab, golimumab abatacept, rituximab, secukinumab, ixekizumab, belimumab, anakinra, canakinumab. Duration of therapies not mentioned.	Not covered; see "Association between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection among Older Patients with Selected Immune-mediated Diseases"	EULAR recommends giving the live attenuated herpes zoster vaccine in mildly immunosuppressed AIIRD patients on a case-by-case basis and preferably only to those seropositive for VZV antibodies (to prevent primary varicella infection). EULAR notes that the newly licensed Shingrix vaccine which has been recommended for patients aged 50 and over (including immunosuppressed patients) may be the future preferred vaccine for AIIRD.	Findings were like the 2011 guidelines. All recommendations are still expert opinion. Also recommends that vaccines should be administered prior to planned immunosuppression; for B-cell specific therapy, ≥ 6 months after administration and 4 weeks before the next course.
Bye et al. (2016)	To identify 'at risk' IBD patients who may be targeted with a new adjuvant herpes zoster subunit vaccine	Retrospective cohort study	IBD (CD & UC)	N/A Mean age of those with VZV infection = 42 years (Range 21-81 years)	Anti-TNF biologic monotherapy and dual therapy, type unspecified. Time from initiating therapy to VZV infection ranged from 3 months to over 10 years	HZ infection is associated with increasing IBD severity and dual therapy (particularly with thiopurine). Of the 30 cases of HZ identified (25 CD, 5 UC)- none had previously received the HZ vaccine. Of this group, 10% were on anti-TNF monotherapy and 47% were on dual therapy (anti-TNF and thiopurine therapy [93%] or methotrexate [7%]). Age and length of immunosuppressive therapy do not seem to predict HZ infection.	Severe IBD patients and/or patients on dual-immunosuppressive therapy could benefit from immunisation with the new non-live, non-attenuated vaccine.	N/A

Abbreviations:

Table 2. **Papers Deemed Fit for Inclusion in Final Analysis (Cont.)**

Reference	Objective	Design	Population	Study Population and Age	Intervention and Duration	Effect/Benefit	Recommendations	Other comments
Cheetham et al. (2015)	To characterise the potential risk of disseminated VZV and herpes zoster post-administration of the zoster vaccine in patients who were currently receiving immunosuppressant medications	Retrospective cohort study	Not explicit; i.) Unclear what the (individual) indication was for patients using etanercept, ii.) Split participants into groups who had "inflammatory and immune-mediated conditions", which were broken down further by systems; autoimmune diseases may or may not have featured	145 (on etanercept); study looked at a total of 14,554 patients on various immunosuppression therapy (only etanercept was the relevant featured biologic therapy) N/A	Etanercept	No cases of disseminated VZV were identified with either current or remote usage of immunosuppressant drugs, including etanercept, in the 42-day window post-vaccination. Twenty-five cases of herpes zoster occurred during the 42-day window in the current-user group vs. 17 cases in the remote-user group; overall, this led to the conclusion that during the 42-day period, there is a modest increase in HZ risk in the group undergoing current immunosuppression vs. those with remote exposure. There is no specific discussion surrounding etanercept, so little conclusion can be drawn.	The findings support current recommendations that patients should withhold their immunosuppressant drugs for 4 weeks before zoster vaccine immunization. This is a general recommendation and is not/does not seem to be etanercept-specific.	N/A
Zhang et al. (2012)	To examine the link between HZ vaccination and HZ incidence within and beyond 42 days after vaccination in patients with selected autoimmune diseases in the context of biologics and other autoimmune therapies	Retrospective cohort study	RA, psoriasis, psoriatic arthritis, ankylosing spondylitis (AS), and/or IBD 463,541 patients; 18,683 received the vaccination	463,541 patients; 18,683 received the vaccination All >60y/o; mean age = 74 ± 8 years	Anti-TNF biologics (adalimumab, etanercept, infliximab, certolizumab, and golimumab) & non-TNF biologics (abatacept and rituximab)	No cases of varicella infection were documented within the 42 days post-vaccination and starting biologic therapy. Vaccination was associated with a decrease in VZV risk by 40% over a median 2-year follow-up period.	Unclear; questions current recommendations contraindicating the HZV vaccine in autoimmune patients receiving biological therapy.	Study concludes by suggesting the need for an RCT specifically addressing this topic.
Eberhardson et al. (2017)	To demonstrate the immunogenicity and safety of ZVIN in patients with RA, SLE, IBD, AS, MS, PsO, and other autoimmune diseases receiving immunosuppressive therapy who are receiving either biologic or non-biologic immunosuppressive therapy	Randomised control trial	AS, IBD (CD and UC), cerebral sarcoidosis, MS, psoriasis, psoriatic arthropathy, RA, SLE	354 for total study; 170 on biologics Adults ≥18	Not explicitly mentioned	This was not directly covered. The study indirectly measured (potential) HZV infection by measuring VZV-specific immune response markers. To this end, the inactivated VZV vaccine (ZVIN) was well tolerated and showed statistically significant VZV-specific immune responses approximately 28 days after the last dosage regime. Overall, the frequency of adverse events also decreased with subsequent vaccine doses.	The results may provide relevant information for this patient population who may benefit from the prevention of HZV and HZV-related complications. This is assuming further phase 3 studies confirming the efficacy, immunogenicity, and safety of the ZVIN vaccine are conducted.	Indirect measurement of immunosuppression by measuring gpELISA and IFN-γ ELISPOT responses in patient levels. However, although it meets the threshold this does not mean the vaccine is safe for usage.

(IBD), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE)[12,18]. This made reviewing the nuances in biologic immunosuppression of individual diseases difficult.

Despite this, most varicella-zosters vaccination in immunocompromised patients research pertained to IBD. Current European Crohn's and Colitis Organisation (ECCO) guidelines recommend VZV immunisation at least three weeks prior to commencing immunomodulatory therapy[9]. Despite some conflict on vaccine timing, all studies agreed that all IBD patients should undergo VZV-IgG serological testing prior to vaccination and that prophylactic vaccination does have a protective role, especially in seronegative patients.

For autoimmune rheumatic disease, the evidence is less clear. Our literature for these groups were all systematic reviews with no concrete data and recommended against vaccination[19], or only in mildly immunosuppressed patients[20]. If looking at vaccination without biologics, one study found that despite a higher absolute shingles incidence rate of 50% compared to healthy populations, the zoster vaccine was still protective[21]. Whilst HZ vaccination is likely useful for autoimmune rheumatic patients, its safety remains unclear when factoring in biologic therapy.

Demographics: Age

Amongst different age groups, current data recommends the *Shingrix* vaccine in adults over 50 years of age, including immunocompromised patients[16]. However, National Health Service (NHS) guidelines in the UK prohibit vaccination in patients older than 80 years of age[3], given data showing *Zostavax*'s efficacy wanes with age[21]; this is supported by another study demonstrating only 38% efficacy in immunocompetent patients over 70 years of age[22]. Presumably, this pertains to patients undergoing biologic therapies too, suggesting vaccination benefits do not outweigh the risks in older patients.

Timeline Indications

Timing of administration is important, given that the current *Zostavax* vaccine is live, and biologics suppress the immune response. Amongst those supporting vaccination, there is no consensus on when to start and/or stop biologics following vaccination. Recommendations on when biologics should begin post-vaccination range from three weeks to three months[9,11]; some instead recommend a case-by-case approach[23]. Other literature simply deferred to national guidelines on general vaccination procedures in immunocompromised patients[16].

There was even less literature on when to stop biologics if vaccinating later. This is problematic, as many patients have an ongoing disease, but no prior VZV exposure. The only paper that explicitly mentioned this recommended following current guidelines on varicella-zoster vaccination i.e., withholding immunosuppressant drugs for four weeks prior[13]. However, there was no reference made to stopping immunosuppressant medication prior to vaccination when recommencing treatment for IgG-seronegative VZV patients[9].

Current NHS guidelines state that patients receiving the live vaccination should wait for an established immune response before beginning immunosuppressive therapy[3]. This is supported by the Center for Disease Control (CDC) in the USA[24], which notes that waiting four weeks should be sufficient for viral live vaccines. However, they recommend against delaying therapy if this would worsen the underlying condition, as most live vaccines are attenuated; this should only occur following specialist consultation on a case-by-case basis[25].

Long-term, *Zostavax*'s efficacy wanes over time[26]. Different studies show different extents of change, but specific to autoimmune patients on biologics, it is most probable that *Zostavax* is protective for at least two years[10].

Live vs Non-live

The current VZV vaccine, a live attenuated vaccine known as *Zostavax*, has shown efficacy in immunocompromised patients by providing 70-90% immunity persisting for at least 10 years[9]. The European Alliance of Associations for Rheumatology vaccination recommendations for autoimmune inflammatory rheumatoid disease (AIIRD) patients have shown vaccine efficacy after 42 days on biologic disease-modifying antirheumatic drugs with no HZ incidence increase[16]. Interestingly, trials have shown a potential reduction of HZ risk by up to 70% in adults over 50 years of age, with lower HZ incidence after 2 years, regardless of immunosuppressive medications[16]. Current clinical practice considerations are based primarily on *Zostavax*. However, giving live-attenuated vaccines to immunosuppressed patients, especially those on low-dose biologics, remains controversial[12].

A newer non-live recombinant vaccine, *Shingrix*, is currently recommended for adults over 50 regardless of previous VZV vaccination and immune status. Whilst *Shingrix* is currently undergoing clinical trials and is not recommended for immunosuppressed patients[27], it is promising. If *Shingrix* was deemed effective, it would likely see larger usage in 'at-risk' patients. Additionally, it would be less likely to be contraindicated with concurrent biologic therapy.

Pharmacoeconomics

When evaluating the role of prophylactic vaccination, consideration can be given to cost-effectiveness. One US study found *Zostavax*'s cost-effectiveness ratio per QALY (Quality-Adjusted Life Year) gained between $\$25,379 - \$27,609$[28]. Incidentally, this is within the Irish healthcare system's incremental cost-effectiveness ratio of $€20,000 - €45,000$[29]. This suggests that prophylactic vaccination is economically viable, implying a role to play in clinical practice assuming safety can be definitively established.

Limitations

This review's conclusion was limited by the few available studies; most existing literature reviewed either HZ infections and autoimmune suppression (mainly with non-biologic therapy), or prophylactic vaccination in autoimmune patients, without combining all three. This made it harder to summarise our findings. In making our judgement, we had to extrapolate indirect

literature on this subject.

One possibility for improvement would be to expand the criteria, such as including data prior to the year 2000 as well as studies on paediatric patients. Studying prophylactic vaccinations of other opportunistic diseases in similar autoimmune cohorts could also reveal more about the general safety and efficacy of vaccination prior to biologic therapy. Although not specific, this could yield a clearer understanding of the vaccination-biologics interaction, which could help inform us, given the limited findings we have.

Conclusion

We believe there is a definite role for HZ vaccination in prophylaxis against shingles in autoimmune patients undergoing biologic therapy. Although some suggest otherwise, we recommend erring on caution and following national vaccination guidelines as to when and how to vaccinate; case-by-case exceptions ought to be considered too. However, further research is required, particularly regarding specific autoimmune conditions and biologic agents as well as *Shingrix*, to improve the formulation of clinical guidelines on the use of the HZ vaccine in the immunocompromised[30].◂

Declarations

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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