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

Alicia Ryan[1, 2], Alex Soo[1, 2], Niall O'Rourke[1, 2], Ayub Nasrudin[1, 2], Dan Khan[1, 2], Fiona Lafferty[1, 2], James Kelly[1, 2], Nicola Byrne[1, 2], Serhiy Semenov [1,2]

[1] Department of Gastroenterology, Tallaght University Hospital
[2] School of Medicine, Trinity College Dublin

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, and disease may be more severe. 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 for the following terms: prophylaxis, prior, shingles vaccine, varicella zoster, infliximab, biological therapy, guidelines. Eligible studies met the following criteria: published in English, published since 2000, any shingles vaccine type and dose, vaccine monotherapy, autoimmune disease biological therapy. There was no specific target for gender, age or population. Randomised controlled trials, meta analyses and systematic reviews were included. Studies were excluded based on the following criteria: duplicate studies, non-English language papers, papers not addressing autoimmune disease therapy, clinical trials and cohort studies.

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.

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Conclusions

Patients with autoimmune disease should be considered for the herpes zoster vaccine prior to initiating biological therapy, though the specifics of vaccination administration is unclear. 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, Vaccine, Prophylaxis

1 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, ranging from postherpetic neuralgia (PHN) – long-term pain continuing after the rash has subsided[2] – to being potentially fatal[3].

Within the general population, shingles occurs approximately every 3-5/1000 person years, though these rates are higher amongst elderly autoimmune patients, particularly those on immunosuppressive therapy[2]. This is worrying given that immunosuppressive medications like biologics have expanded the medical field in terms of treatment options. Widely used for their minimal toxicity profile[5], higher efficacy and target specificity, biological agents including tumour necrosis factor-alpha (TNFα) inhibitors have become mainstream therapeutic options for autoimmune diseases[6]. Whilst mediating their therapeutic effect by targeting abnormal immune responses, targeting the immune response can cause immunosuppression[7,8] leading to VZV reactivation.

Shingles prophylaxis to prevent VZV reactivation, with the shingles vaccine one avenue currently being explored. 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[9].

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.

2 Methods

A literature search of PubMED and EMBASE databases were carried out. The databases were searched for titles and abstracts containing keywords (see *Figure 1*) to identify the risk of various infections among patients receiving biological therapy for autoimmune diseases.

Boolean search parameters:
"Prophylaxis" OR "Primary Prevention" AND "Shingles Vaccine" OR "Varicella Zoster Vaccine" AND "Autoimmune Disease" AND "Adult Patients"' OR "Infliximab" OR "Biological Therapy" AND "Guidelines"

2.1 Search Strategy

PubMED and EMBASE were chosen, given their common use in medical literature. The search was designed to include publications of full text articles that were published within the past 19 years (2000-2019). The first live-attenuated vaccine for prevention of HZ, *Zostavax*, was released by the FDA in 2006[10]. 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[11]. This time parameter ensured we could account for the emergence of biological therapy in autoimmune diseases.

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

2.2 Inclusion/Exclusion Criteria

Studies were included in the literature review based on the following: (1) Published in English, (2) published since 2000, and involved studies concerning (3) VZV monotherapy-vaccination, (4) any autoimmune adults over 18 years, (5) any biologic therapy-caused immunosuppression. Studies were excluded if they remained unpublished or had data not specific to vaccination or biologics. This was supplemented by a grey literature search.

The number of studies retrieved from each search and excluded throughout the literature search and the number of studies for inclusion are displayed in a PRISMA diagram (Figure 2).

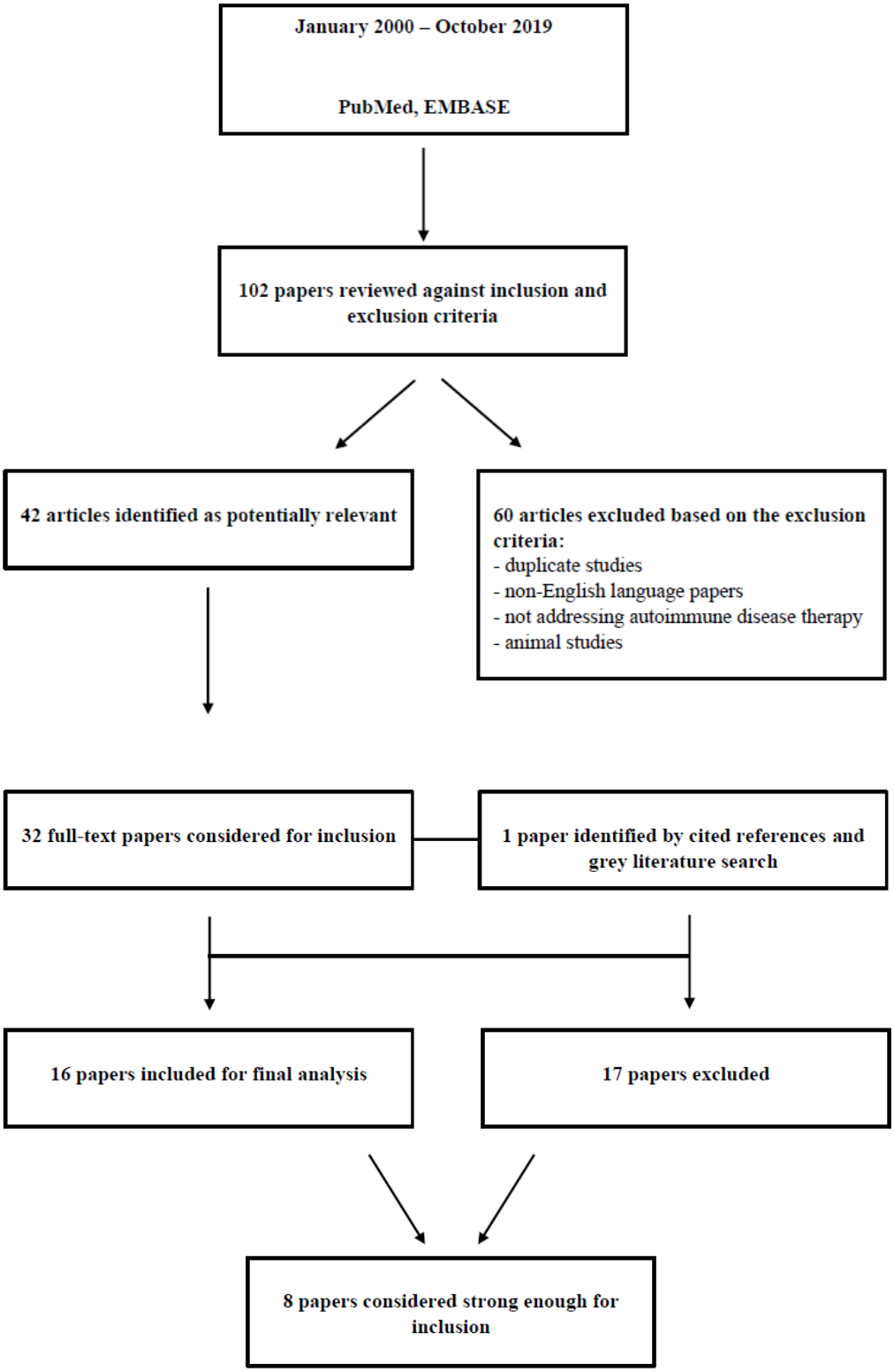

Figure 2. PRISMA chart highlighting inclusion of articles for the literature review

Reference	Objective	Design	Population	N and Age	Intervention and Duration	Effect/Benefit	Recommendations	Other comments
Zahid et al, 2017	To highlight the treatment for HZ infection and discuss the protective roles prophylactic antiviral drugs & vaccinations can play in preventing HZ complications in patients on immunosuppressive therapy	Literature Review	Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Granulomatosis with polyangiitis	N/A N/A	Specific biologics not mentioned, only "low-dose biologics". Time period not specified either.	With prior vaccination, there is a low risk of HZ infection whilst on immunosuppressive therapy. No cases of disseminated VZV infection were found in any of the reviewed studies.	Whilst some current guidelines recommend against Zostavax/live-attenuated vaccines in immunocompromised patients, the authors of this study think it prudent to vaccinate immunocompromised patients approximately 3 months prior to starting immunosuppressive therapy.	N/A
Papadopoulou et al, 2013	To compare existing recommendations on vaccination of adult patients with autoimmune rheumatic diseases (ARDs) in Europe, North America & 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 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-	Case-Control Study	IBD (CD & UC)	121; 86 of them were on anti-TNFs	Infliximab, Adalimumab. Duration of therapy not mentioned;	Most (90.7%) patients using anti-TNF biologics were seropositive for the VZV IgG, suggesting that in this group, biologic	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	Prophylactic vaccination data not included, measured via self-questionnaire on

	treated IBD patients (including anti-TNFs biologics)			Study cohort mean age = 37 +/- 12.8	study only recorded whether biologics were used at time of serological testing.	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.	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.	prior exposure to VZV. This can include the VZV vaccine or/and past history of VZV-related illnesses.
Furer et al, 2019.	To update the present EULAR recommendations for vaccination in patients with AIIRD; including information on the incidence/prevalence of vaccine preventable infections and the efficacy, immmunogenicity and safety of vaccines provided to AIIRD patients undergoing immunosuppressive therapies	Systematic review	AIIRD patients (adults & paediatrics) on immunosuppressive therapy (glucocrticoids, conventional synthetic / biologial / targeted synthetic DMARDs	N/A 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 licenced 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 similar to 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	Retrospective cohort study	IBD (CD & UC)	N/A Mean age of those with	Anti-TNF biologic monotherapy and dual-therapy, type	HZ infection associated with increasing IBD severity and dual-therapy (particularly with thiopurine). Of the 30	Severe IBD patients and/or patients on dual-immunosuppressive therapy could benefit from immunisation with the new non-live, non-attenuated vaccine.	N/A

	herpes zoster subunit vaccine			VZV infection = 42 years (Range 21-81 years)	unspecified. Time from initating therapy to VZV infection ranged from 3 months to over 10 years	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.		
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	Retrospecti-ve cohort study	Not explicit; i.) Unclear what the (individual) indication was for patients using etanercept, ii.) Broke down participants into groups who had "inflammato ry and immune-	145 (on etanercep t); study looked at a total of 14,554 patients on various immunos uppressio n therapy (only etanacept was the relevant featured	Etanercept	No cases of disseminated VZV were identified with either current or remote usage of immunosuppresant 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	The findings supports 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

			mediated conditions", which were broken down further by systems; autoimmune diseases may or may not have featured	biologic therapy) N/A		group undergoing current immunosuppression vs. those with remote exposure. There is no specific discussion surrounding etanercept, so little conclusion can be drawn.		
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 disease in the context of biologics and other autoimmune therapies	Retrospecti-ve 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 vaccinati-on 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 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 a 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	Randomised control trial	AS, IBD (CD and UC), cerebral sarcoidosis, MS, psoriasis, psoriatic	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	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 immunosuppressi on by measuring gpELISA and IFN-γ ELISPOT responses in patient levels.

	immunosuppressive therapy who are receiving either biologic or non-biologic immunosuppressive therapy		arthropathy, RA, SLE			(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.		However, although it meets the threshold this does not mean the vaccine is safe for usage.

Table 1. Papers deemed fit for inclusion on final analysis.

3 Study Outcome

Study findings were mixed, differing in whether autoimmune patients on biologics had higher incidences of developing shingles. All, however, did not find a definite immediate link between HZ infection following biologic therapy. This led to mixed recommendations. Only one study[12] recommended vaccination being acceptable with biologic therapy, 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 eight 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 even then, most examined too small numbers for a significant conclusion within their own settings.

Only one study[13] was deemed significantly relevant in study scope, but its findings were unclear. Another study[14] demonstrated statistically significant VZV-specific immune markers following vaccination, though laboratory markers does not directly translate into being disease-free. Given all this, any links between biologics and prophylactic vaccination remained probable at best.

4 Discussion

4.1 Biological Therapy

Most biologics reviewed in our papers were TNFα inhibitors; this makes sense, given that TNFα is key in many inflammatory diseases[15]. Aside from the etanercept study[16], 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[17] increased HZ risk, we could not gauge the different extent any particular 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[18] than other immunosuppressive therapies, an alternate study with IL-17 inhibitors found no HZ risk change in psoriasis patients. Presumably important, it is also unclear what effect biologic dosage could have; one study[19] mentioned 'low-dose biologics', but did not evaluate whether the resulting small HZ risk was because of the low dose, or in spite of it.

In the bigger picture, it is also unclear if, or to what extent, immunosuppressive therapy usage in general increased HZ risk; one study[20] 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.

4.2 Demographics: Autoimmune Disease Cohorts

Encompassing over 80 different illnesses[21], most biologics are only used for IBD, RA, SLE and AS[15]. This made it difficult reviewing the nuances in biologic immunosuppression of individual diseases. Even then, most zosters vaccination in immunocompromised patients

research pertained to IBD. Current ECCO guidelines[12] recommends VZV immunisation at least three weeks prior to commencing immunomodulatory therapy. 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[22] or only in mildly immunosuppressed patients[23]. If looking at vaccination without biologics, one study[24] found that despite a higher absolute shingles incidence rate of 50% compared to healthy populations, the zoster vaccine was still protective. Whilst HZ vaccination is likely useful for autoimmune rheumatic patients, its safety remains unclear when factoring in biologic therapy.

4.3 Demographics: Age

Amongst different age groups, current data recommends the *Shingrix* vaccine in adults over 50, including immunocompromised patients[19]. However, NHS guidelines prohibit vaccination above 80 years in all, given data[24] showing *Zostavax's* efficacy wanes with age; this is supported by another study demonstrating only 38%[25] efficacy in immunocompetent patients over 70. Presumably, all this pertains to patients undergoing biologic therapies too, suggesting vaccination benefits do not outweigh the risks in older patients.

4.4 Timeline Indications

Timing of administration is important, given that the current Zostavax vaccine is live and biologics suppresses the immune response. Amongst those supporting vaccination, there is no consensus when to stop or/and begin biologics following vaccination. Recommendations on when biologics should begin post-vaccination range from 3 weeks[12] to 3 months[15]; some instead recommend a case-by-case approach[26]. Other literature simply deferred to national guidelines on general vaccination procedures in immunocompromised patients[19].

There was even less literature on when to stop biologics if vaccinating later, problematic given that many patients have ongoing disease but no prior VZV exposure. The only paper[16] explicitly targeting this recommended following current general guidelines on zoster-vaccine immunisation of withholding immunosuppressant drugs 4 weeks prior. When re-initiating treatment for VZV IgG seronegative patients, there was no mention of stopping immunosuppression prior to vaccination[12].

Current NHS guidelines states patients receiving the live vaccination should wait for an established immune response before immunosuppressive therapy. This is supported by the CDC, which notes that waiting four weeks should be sufficient for viral live vaccines[27]. However, they recommend not delaying therapy if this would worsen the underlying condition, as most live vaccines are attenuated; this should only occur following specialist consult on a case-by-case basis[28].

Long-term, Zostavax's efficacy does wane over time[29]. 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 2 years[13].

4.5 Live vs Non-live

The current VZV vaccine, a live attenuated known as *Zostavax*, has shown efficacy in immunocompromised patients by providing 70-90% immunity persisting for at least 10 years[12]. EULAR vaccination recommendations for AIIRD patients[19] has shown vaccine efficacy after 42 days with AIIRD patients on bDMARDs, with no HZ incidence increase. Interestingly, trials have shown a potential reduction of HZ risk by up to 70% in adults over 50 years, with lower HZ incidence after 2 years regardless of immunosuppressive medications[19]. 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[15].

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[30] and is not recommended for immunosuppressed patients, it is promising. Assuming it does so, *Shingrix* would likely see larger usage in previously more 'at-risk' patients and is less likely to be contraindicated with concurrent biologic therapy.

4.6 Pharmacoeconomics

When evaluating a role for prophylactic vaccination, consideration can be given to cost effectiveness. One US study found *Zostavax's* cost effectiveness ratio per QALY gained between $25,379-$27,609[31]. Incidentally, this is within the Irish healthcare system's incremental cost effectiveness ratio of €20,000-€45,000[32]. Vaccination also likely costs less than alternative prophylactic means, such as prophylactic acyclovir dosing. This all suggests prophylactic vaccination is economically viable, implying a role to play in clinical practice assuming safety can be definitively established.

4.7 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 2000 and 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.

5 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 when and how to vaccinate; case-by-case exceptions ought to be considered too. Further research[33] however is required, particularly regarding specific autoimmune conditions and biologic agents as well as *Shingrix*, with a view to improve the formulation of clinical guidelines on the use of the HZ vaccine in the immunocompromised.

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