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# **Herpes zoster and vaccination strategies in inflammatory bowel disease: a practical guide**

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LG wrote the article. LG and LPB conceived the study. CR, EHC, SCN and LPB critically revised the manuscript. The manuscript was approved by all authors.

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L Guillo declares no conflict of interest. C Rabaud has served as a speaker, consultant and advisory board member for Astellas, Janssen, Gilead, Merck Sharp and Dohme. EH Choy has received research grants, honoraria and served as member of advisory boards and speaker bureaus of Abbvie, BioCancer, Biocon, Biogen, Bristol Myer Squibbs, Chugai Pharma, Eli Lilly, Gilead, Janssen, Merck Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB. Siew C Ng has received research funds from Ferring and Abbvie, and speaker honorarium from Ferring, Abbvie, Takeda, Pfizer, Olympus, Tillotts, Menarini, Janssen. L Peyrin-Biroulet has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, HAC- Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance.

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**Abstract (word count 130)**

Herpes zoster (HZ) is a painful dermatomal cutaneous eruption due to the reactivation of the latent varicella-zoster virus (VZV). Patients with inflammatory bowel disease (IBD) have an increased risk of shingles compared to the general population and this risk can be increased with the use of immunosuppressive therapy. Live zoster vaccine (LZV) and recombinant zoster vaccine (RZV) have demonstrated efficacy for the prevention of HZ. RZV seems to offer greater efficacy and long-term protection profiles. However, their use in clinical practice is still unclear and updated vaccination recommendations are lacking. This review will discuss risk for shingles in patients with IBD, available vaccines and their efficacy and safety profiles. We will also provide guidance on who, when and how to vaccinate for HZ in routine clinical practice amongst patients with IBD.

**Keywords:** Herpes zoster, shingles, herpes zoster vaccine, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, opportunistic infection

## Introduction

Herpes zoster (HZ), also known as shingles, is a painful dermatomal cutaneous eruption which occurs due to the reactivation of latent varicella-zoster virus (VZV) lying within the dorsal root ganglia or cranial nerves after the primary infection<sup>1,2</sup>. The main complication of HZ is postherpetic neuralgia, ranging from 2.6% to 52.0% amongst all cases<sup>3</sup>, which consists of a pain syndrome lasting from months to years after the initial rash has subsided and can substantially impact quality of life<sup>1</sup>.

Risk of HZ increases with old age and immunodeficiency condition and its incidence rate in immune-mediated inflammatory diseases (IMIDs) is approximately 1.5 to 2-fold higher than in the general population<sup>4-6</sup>. Inflammatory bowel disease (IBD) which comprised of Crohn disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of the gastrointestinal tract,<sup>7,8</sup> also known to carry a higher risk of HZ<sup>6,9</sup>. Corticosteroids, anti-tumor necrosis factor (anti-TNF) agents, and other biologics may increase the risk of opportunistic infections, including shingles<sup>10,11</sup>. For instance, in the VARSITY trial, 15 cases of zoster in 386 patients with UC were reported in the adalimumab-treated group<sup>12</sup>. The JAK inhibitor, tofacitinib, has been approved for the treatment of patients with refractory UC whilst two others newer JAK inhibitors, filgotinib and upadacitinib, will be available soon. Recently, a meta-analysis showed that patients with immune mediated diseases (IMIDs) have an overall increased risk of herpes zoster with JAK inhibitor treatment<sup>13</sup>.

Live zoster vaccine (LZV) (Zostavax<sup>®</sup>) and recombinant zoster vaccine (RZV) (Shingrix<sup>®</sup>) have both demonstrated efficacy for the prevention of HZ<sup>14,15</sup>. Both are recommended in immunocompetent adults aged  $\geq 60$  years for LZV and aged  $\geq 50$  years for RZV<sup>16,17</sup>. In 2015 the American College of Rheumatology (ACR) recommended vaccination with LZV for patients with rheumatoid arthritis (RA) aged  $\geq 50$  years before initiating biologics therapy<sup>18</sup>. In 2017 the American College of Gastroenterology (ACG) also recommended

vaccination for patients with IBD aged  $\geq 50$  years<sup>19</sup>. However, updated recommendations for prevention of HZ and vaccination in IBD are still lacking. Here, we reviewed available evidence regarding HZ risk in patients with IBD and discussed the efficacy and safety of HZ vaccination and provided guidance for routine practice.

## **Risk for herpes zoster in IBD patients**

### *Epidemiology and risk factors*

In the general population, the incidence rate (IR) of HZ ranges from 1.2 to 4.9 cases per 1,000 person-years (py)<sup>20–22</sup>. The incidence in IMIDs, such as IBD, is approximately 1.5 to 2-fold higher than in the general population<sup>4,5,22–24</sup>. The incidence rate (IR) in patients with IBD ranges from 6.67 to 9.2 cases per 1,000 py<sup>21,25,26</sup>. Marehbian et al.<sup>24</sup> also reported a higher IR of 89 cases per 10,000 py with a rate ratio of 1.83 compare to the general population. Patients with CD are at higher risk of shingles than those with UC. Indeed, IR ranges from 814 to 854 versus 664 to 670 cases per 100,000 py respectively for CD and UC<sup>23,27</sup>. These results were confirmed in two other studies<sup>9,21</sup>, while in another study, the IR in UC was superior than in CD<sup>25</sup>. A meta-analysis of cohort studies, including more than 1,000,000 patients, reported a relative risk (RR) of 1.74 in CD and of 1.40 in UC compared to non-CD or non-UC patients (*Table 1*)<sup>28</sup>.

One of the established risk factor of shingles is the increased age<sup>1,3,4</sup>. A meta-analysis of zoster infection risk found a RR of 1.65 with older age<sup>6</sup>. Regarding IBD, this age relationship is also observed in the occurrence of HZ. Gradual increase in risk is observed with a highest reported incidence rate among over 60 years old (11.5 cases per 1000 py<sup>25</sup>, around 1,500 cases per 100,000 py<sup>23</sup>) and over 65 years old (15.48 cases per 1,000 py<sup>22</sup>, around 1200 cases per 100,000 py<sup>9</sup>). Significantly increase number of HZ cases has been noted for the age groups over 45s<sup>9</sup>, and over 50s<sup>22,23,25</sup>. Furthermore, IR among those under 50s is approximately the same as

the age group of the 50-60s in the general population<sup>23</sup>. A retrospective cohort study showed that in patients with IBD and IMIDs, the IR among the 30s to 50s was similar or higher, respectively, than the corresponding rate in adults without IMIDs aged  $\geq 60$ <sup>5</sup>. In a large cohort including 108,604 IBD patients, it was reported that patients with HZ have significantly more comorbidities including diabetes, cardiac conditions, liver or renal diseases and chronic pulmonary diseases<sup>23</sup>. A meta-analysis confirmed that chronic diseases co-morbidities, such as diabetes, cardiovascular, pulmonary and renal disease increased risk of HZ (RR of 1.24 to 1.41). Moreover, this study reported that family history of zoster is a strong risk factor with a RR of 2.48, and that female gender is also a risk factor but with a lower RR of 1.19<sup>6</sup>. Ethnicity also appears to be a risk factor for shingles. Asian patients have higher rates than North America, Europe or Latin American populations; the rate is particularly high in Japanese and Korean populations with crudes IR ranging from 6.49 to 18.34 cases per 1,000py<sup>29-32</sup>. A retrospective study demonstrated that IBD is ranked at the fourth position of the immunocompromising or chronic disease conditions, after the hematopoietic hematological transplant, hematological malignancy and systemic lupus, in Japanese population<sup>33</sup>. While, black ethnicity is associated with a lower risk of HZ (RR= 0.69) (*Table 1*)<sup>6</sup>.

#### *Treatment-related risk*

Treatment for IBD is associated with an increased risk of HZ, mainly for treatment which target or disrupt cell-mediated response<sup>34</sup>.

Two retrospective cohort studies showed that 5-aminosalicylic acid (ASA) use was not associated with an increased risk of HZ, while corticosteroids and thiopurines (azathioprine and 6-mercaptopurine) use were significantly associated with an increase IR of shingles<sup>9,23</sup>. Two additional retrospective studies also reported an elevated risk of HZ with corticosteroids and thiopurines<sup>21,24</sup>.

Anti-TNF agents exposed patients to opportunistic infections. Risk of shingles is also increased when treated with anti-TNF agents. The odds ratio (OR) ranges from 1.33 to 1.81 compared to patients with IBD not treated with anti-TNF drugs or who received 5-ASA<sup>23,24</sup>. Combination therapy of anti-TNF agents with thiopurine further increased the risk with OR ranging from 1.65 to 3.68<sup>21,23,24</sup>. Colombel et al.<sup>35</sup> reviewed six major clinical trials on adalimumab comprising 3160 CD patients, whereby 46 cases of HZ were registered and 6 were considered severe. In VARSITY study, which compared adalimumab to vedolizumab in patients with UC, IR was 4.2 per 100 py in the adalimumab group<sup>12</sup>. Although anti-TNF agents was associated with a higher risk of shingles in patients with UC there was no signal of developing severe form of shingles defined as a multidermatomal, ophthalmic, visceral, disseminated, with secondary bacterial infection or the requirement of an intravenous antiviral drug<sup>36</sup>.

Data concerning vedolizumab are reassuring for the risk of HZ. A retrospective study including six trials on vedolizumab reported an IR of 0.5 cases per 100 py<sup>37</sup>, and these findings were consistent with data from the VARSITY study<sup>12</sup>. In GEMINI I, a phase III trial, only two cases of HZ were registered in the vedolizumab arm, and two cases were reported in the placebo arm<sup>38</sup>. Among the United States Veterans Affairs Healthcare System (VAHS) cohort, no HZ was reported for patients with IBD in the Vedolizumab group<sup>21</sup>.

Safety data for Ustekinumab are limited. However, three major studies, CERTIFI, UNITI and UNIFI, showed no increased risk of HZ<sup>39-41</sup>. For psoriasis treatment, safety data did not seem to show an increased risk of shingles<sup>27</sup>, however additional safety studies are necessary to confirm these findings

Tofacitinib, the first JAK1/JAK3-inhibitor molecule, has been approved for the treatment of patients with refractory UC and its efficacy has been shown in the OCTAVE study<sup>42</sup>. Tofacitinib have been associated with an increased risk of HZ in both patients with RA



and IBD, with an IR ranging from 3.4 to 4.1 cases per 100 py, and a dose dependent relationship with higher risk at 10 mg twice daily than 5 mg twice daily dosage<sup>29,43-45</sup>. Filgotinib and Upadacitinib are selective JAK1-inhibitors currently being tested in both CD and UC. Approximately 1.3% and 1.4-2% of patients with RA developed HZ at a daily dosage of 100 mg and 200 mg of Filgotinib, respectively, in the FINCH 2 and DARWIN 1 studies<sup>46,47</sup>. In the DARWIN 2 study, one case (1.4%) developed HZ at daily dosage of 50 mg and none developed HZ at daily dosage of 100 mg and 200 mg<sup>48</sup>. Moreover, in DARWIN 1, HZ was noted in 2% of patients on the placebo arm. Importantly there no significant difference in adverse events between placebo and Filgotinib groups<sup>47</sup>. In patients with CD patients, the FITZROY phase 2 study found HZ in 3% of patients treated with daily dosage of 100 mg to 200 mg Filgotinib<sup>49</sup>. Recently, the SELECTION phase 2b/3 trial, which explored the use of Filgotinib 100 mg to 200 mg once daily in patients with UC, reported low rates of HZ ranging from 0.4% to 0.8% for both induction and maintenance therapy<sup>50</sup>. The use of Filgotinib for the treatment of patients with UC will soon be validated. Three phase 3 studies investigating the use Upadacitinib in patients with RA showed that 0.5-1% and 1-2% of patients receiving 15 mg and 30 mg Upadacitinib once daily, respectively, developed HZ<sup>51-53</sup>. Recently, a retrospective study compiling four phase 2 and 3 trials in RA showed that 0.6% to 1.4% of patients treated with Upadacitinib 15mg or 30mg once daily developed HZ<sup>54</sup>. In patients with CD, the CELEST phase 2 trial, reported one case of HZ in induction groups receiving 12 mg (1.7%) and 24 mg (2.8%) once daily dose and 1 case in the 24 mg (2.8%) once daily maintenance group<sup>55</sup>. In patients with UC, the U-ACHIEVE phase 2 trial, reported only one case of shingles (1.8%) in the 45 mg once daily maintenance group<sup>56</sup>. Whether JAK1 inhibitors (Filgotinib and Upadacitinib) are associated with a lower risk of developing HZ than Tofacitinib require further investigation.

## **Available vaccines**

### *Live zoster vaccine (LZV): Zostavax<sup>®</sup>*

LZV, an attenuated form of VZV. Zostavax<sup>®</sup>, has been approved for the prevention of HZ and its complications among adults aged  $\geq 60$  years by the US Food and Drug Administration (FDA) since 2006<sup>16</sup>, and adults aged  $\geq 50$  years by the European Medicines Agency (EMA) since 2008<sup>57</sup> and the FDA since 2011<sup>58</sup>. The US Advisory Committee on Immunization Practices (ACIP) recommended the use of LZV since 2008 for adults aged  $\geq 60$  years<sup>16</sup>. Zostavax<sup>®</sup> cost ranges from \$134.16 (Centers for Disease Control and Prevention (CDC) price) to \$216.66 (private price) per dose<sup>59</sup>, but cost and reimbursement policy depend on individual country's healthcare system. Each 0.65 mL dose contains not less than 19,400 plaque-forming units of the Oka/Merck strain of VZV<sup>57</sup>. A single dose administered subcutaneously, or intramuscular, in the deltoid region is recommended and generally well tolerated. LZV should be stored in the freezer ( $-50^{\circ}\text{C}$  to  $-15^{\circ}\text{C}$ ,  $-58^{\circ}\text{F}$  to  $5^{\circ}\text{F}$ ) and it can also be stored in the refrigerator ( $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$ ,  $36^{\circ}\text{F}$  to  $46^{\circ}\text{F}$ ) for up to 72 hours before reconstitution, and should be used immediately within 30 minutes after reconstitution<sup>14,57,60</sup>. Concomitant administration with a quadrivalent seasonal inactivated influenza vaccine (IIV4) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is possible without loss of efficacy compared the sequential vaccination<sup>61,62</sup>. Contraindications to LZV include primary and acquired immunodeficiency states (acute and chronic leukemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; HIV/AIDS; cellular immune deficiencies), immunosuppressive therapy including high-dose corticosteroids, active untreated tuberculosis and pregnancy (*Table 2*)<sup>57</sup>.

### *Recombinant zoster vaccine (RZV): Shingrix<sup>®</sup>*

Shingrix<sup>®</sup> is approved for the prevention of HZ and its complications among adults aged  $\geq 50$  years by the US FDA since 2017<sup>17</sup>, and the EMA since 2018<sup>63</sup>. The US ACIP recommended it since 2018 for adults aged  $\geq 50$  years<sup>17</sup>. Shingrix<sup>®</sup> cost ranges from \$101.51 (CDC price) to \$151.51 (private price) per dose<sup>64</sup>, but its price and reimbursement depend on the country and healthcare system. For now, it is available only in the US, Canada and China. Each 0.5 mL dose of RZV contains 50 $\mu$ g VZV glycoprotein E antigen (gE) and the AS01<sub>B</sub> adjuvant system (50 $\mu$ g gE/AS01<sub>B</sub>)<sup>63,65</sup>. Two doses administered intramuscularly in the deltoid region 2-6 months apart is recommended. RZV should be stored in the refrigerator (2°C to 8°C, 36°F to 46°F) and be used within 6 hours after reconstitution<sup>15,63,65</sup>. Concomitant administration with IIV4 and PPSV23 is possible without loss of efficacy compared to sequential vaccination<sup>66,67</sup>. RZV is also effective in case of previous vaccination with LZV in adults over 65 years old<sup>68</sup>. Main contraindications included hypersensitivity to the active substance or any excipient, no contraindication Administration of RZV to immunocompromised subjects should be based on careful consideration of potential benefits and risks (*Table 2*)<sup>63</sup>.

## **Efficacy and safety data**

### *Efficacy data*

It has been demonstrated that a single dose of live zoster vaccine (LZV) was immunogenic in adults aged over 60s. However, response was significantly lower in patients aged over 70s<sup>69</sup>. The Zostavax Efficacy and Safety Trial (ZEST) reported an efficacy of 69.8% against HZ in adults aged 50-59 years<sup>60</sup>, while the Shingles Prevention Study (SPS) reported an efficacy of 51.3% in adults aged over 60 years and 37.6% in subjects over 70 years<sup>70</sup>. Efficacy rates based on different age groups are as follows: 69.8% in the 50-59s, 63.9% in the 60-69s and 37.6% in the over 70s<sup>60,70</sup>. Two studies demonstrated that LZV was protective for about five years<sup>71,72</sup>. However, short-term and long-term studies showed that vaccine efficacy

tended to decrease in the second year, with rate of 62.0%, 48.9% and 44,6% at year 1, 2 and 4 respectively<sup>72</sup>, and this rate decreased to 21.1% through 11 years (*Table 2*)<sup>73</sup>. A retrospective study with 463,541 patients with IMIDs, including RA, psoriasis, psoriatic arthritis, ankylosing spondylitis and IBD showed that patients vaccinated with LZV was associated with a lower IR of HZ than unvaccinated patients over a median follow-up of 2 years<sup>74</sup>. In the VAHS cohort, vaccination in IBD patients was associated with a significant reduction of HZ risk versus unvaccinated patients (adjusted hazard ratio of 0.54)<sup>75</sup>. In contrast, Winthrop et al.<sup>76</sup> reported that LZR may not provide adequate long-term protection in a long-term effectiveness study of RA patients treated with tofacitinib.

Concerning RZV, immunogenicity studies showed a dose-dependent relationship. Moreover, a two-dose schedule produced 1.5 to 2.5-fold greater humoral immunity<sup>77,78</sup>. The ZOE-50 and ZOE-70 studies respectively reported an efficacy against HZ of 97.2% in the over 50 and of 89.8% in the over 70 years<sup>79,80</sup>. Furthermore, vaccine efficacy did not differ between different age groups. Efficacy rates across different age groups are as follows: 96.6 to 96.9% in the 50-59s, 94.1 to 97.4% in the 60-69s and 89.8 to 97.9% in the over 70s<sup>79</sup>. RZV was also associated with reduced pain symptoms and risk of PHN in case of breakthrough shingles<sup>81,82</sup>. Shingrix<sup>®</sup> is at least protective for four years with minimal decline in effectiveness over this period, with rates of 97.6% and 87.9% respectively at one and four years (*Table 3*)<sup>80</sup>. Further data showed that responses remained substantially above the pre-vaccination level for up to nine years and a statistical model predicted that the immune responses remained above the pre-vaccination level for up to 15 years<sup>83</sup>. In a retrospective study of 403 patients with RA and other systemic rheumatic diseases who received RZV, it was noted that only three cases of HZ occurred 2, 10, and 11 months after the vaccination<sup>84</sup>. Recently, Kochhar et al. demonstrated that HZ risk was significantly lower in patients with IBD receiving 2 doses of RZV compared to those who did not but they were still at higher risk than the general population who received

2 doses<sup>85</sup>. However, long-term efficacy data in immunocompromised subjects and booster schedule are necessary.

### *Safety profile*

The most frequent adverse events (AE) for LZV is injection-site reaction (48.3%) of mild to moderate intensity. Headache is the most common systemic reaction reported in 9.4% of subjects (*Table 1*)<sup>60,70,86</sup>. Zostavax<sup>®</sup> can be safely used with methotrexate, low to intermediate dose of corticosteroids (<20 mg/day of prednisone or equivalent) and thiopurines<sup>87</sup>. Safety data about anti-TNF agents are reassuring. A retrospective study reported no case of HZ within 42 days of vaccination in 59 IBD patients who were treated with an anti-TNF agent<sup>88</sup>. Zhang et al.<sup>74</sup> also found no cases of HZ within 42 days of vaccination in a large cohort of 551 patients with AI diseases including 117 patients with IBD who were treated with an anti-TNF agent. While another cohort study showed a modest increased risk of HZ in the 42 days after vaccination in patients taking immunosuppressant drugs<sup>89</sup>. However, in this cohort 83.9% of patients were taking corticosteroids either alone or in combination therapy with other immunosuppressant agents, which at higher risk of shingles. Winthrop et al.<sup>90</sup> found that patients who began tofacitinib 2-3 weeks after receiving LZV had similar immune response to those in the placebo group at week 14.

RZV demonstrated a good safety profile. Injection-site reaction of mild to moderate intensity was the most frequent AE reported in 74.1 to 81.5% of patients. Myalgia, fatigue and headache were the most common systemic reaction seen in 1.4 to 2.4% patients (*Table 1*)<sup>79,80</sup>. A recent prospective study in patients with IBD showed a similar rate of 74.6% of local AE and a low rate of flare (1.5%) after vaccination with RZV<sup>91</sup>. A systematic review reported that RZV had a RR of 1.79 for injection-site events when compared with LZV<sup>92</sup>. Four phase 3 studies demonstrated that RZV is immunogenic and humoral responses persisted for at least 12 months

after vaccination in immunocompromised adults with solid tumors on chemotherapy, post renal transplantation, hematologic malignancies and autologous hematopoietic stem cell transplant<sup>93-96</sup>. Although the use of RZV in immunodeficiency situations seems reassuring, data on IBD patients are lacking.

### **Who, when and how-to vaccinate patients with IBD ?**

Among patients with IBD who were followed in the nationwide VAHS cohort, only 20.96% of patients were vaccinated against shingles<sup>97</sup>, and the median age at the time of vaccination was 64.9 years<sup>88</sup>. In another study, rate of HZ vaccination was of 15.5 per 1,000 py<sup>26</sup>. These data demonstrated the low vaccination coverage and the delay in access to vaccination. In IMIDs patients aged 30 to 50 years IR of HZ was similar or highest than the corresponding rate in adults without AI aged  $\geq 60$  years<sup>5</sup>, suggesting that vaccination should be considered earlier in this population. Ethnicity may affect the risk of HZ. It was found that Asian population has a higher risk for HZ than Caucasian populations. This risk was more pronounced with Tofacitinib treatment<sup>29,31,43</sup>. The SELECT-SUNRISE study, which tested Upadacitinib at 30 mg once daily dosage in RA Japanese population, have also reported a higher risk, with 6% of patients with HZ versus 1-2% in the non-Japanese population as we have shown previously<sup>98</sup>. In 2015 the ACR recommends vaccination with LZV for patients with RA aged  $\geq 50$  years before initiating biologics therapy or Tofacitinib<sup>18</sup>. In 2017, the ACG clinical guidelines for IBD recommend that patients over 50 years, including those are immunosuppressed, should consider vaccination against HZ<sup>19</sup>. These guidelines encourage increased access to vaccination for IBD patients. Moreover, in patients with IBD, HZ appears to be the most frequent vaccine-preventable disease compared to others (e.g. pneumococcal, influenza or hepatitis) who have same the same rate of hospital admission as the general population<sup>99</sup>. Vaccination with RZV appears to be greater than LZV both in terms of

effectiveness and duration of protection<sup>92,100</sup>. Recently, a cost-effectiveness study comparing both vaccines demonstrated that RZV had a lower cost-effectiveness ratio than LZV<sup>101</sup>. Furthermore, in 2018 the Advisory Committee on Immunization Practices (ACIP) of the USA recommends RZV preferentially over LZV in immunocompetent adults aged  $\geq 50$  years<sup>17</sup>.

Updated vaccination recommendations for the prevention of HZ are still lacking for patients with IBD. To guide physicians in the use of vaccination for HZ in IBD, we propose that RZV should be considered for patients aged  $\geq 50$  years with or without immunosuppressive therapies (including high dose corticosteroids ( $\geq 20$  mg/day of prednisone or equivalent), biologics or JAK inhibitors), and for adult patients before starting treatment with biologics or JAK inhibitors regardless of age. If RZV is not available, LZV should be considered for patients aged  $\geq 50$  years without immunosuppressive therapies, and for adult patients before starting treatment with biologics or tofacitinib regardless of age. Its use in patients who have been treated with immunosuppressive therapies must be avoided. Vaccination with RZV should be considered 5 years after LZV to prevent loss of protection (*Figure 1*).

## **Conclusion**

Patients with IBD have an increased risk of HZ compared to the general population, with a higher rate in patients with CD than UC. Family history, Asian population and old age are strong risk factors for HZ. Furthermore, this risk can be increased with the use of an immunosuppressive therapy. JAK inhibitors is associated with the risk of developing HZ, particularly for Tofacitinib, due to its mechanism of action.

Two vaccines are available for the prevention of HZ including a live vaccine and a recombinant vaccine. LZV is effective but long-term protection appears limited to only four years, and it is contraindicated in patients under immunosuppressive therapy. RZV showed greater efficacy against HZ, offered better long-term protection, can be used in

immunocompromised patients and had reassuring safety and efficacy results, but it is currently not recommended in patients with IBD due to lack of data. This paper offers a practical guide and recommendations of RZV and LZV for HZ prevention in patients with IBD aged  $\geq 50$  years or before starting treatment with biologics or JAK inhibitors regardless of age.



**Table 1: Risk factors for herpes zoster**

<b>Factor</b>	<b>Risk</b>
Older age	RR 1.65 <sup>6</sup>
Family history of HZ	RR 2.48 <sup>6</sup>
Female	RR 1.19 <sup>6</sup>
Co-morbidities*	RR 1.24 – 1.41 <sup>6</sup>
CD	RR 1.74 <sup>28</sup>
UC	RR 1.40 <sup>28</sup>
IBD	6.67 to 9.2 cases per 1,000py <sup>21, 25,26</sup>
Asian population	6.49 to 18.34 cases per 1,000py <sup>29-32</sup>
Black population	RR 0.69 <sup>6</sup>

CD, Crohn's disease; IBD, inflammatory bowel disease; py; person-years; RR, relative risk; UC, ulcerative colitis;

\* Co-morbidities: diabetes, cardiovascular, pulmonary and renal chronic disease

**Table 2: Comparison of vaccines characteristics**

<b>Category</b>	<b>LZV</b>	<b>RZV</b>
<b>Vaccine type</b>	Live attenuated	Recombinant
<b>FDA approval</b>	2006	2017
<b>ACIP recommendation</b>	≥ 60 years	≥ 50 years
<b>Cost</b>	\$134.16 (CDC price) to \$216.66 (private price) per dose	\$101.51 (CDC price) to \$151.51 (private price) per dose
<b>Number of doses</b>	Single 0.65 ml dose	Two 0.5 ml doses
<b>Spacing between dose</b>	N/A	2-6 months
<b>Storage</b>	Freezer: -50°C to -15°C (-58°F to 5°F)	Refrigerator: 2°C to 8°C (36°F to 46°F)
<b>Administration</b>	SC injection in deltoid	IM injection in deltoid
<b>Concomitant validated administration</b>	IIV4 and PPSV23	IIV4 and PPSV23
<b>Contraindications</b>	Primary and acquired immunodeficiency states (acute and chronic leukemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; HIV/AIDS; cellular immune deficiencies), immunosuppressive therapy including high-dose corticosteroids, active untreated tuberculosis and pregnancy	Hypersensitivity to the active substance or any excipient
<b>Injection site reactions</b>	48.3%	74.1 to 81.5%
<b>Adverse events</b>	Headache	Myalgia, fatigue and headache

ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; IIV4, quadrivalent seasonal inactivated influenza vaccine; IM, intramuscular; LZV, live zoster vaccine; N/A, not available; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; SC, subcutaneously; HIV/AIDS, human immunodeficiency virus/acquired immuno-deficiency syndrome;

**Table 3: Comparison of vaccines efficacy**

Category	LZV	RZV
50 to 59 years	69.8%	96.6 - 96.9%
60 to 69 years	63.9%	94.1 - 97.4%
≥ 60 years	37.6%	89.8 - 97.9%
Year 1	62%	97.6%
Year 4	44.6%	87.9%

LZV, live zoster vaccine; RZV, recombinant zoster vaccine;

**Figure 1: Proposed recommendations**

Vaccines	Aged ≥ 50 years without immunosuppressive therapies*	Aged ≥ 50 years under immunosuppressive therapies*	Before starting biologics or JAK inhibitors	Population at high-risk**
RZV	Yes	Yes	Yes	Yes
LZV	Yes***, if RZV isn't available	Must be avoided	Yes***, if RZV isn't available	Yes***, if RZV isn't available

LZV, live zoster vaccine; RZV, recombinant zoster vaccine;

\* Including high dose corticosteroids (≥20 mg/day of prednisone or equivalent), biologics or JAK inhibitors.

\*\* Asian population, family history of zoster, co-morbidities (diabetes, cardiovascular, pulmonary and renal chronic disease)

\*\*\* Vaccination with RZV should be considered 5 years after LZV to prevent loss effective protection.

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