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Review Article

Review Article

Varicella Zoster Virus in Inflammatory Bowel Disease Patients: What Every Gastroenterologist Should Know

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Abstract

Primary varicella zoster virus [VZV] infection results in varicella [chickenpox] and its reactivation results in herpes zoster [HZ; shingles]. Patients with inflammatory bowel disease [IBD] are susceptible to complications of primary VZV infection and have an increased risk of HZ. Concerns of VZV and HZ infection in the IBD population have been highlighted by the emergence of JAK inhibitors and their safety profile in this patient population, as with tofacitinib for the treatment of ulcerative colitis [UC]. The current pipeline of emerging therapies includes novel molecules targeting multiple pathways, including JAK/signal transducer and cytokine signalling pathways, such as JAK/STAT. Hence VZV and HZ will be increasingly relevant for gastroenterologists treating IBD patients in light of these emerging therapies. This review will focus on the epidemiology, disease course, prevention, and management of these two distinct infections in patients with IBD.

Key words: Varicella; herpes zoster; inflammatory bowel disease

1. Introduction

The inflammatory bowel diseases [IBD], Crohn's disease [CD] and ulcerative colitis [UC], are characterised by an impaired immune response to luminal antigens in genetically susceptible hosts, with a relapsing-remitting and progressive course. Immunomodulatory [IM] or immunosuppressive therapies[1,2] for IBD, including thiopurines, methotrexate, several biologics and oral small molecule agents, increase the risk of infection.[3] Although the terms IM and IS are often used interchangeably, for the purposes of this paper the term immunosuppressants [IS] will be used.

Varicella is caused by primary infection with the varicella zoster virus [VZV] and is a self-limiting disease usually occurring in childhood. Primary VZV infection typically causes mild to moderate symptoms in immunocompetent children. However, in immunocompromised individuals[4] and in the elderly population, a higher incidence of serious complications can occur.[5] The combination of aberrant immune regulation in IBD and the frequent use of IS therapy renders IBD patients more susceptible to complications of primary VZV.

Herpes zoster [HZ] also may result in serious complications in immunosuppressed patients and, despite being a vaccine-preventable disease, HZ represents one of the most frequent opportunistic infections[6] in IBD patients.

The objective of this review is to provide gastroenterologists with up-to-date knowledge and guidance regarding the epidemiology, risk factors, management, and prevention of VZV and HZ.

2. Varicella

2.1. Epidemiology

Varicella zoster virus [VZV] is an alpha herpes virus that causes varicella [chickenpox; VZ] and, after decades of latency in ganglionic neurons, it reactivates as herpes zoster [shingles; HZ] in nearly 30% of individuals during their lifetime.[7]

The primary infection with VZV is highly contagious, with a secondary attack rate between 65–100% among susceptible children.[8,9] More than 90% of teenagers in Western countries have chickenpox exposure, defined by positive VZV IgG, by the age of 15 years.[10] However, it is important to note that seroprevalence of chickenpox is only just over 50%[11] in adolescents from tropical and Asian countries, and consequently seroconversion occurs in late adolescence and adulthood rather than in childhood.[12]

In contrast to the adult IBD population in whom the majority have previous VZV exposure, paediatric IBD onset may occur before acquired VZV protection. Serological protection against varicella was identified in 77%[13] and 71%[14] of children with IBD in studies from the USA and Canada, respectively.

ECCO Guidelines recommend screening according to history of VZV exposure, and reserving VZV IgG serology in cases of uncertain history or in those without a vaccination history.[15] However, serology may play a role in the majority of patients, as studies have shown that 40% of IBD patients are unaware if they had previous varicella exposure and 30% do not know their vaccination status.[16]

Furthermore, relying solely on patient history has limitations. A small percentage of patients [around 6–10%] with apparent positive history of VZ exposure have negative VZV serology.[17,18] Additionally, all 17 patients who reported negative history of varicella exposure were seropositive in a recent survey of 121 patients.[17] Relying solely on serology in those without a positive history of VZV exposure equally has limitations. Negative serology can occur in previously immunised children [false-negative rate of 34%][19] due to the 10-fold lower concentration of induced antibody formation[20] compared with natural infection.

In view of these limitations we recommend the following strategy in daily clinical practice, which diverges slightly from the ECCO guidelines of 2014[15]:

- Vaccination documentation should be verified. In patients with documented vaccination with two doses of attenuated varicella live vaccine, no further action is required.
- All other IBD patients should be evaluated by VZV IgG serology [regardless of positive or negative history of VZV exposure] in order to identify those patients with a false-positive VZV history as well as patients with a false-negative history in whom immunity against varicella is documented.

2.2. Clinical manifestations and complications

The incubation period for chickenpox is between 10 and 21 days. After initial infection, two peaks of viraemia typically occur, the first after 4–6 days with virus multiplication in regional lymph nodes and subclinical viremia, the second after 10–21 days with a maculopapular-vesicular rash. This is the period of the highest contagiousness.[21] Since the virus can be transmitted via droplets and aerosol 2 days before onset of a rash, infected subjects are contagious in their subclinical phase and remain contagious until complete encrustation of all skin lesions.[22] It must be emphasised that the infectious period can persist for several weeks in immunosuppressed individuals.[22]

In contrast to the benign clinical course in children aged 14 years or less, who have a mortality of 0.7–1.6 per 100 000 varicella cases,[4,5] the mortality in adults is 25 times higher, with a death rate of 21.3 per 100 000 varicella cases.[5]

Although complications of primary VZV infection, such as encephalitis and cerebellar ataxia, pneumonia, and bacterial superinfections of the skin,[23] develop mainly in children, the risk of hospitalisation is higher in adults, with hospital admission rates reaching 6–8% in those over 65 years.[4,24,25] Another at-risk patient population group are pregnant women, who are particularly vulnerable to the complications of VZV such as pneumonia which is estimated to be 10–20%, and may also have foetal transmission with subsequent congenital varicella syndrome.[26] Immunocompromised individuals comprise the third at-risk group who are at increased risk for invasive infections such as osteomyelitis, pneumonia, hepatitis, necrotising fasciitis, and sepsis, with an estimated mortality of approximately 10%.[27]

In IBD patients, 23 cases with primary varicella infection are reported in the literature.[28–31] Nearly all patients received at least one IS, one-third of patients developed varicella pneumonia [7/23; 30%], and 5/23 [22%] of patients died. Interestingly 80% of the fatal cases were CD patients, all of whom were under IS.

2.3. Diagnosis

In children without previous VZV exposure, the characteristic rash is sufficient to establish the diagnosis. Further investigations are only required in cases of uncertainty.

In adults, the positive predictive value of clinical diagnosis based on the rash appearance decreases as result of the lower incidence of VZV in adulthood. Therefore in adults, laboratory confirmation of suspected primary VZV infection may be considered or the advice of an infectious disease specialist should be sought in order to exclude other causes of vesiculopapular exanthemas, such as drug reaction, pustular psoriasis, atypical measles, herpes simplex virus [HSV], and other infectious diseases. Additionally, an accurate and prompt diagnosis is essential in order to treat adult IBD patients, potentially under immunosuppressive therapy, within 72 h of presentation.

Obtaining material from the base of the macular and/or papular skin lesions with polymerase chain reaction [PCR] analysis is a simple diagnostic technique that is considered the gold standard, with high sensitivity and specificity for the diagnosis of acute varicella.[32]

Although IgM and IgA antibodies are positive 1–2 days after the beginning of the rash, negative IgM does not rule out acute VZV infection. Therefore, serological testing has no role in diagnosing

chickenpox. IgG typically rises within a few weeks after IgM response and indicates a previous infection with VZV or vaccination.

2.4. Treatment

Since varicella is a self-limiting disease, symptomatic treatment in children is sufficient. However, antiviral therapy is indicated in patients presenting with complications and in immunocompromised patients. Since the risk of complications is higher in immunocompetent adults than in immunocompetent children,[25,33] antiviral therapy may also be considered and is recommended by experts in immunocompetent adults.[34]

Hence, we recommend in adult IBD patients an oral therapy with valaciclovir [Valtrex®, 1 g t.i.d.] within 72 h of onset of disease for 5–7 days.[35] In any patients with disseminated disease or solid organ involvement, intravenous aciclovir therapy [Zovirax®, 10-12 mg/kg body weight every 8 h] should be started as soon as possible and continued until clinical improvement with no occurrence of new cutaneous lesions. Transition to oral therapy may be considered after 7 days of intravenous treatment. Regular monitoring of renal function is necessary, as acyclovir is nephrotoxic. Resistant VZV can be treated with intravenous foscarnet [Foscavir®].[36] In the IBD population, IS therapy should be withheld and can be restarted once the vesicles have completely healed.

Immunocompromised patients without previous VZV immunity, including IBD patients under IS, who have been exposed to a person with chickenpox, should receive post-exposure primary prophylaxis, as secondary attack rates occur in >90% in susceptible individuals, even after short contact time [>5 min].[20] In these patients, passive immunization with VZV immune globulin [VZIG or Varitect®][37] should be administered as soon as possible, but no later than 10 days after exposure.[38] Since the protection after passive immunisation is estimated to be 70% and immunosuppression may prolong the incubation period, patients should be monitored for varicella for a minimum of 28 days.[39] In case of failure of the post-exposure prophylaxis, patients should receive antiviral therapy.

2.5. Prevention

Varicella vaccination is a live vaccine [Varivax® or Varilrix®] that is administered in two doses at least 4 weeks apart, regardless of age, and contains attenuated chickenpox from the Oka strain in a number of 1350–2000 PFU [plaque-forming units]. Other vaccines [live and inactivated] may also be administered at an interval of 4 weeks between different live vaccines. Since two doses offer a high level of protection [80–85%] and is more than 98% effective in prevention of moderate to severe disease, no serological confirmation of acquired immunity is necessary.[40]

Several recommendations are available regarding who should be vaccinated against VZV. Globally, most countries routinely immunise children. Nevertheless, several countries in Europe only vaccinate non-immunised adolescents between 11 and 15 years of age, according to the hypothesis that the incidence of HZ has increased in the unvaccinated middle-aged population because of a reduction of the wild-type VZV, with subsequent decrease in boosting immunity. However, this assumption has never been formally proven and appears to be erroneous,[41,42] as illustrated by the fact that HZ incidence has risen in the USA since the 1950s, decades before the development of the vaccine. Furthermore, HZ incidence has increased in countries without a VZV vaccination policy such as the UK, Spain, and Canada.[41,42]

An argument for routine VZV vaccination is that the incidence of HZ in vaccinated children is five times lower than in children who contract wild-type VZV.[43] It should be noted that vaccinated individuals may still contract wild-type VZV [breakthrough varicella], yet usually with a milder disease course and less contagiousness than primary VZV.[42,44] Although the precise duration of protection after vaccination is unknown, recent data demonstrate a long-lasting immunity over many years after two doses,[45,46] without an increasing risk of breakthrough varicella over time.[47]

Two potential post-exposure prophylaxis options for VZV are available. Administration of passive immunisation should be considered and administered less than 10 days after exposure in immunosuppressed patients, in whom the varicella vaccine is contraindicated. Varicella live vaccine, in patients without IS, is an effective option if given within 3–5 days after exposure to VZV.

Most guidelines recommend avoiding live vaccines in immunosuppressed patients because of the risk of uncontrolled replication of the vaccine strain.[48] In patients treated with IS, current recommendations advise vaccinating patients at least 4 weeks before starting IS or at a defined interval of some months after stopping IS[15,49–51] [see Table 1].

However, it should be kept in mind that robust data regarding safety of live VZV vaccine in patients receiving IS are sparse. A case series of six children with IBD treated with IS, including combination therapy with anti-tumour necrosis factor [TNF and IS, demonstrated safety of the live attenuated varicella vaccine.[52] Furthermore, a prospective study of 23 children with IS demonstrated safety of the live attenuated varicella vaccine when employing a pre-vaccination checklist evaluating humoural and cellular immune competency.[53] In cases of an uncontrolled VZV replication after vaccination, aciclovir treatment is effective in most cases.[49]

The Infectious Diseases Society of America [IDSA] guideline recommends vaccination of the immunocompromised host[50] and that patients with low-level IS, such as prednisone ≤ 20 mg/day or equivalent, short-term [≤14 days] corticosteroid therapy, azathioprine [≤3.0 mg/kg/day], or methotrexate [≤0.4 mg/kg/week or ≤ 20 mg/week], may receive live attenuated varicella vaccine. This is in line with the guideline of the Swiss Federal Advisory Commission on Immunisation, which also states that the live attenuated varicella vaccine can be administered in patients receiving vedolizumab.[51] However, due to scarcity of data, this recommendation is based on expert opinion, taking into account the gut-selective mode of action of vedolizumab. In complex cases, infectious disease specialist advice should be obtained.

Aside the safety issues, the immunological response to vaccines may be theoretically diminished in IS-treated patients.[54] However, most studies demonstrate efficacy of the live attenuated varicella vaccine with an adequate immune response in patients with IS.[52,53,55]

3. Herpes zoster

3.1. Epidemiology

Reactivation of latent VZV results in herpes zoster [HZ]. The lifetime risk of HZ in the general population is approximately 20–30% and increases to 50% in unvaccinated persons reaching the age of 85 years.[56] Under the age of 50 years, HZ has an incidence rate of 3–4/1000 patient-years [py] and increases every year to an incidence rate of 14/1000 py in those 80 years old.[57]

As T cell immunity against VZV diminishes over time, the major risk factor for HZ is increasing age.[58] Furthermore immunocompromised individuals, especially with impaired T cell immunity, such as patients under IS therapy, have an up to 10-fold higher risk for HZ than the general population,[59,60] with a higher likelihood of more severe disease and recurrence.[61]

Table 1. Summary of diagnosis and management of varicella in IBD patients.

Who should be screened for varicella?	Every IBD patient regardless of immunosuppression [ideally at diagnosis of IBD]
How should varicella be screened?	In case of two documented varicella live vaccines, protection can be assumed In all other patients regardless of history, VZV IgG testing should be performed
Who should receive which vaccination scheme?	All immunocompetent patients with undetectable VZV IgG should receive live attenuated zoster vaccine [Varivax® or Varilrix®] in two doses at least 4 weeks apart. The last vaccine should be administered 4 weeks before IS therapy.a The interval between the first vaccine dose and the stopped IS is dependent on the IS agent[b]
How can primary varicella be diagnosed?	In all adults and in all immunosuppressed IBD patients, a PCR analysis of the base of a macular or papular skin lesion should be considered [negative IgM does not rule out primary VZV infection]
Who should be treated?	All adult and immunosuppressed IBD patients should be treated
Which therapy should be initiated in the case of exposure to VZV [primary varicella and HZ] in non-immunised patients?	Immunocompetent adult IBD patients can receive active immunisation [Varivax® or Varilrix®] within 5 days of exposure Immunocompromised IBD patients should receive passive VZV immunization with VZV IgG or Varitect® within 10 days of exposure [notee: monitoring for varicella for 28 days mandatory due to protection rate of only 70%]
Which therapy should be initiated in the case of primary varicella?	Uncomplicated primary varicella in adult IBD patients without IS: ideally initiate therapy within 24 h after onset of disease with valaciclovir 1g t.i.d for 5–7 days. In case of new lesions after 24 h in an untreated patient, a delayed start of therapy can be considered IBD patients with IS, disseminated disease or organ involvement: consider acyclovir 10-12 mg/kg IV t.i.d. If no further new lesions are seen, a switch to oral therapy with valaciclovir 1 g t.i.d. is possible. The duration of therapy should be 7–10 days
Which preventive measures are mandatory?	In health care facilities, patients with primary varicella should be isolated [airborne precautions] and only have contact with health care providers with evidence of immunity. Consider vaccination [see above]. Furthermore, all health care providers, even if considered immune, should wear an FFP2 mask when entering the patient's room. Patients must avoid contact with susceptible persons at risk including pregnant women, immunosuppressed patients, premature infants born to susceptible mothers, infants with gestational age 28 weeks or less

IBD, inflammatory bowel disease; VZV,varicella zoster virus; HZ, herpes zoster; IS, immunosupression; PCR, polymerase chain reaction; IV, intravenous; TNF, tumour necrosis factor.

[a]Exclusion: budesonide, prednisone <2 weeks, prednisone <20 mg/day, vedolizumab, methotrexate ≤20 mg/week, azathioprine ≤ 3.0 mg/kg body weight/day can be administered without interval after the last vaccine dose.

[b]No interval: budesonide, prednisone <2 weeks, prednisone <20 mg/day, vedolizumab, methotrexate ≤20 mg/week, azathioprine ≤3.0 mg/kg body weight/day at 1-month interval: high dose [>20 mg/day] or >2 weeks prednisone. Three-month interval: ciclosporin A, tacrolimus, methotrexate >20 mg/week, azathioprine >3 mg/kg body weight/day, anti-TNF agents, ustekinumab.

Since rising prevalence of IBD is observed in seniors and new immunosuppressive therapies are emerging, gastroenterologists will be increasingly confronted with HZ in the near future.[62]

Compared with the general population, an elevated HZ risk in European and American IBD patients had been observed at between 6.6 and 9.2 cases/1000 py.[63–67] An even higher risk could be demonstrated in Asian IBD patients, with an incidence rate up to 19.3 cases/1000 py.[68,69]

Additionally, a significantly increased risk of HZ could also be demonstrated in young patients with IBD [0–17 years old] with an incidence rate of 8.5 cases/1000 py in young females and 5.8 cases/1000 py in young males.[63] Results are inconsistent in various studies concerning the impact of gender and subtype of IBD on VZ incidence.[63–65,67,68]

In addition to age and race, immunosuppressive therapy plays a major role in the risk of HZ, with the most robust evidence on corticosteroids,[64,65,67,68,70,71] with a nearly 2-fold increase observed in Caucasians,[65,67] and a nearly 3-fold increase in Korean patients[68] [Table 2]. Thiopurine use is associated with an elevated risk (up to an adjusted odds ratio [OR], 3.1; 95% confidence interval [CI], 1.7–5.6)[64] in most studies.[6,64,65,67] Furthermore, a 3-fold elevation in risk of HZ was observed in four trials in patients treated with combination anti-TNF/IS therapy.[6,65,67,70]

No robust data exist on the HZ risk with methotrexate. The existing data in patients with rheumatoid arthritis [RA] are conflicting. However, if at all, the risk increase would be negligible.[72,73]

Contradictory results exist with anti-TNF monotherapy. Whereas older studies suggested a higher risk of HZ[65,70] [albeit not considering active inflammation as a confounder], recent data[67,68,71] indicate that anti-TNF monotherapy is not an independent risk factor for HZ in IBD, after adjusting for indicators of disease severity[68] and IBD flare[67] in multivariate analysis.

Few case reports suggest an increased risk with ustekinumab,[74] and a recent large cohort study in psoriasis patients found no association between biologics, including ustekinumab, and HZ.[75] However, the dose of ustekinumab in dermatology patients is generally lower than in IBD patients and an intravenous loading dose is not administered.

Tofacitinib has received substantial attention in the literature for a significantly increased risk of HZ but not other infections.[76] The risk appears to be dose-dependent, with 2- to 6-fold increase in risk compared with placebo.[76,77] In other words, the number needed to harm in patients treated with 5 mg tofacitinib b.i.d. is 99 and further decreases to 22 with 10 mg b.i.d.[78]

Duration of treatment was not a risk factor for HZ development. Additional risk factors for HZ during tofacitinib treatment were older age, previous anti-TNF failure, diabetes mellitus, corticosteroids at baseline, and non-White race. The latter was mainly driven by higher rates in Asian patients (incidence ratio [IR, 6.49; 95% CI, 3.55–10.89). Since the risk of HZ is increased with other JAK inhibitors, a class effect can be assumed.[79] Little is known regarding the potential implications of the JAK1-3/Tyk2 selectivity profile of a given JAK inhibitor and HZ risk.

Table 2. Summary of diagnosis and management of herpes zoster in IBD patients.

What are risk factors of HZ? High-risk groups are emphasized in bold	- All IBD patients have an increased risk of HZ [2–fold compared with the general population] - Risk increases with age [above 50 years of age can be considered as high-risk patients]. Some data assume an increased risk in younger IBD patients [<18 years of age] - Asian race - Uncontrolled active disease - Past history of shingles Medication: Tofacitinib: Up to 6-fold increased [dose-dependent, additional risk factors: Asian race, older age, diabetes, corticosteroids, previous anti-TNF failure] - Corticosteroids: 2 to 3-fold increased - Thiopurines: around 3-fold increased - Methotrexate: few data, risk minimally increased - Ustekinumab: few data, risk probably not elevated - Anti-TNF monotherapy: contradictory results - Anti-TNF + IS [3-fold increased]
Which vaccines are available?	Recombinant glycoprotein E vaccine [Shingrix®]: protection against HZ of 97%. Can be administered in patients with a history of HZ and in patients who have already received the live attenuated zoster vaccine Live attenuated zoster vaccine [ZV] [Zostavax®]: protection against HZ 38–70%, protection against PHN 67%. Can be administered in patients after HZ with a 3-year delay. Contraindicated in moderate to high dose immunosuppressed patients. In low-grade immunosuppressed patients, vaccine possible.[a] Intervals before and after stopping are equal to the scheme of Varivax® or Varilrix®
Should you perform VZV serology before Shingrix® vaccination?	In immunocompetent patients, VZV IgG should not be tested before vaccination [indication for the vaccination does not depend on the titre and higher titres do not protect from HZ]. However, since all immunosuppressed patients should have a protection against varicella, all IBD patients should be tested at diagnosis [unless two documented varicella live vaccines are available] regardless of Shingrix® vaccination
Who should get the vaccination?	Vaccination with Shingrix® should be considered in all high-risk IBD patients [see above]. A case-by-case decision should be made if multiple risk factors are present In case of unavailability of Shingrix®, a universal recommendation for vaccination with Zostavax® cannot be made
How to diagnose HZ?	Diagnosis can be made clinically, based on the skin rash appearance among other features. Atypical, recurrent or disseminated lesions should be tested with PCR analysis of the skin lesion In disseminated or systemic disease, a PCR for VZV DNA in serum should be performed
Who and how should HZ be treated?	Patient without immunosuppressive therapies should receive valaciclovir 1 g t.i.d. for 7 days within 72h. In case of presentation >72h, patients with new skin lesions may be considered for treatment All immunosuppressed patients with disseminated HZ should receive intravenous acyclovir 12 mg/kg body weight every 8 h within the first 72 h. After clinical improvement, a switch to oral therapy can be considered. The total duration should be 7–10 days. Immunocompromised patients should also be treated in case of presentation >72 h
Which preventive measures are mandatory?	In health care facilities, only immunosuppressed patients with HZ or immunocompetent in case of disseminated disease should be isolated [airborne and contact precautions]. Otherwise immunocompetent patients only need standard precautions, but need to cover lesions completely until lesions are dry and crusted

IBD, inflammatory bowel disease; VZV,varicella zoster virus; HZ, herpes zoster; IS, immunosupression; PCR, polymerase chain reaction; PHN, post-herpetic neuralgia; TNF, tumour necrosis factor.

[a]Low-dose IS: budesonide, prednisone <2 weeks, prednisone <20 mg/day, vedolizumab, methotrexate ≤20 mg/week [in some countries, eg, in Switzerland, contraindicated], azathioprine ≤3.0 mg/kg body weight/day. Moderate- to high-dose IS: high dose [>20 mg/day] or > 2 weeks prednisone, ciclosporin A, tacrolimus, methotrexate >20 mg/week, azathioprine >3 mg/kg body weight/day, anti-TNF alpha agents, ustekinumab.

One of the most important and clearly underestimated risk factor for HZ is disease activity severity.[67,68] In a multivariate analysis, IBD flare was an independent risk factor and had the strongest association with the development of HZ (hazard ratio [HR], 3.69; 95% CI, 3.22–4.23).[67] A summary of the factors increasing the risk of HZ can be found in Table 2.

3.2. Clinical manifestations and complications

In immunocompetent persons, the vesico-papular rash is usually confined to one or two unilateral dermatomes, most frequently located in the thoracic region and preceded by neuropathic pain for several days. In contrast, in immunosuppressed patients, the vesico-papular rash may be multidermatomal [involving nonadjacent or three to six adjacent dermatomes], disseminated [more than six dermatomes], or even non cutaneous. Rarely, HZ even exists without a rash, termed zoster sine herpete, which is difficult to diagnose.[56] Another rare condition is reactivation of varicella in the enteric nervous system [ENS], which results in painful gastrointestinal disorder without skin manifestations.[80]

The most common complication is post-herpetic neuralgia [PHN] which may develop in up to 50% of persons with HZ, with an increasing risk in individuals older than 50 years of age.[81,82] In addition, neurological complications such as meningitis, encephalitis, and even stroke may occur.[83] Further complications include ophthalmic zoster or disseminated disease[84] and progressive outer retinal necrosis[85] which occur more often in immunocompromised

individuals. It must be emphasised, that HZ can transmit VZV to susceptible persons without immunity to VZV, even though it is less contagious than varicella. The main transmission takes place through indirect or direct contact with skin lesions, whereas crusted lesions are not infectious. Interestingly, airborne spread of virus is most frequently directly via the skin and only rarely from the respiratory tract.[86,87]

IBD patients have higher rates of hospital admission when presenting with HZ compared with non-IBD patients[88] and are prone to a complicated disease course due to IS therapies. Among 32 cases of immunosuppressed IBD patients with HZ,[28] 7/32 developed extracutaneous manifestations, with three patients presenting with central nervous system involvement. The majority of these cases occurred in CD patients [75%] and on treatment with azathioprine [78%]. In a recently published cohort of IBD patients,[89] the risk factors associated with complicated HZ disease course were older age, African American ethnicity, and non-use of antiviral treatment, but not exposure to anti-TNF.

Tofacitinib not only increases the risk of HZ, but also is associated with a complicated disease course. Among 69 HZ cases in patients treated with tofacitinib, 12 multidermatomal cases and six patients with disseminated HZ occurred, involving two with ocular herpes and one herpes with meningitis.[76,77,90] Only three patients treated with tofacitinib [4.6%] developed PHN after HZ infection.[90]

3.3. Diagnosis

Although HZ in general is diagnosed on clinical grounds, atypical or recurrent rashes or a disseminated skin disease in immunosuppressed persons may require a PCR assay for VZV DNA to avoid confusion with herpes simplex virus infection.[56] Similar to the diagnosis of varicella, a swab of a skin lesion should be taken. This lesion does not have to contain liquid. However, if the lesions are already encrusted, the superficial scab should be removed and a smear taken from the base of the open lesion. VZV PCR has a sensitivity and specificity of 95% and 100%, respectively.[91] In cases of disseminated disease and suspicion of systemic disease, quantitative PCR for VZV DNA in serum should be performed.[92]

3.4. Treatment

Regarding antiviral therapy, the best available data are for patients >50 years of age, patients who present with moderate to severe pain, severe rash, or facial involvement, and immunocompromised persons and/or with complications.[56] It should be noted that due to data from conflicting studies, it is not clear whether antiviral treatment reduces the incidence of the most common complication, PHN.[93,94] Although four nucleoside analogues are available, namely aciclovir, valaciclovir, famciclovir, or brivudine, the therapy of choice with most robust data in immunocompetent individuals is oral valaciclovir 1000 mg t.i.d. Treatment duration should be limited to 7 days in patients without immunosuppression and uncomplicated HZ [ie, without involvement of head and neck, no haemorrhagic lesions or two or more segments]. In patients treated with immunosuppressive therapy, intravenous aciclovir [8-12 mg/kg body weight every 8 h for 7 days] should be initiated. Since nephrotoxicity may occur,[95] renal function should be checked before starting therapy [reduced dose in renal insufficiency] and 4 days after starting therapy. Initiation of treatment after 72 h should be considered in patients developing new skin lesions, who are immunosuppressed, presenting with HZ ophthalmicus or HZ opticus, or presenting with neurological symptoms or visceral involvement. Due to delay in seeking medical care, 10–20% of IBD patients do not receive antiviral therapy.[89]

3.5. Prevention

The live attenuated zoster vaccine [ZV] [Zostavax®] for prevention of HZ consists of viruses of the strain Oka in a 14x higher dosage than the varicella vaccine[96] and boosts the waning immunity to VZV. In patients between 50 and 59 years of age, the vaccine-induced antibody-mediated protection against HZ is approximately 70%, whereas efficacy is reduced to 38% in persons 70 years of age or more.[96] Prevention of PHN in persons over 70 years of age can be achieved in approximately 67%, similar to younger patients.[97] The evidence is conflicting on the duration of protection after the vaccination. A 5-year follow-up study confirmed a persistent, significant risk reduction of HZ over this time period.[98] However, another trial demonstrated a loss of immunity after 8 years.[99] A recently published Cochrane analysis concluded that the live attenuated HZ vaccine is safe in patients 60 years of age or older with a minimum effect of 3 years.[100]

The vaccination can be administered to persons with a history of HZ without additional risk of adverse events.[101] However, since cellular immune response to VZV is boosted after an HZ infection and can last up to 3 years, it is recommended to delay vaccination for 3 years after HZ.[102] In patients with a history of HZ ophthalmicus, a reactivation could be observed after vaccination. In this patient group, a benefit-risk assessment should be performed before vaccination.[103]

The live attenuated zoster vaccine is contraindicated in pregnancy and precautions must be taken before administering to patients with IS [Table 2]. The vaccine is also contraindicated in patients treated with 2 or more weeks of high-dose corticosteroid therapy [≥20 mg/day of prednisone or equivalent] or patients receiving antitumour necrosis factor [anti-TNF] agents. However, patients with receiving doses of methotrexate [≤0.4 mg/kg/week or ≤20 mg/week] or azathioprine [≤3.0 mg/kg/day] may be given the live attenuated vaccine.[104] History of previous VZV exposure is not mandatory before administering the zoster vaccine in immunocompetent persons because vaccination in individuals with previous VZ does not have any deleterious effect and can in fact boost previously established immune response against VZV.

Recently, a new non-live vaccine against VZV, glycoprotein E [gE] subunit herpes zoster vaccine [HZ/su] [Shingrix®] boosting innate and adaptive immunity without risk of a post-vaccine infection, has emerged. It is associated with a considerably higher rate of preventing HZ as opposed to the live attenuated ZV across all age groups and is equally effective in patients > 70 years of age.[105,106] This vaccine requires two intramuscular injections 2–6 months apart and has an overall prevention rate for HZ of 97%. This high efficacy rate can be explained by a 10-fold T cell response and a sustaining memory T cell response in HZ/su compared with ZV recipients.[107,108] Aside from local reactions [pain, swelling, redness], systemic reactions, such as fatigue [22.8%], myalgia [22.1%], and fever [7.8%], could also be observed.[105] Currently, the Advisory Committee on Immunization Practice recommends vaccinating all patients >50 years with this new subunit HZ vaccine.[109] However, in most countries Shingrix® is presently not reimbursed.

The ECCO 2014 guideline recommends administering the Shingrix® HZV to immunocompetent individuals of over 60 years.[15] The American College of Gastroenterology recommends vaccinating

IBD patients over 50 years, including certain groups of immunosuppressed patients.[110] The British Society of Gastroenterology [BSG] issued more restrictive guidelines, recommending vaccinations in patients aged over 70 years before starting therapy and in patients over 50 years at high risk for HZ.[111]

However, a recent retrospective cohort study demonstrated that only 21% of eligible IBD patients over 60 years of age were vaccinated for HZ.[112] HZ may therefore be considered the most common vaccine-preventable disease in IBD patients.[88]

Two main considerations exist regarding live attenuated HZ vaccination: effectiveness and safety.

Although in the general IBD population, the live attenuated zoster vaccine is efficacious in lowering risk of HZ (adjusted HR [aHR], 0.54; 95% CI, 0.44–0.68),[113] HZ-specific immunoglobulin G response in patients on low-dose IS is lower.[114] However, the clinical significance of this blunted immune response remains unclear.

Two different clinical entities may occur after live attenuated HZ vaccination. One is the reactivation of previous VZV infection with a picture similar to HZ, ie, a painful vesicular rash. However, the major concern is disseminated VZV infection due to the altered immune response.[115] Live attenuated vaccine for HZ seems safe in IBD patients treated with regular doses of methotrexate, azathioprine, or 6-mercaptopurine.[104,114] Although live attenuated HZ vaccination is not recommended under treatment with anti-TNF, several studies, including the ongoing VERVE trial, indicate relative safety.[116–119] No data regarding safety of HZ vaccination are available in patients treated with vedolizumab or ustekinumab.

The issue of safety of Zostavax® in immunocompromised individuals may become irrelevant as a result of the new recombinant HZ subunit vaccine Shingrix®. Unfortunately, the landmark trial of Shingrix® excluded patients with IS.[105,106] Recently published data in severely immunosuppressed patients with haematological malignancies[120] and in patients after renal transplantation[121] showed encouraging results with no safety signals in this vulnerable population. Currently, no data exist on the efficacy or safety of Shingrix® in immunosuppressed IBD patients. However, a trial investigating UC patients on tofacitinib[122] is recruiting.

When selecting which patients to vaccinate, it should be noted that IBD patients aged over 40 years have a higher risk of HZ than healthy individuals 50 years of age. which is the recommended age of vaccination.[109] Furthermore, IBD patients on combination therapy below 50 years have a higher HZ risk than patients over 60 years of age on mesalamine therapy alone.[67] However, the highest risk of HZ development [around a risk of 2% per year] applies to IBD patients >60 years of age receiving combination therapy.

Until more data are available, the following management is advisable. Regardless of age, high-risk patients such as Asian patients, patients with an uncontrolled IBD disease activity, patients with a past history of shingles, and patients with [future] therapy with tofacitinib, should be vaccinated with Shingrix®. Furthermore, patients treated with azathioprine are considered as moderate risk and should be vaccinated at least by the age of 40. Patients aged 50 years should be given the vaccination regardless of their therapy or their disease course. Vaccination can be considered in a case-by-case scenario in patients younger than 50 years.

4. Conclusions

Due to alterations in the immune system, IBD patients represent a vulnerable group susceptible to complications of primary varicella infection and have a substantially increased risk of HZ infection. This risk is heightened as a result of an ageing population and a growing armamentarium of immunosuppressive therapies in the near future. Indications for antiviral therapy for primary varicella and HZ vary depending on age of the patient, concomitant immunosuppressive therapy, and severity of disease.

To counteract the elevated risk, prevention of primary varicella and HZ is key. It is imperative that clinicians assess the vaccination status in all IBD patients in order to vaccinate the non-immunised patients before any necessary immunosuppressive therapy. However, there will always be cases in which the window of opportunity to vaccinate will be missed. In these cases, Shingrix® represents an attractive option despite lacking data in IBD patients. We eagerly await the first results of ongoing studies of Shingrix® in IBD patients[122,123] which will shed light on this topic.

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Author Contributions

PS: substantial contributions to the concept or design of the work, drafting the work, approved the final version, agreed to be accountable for all aspects of the work. SR: interpretation of data for the work, revising it critically for important intellectual content, approved the final version, agreed to be accountable for all aspects of the work. JP: interpretation of data for the work, revising it critically for important intellectual content, approved the final version, agreed to be accountable for all aspects of the work. RG: interpretation of data for the work, revising it critically for important intellectual content, approved the final version, agreed to be accountable for all aspects of the work. PMichetti: interpretation of data for the work, revising it critically for important intellectual content, approved the final version, agreed to be accountable for all aspects of the work. MM: interpretation of data for the work, revising it critically for important intellectual content, approved the final version, agreed to be accountable for all aspects of the work. SV: interpretation of data for the work, revising it critically for important intellectual content, approved the final version, agreed to be accountable for all aspects of the work. SB: interpretation of data for the work, revising it critically for important intellectual content, approved the final version, agreed to be accountable for all aspects of the work. AS: interpretation of data for the work, revising it critically for important intellectual content, approved the final version, agreed to be accountable for all aspects of the work. NM: interpretation of data for

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