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Vaccination in Patients with Inflammatory Bowel Diseases

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Abstract
During the course of disease, a majority of inflammatory bowel disease (IBD) patients requires long-term immunosuppressive therapy with either immunomodulatory agents, biologics, or newer immunosuppressive therapies such as Vedolizumab, a selective α4β7 inhibitor, Ustekinumab, an IL 12/23 p40 inhibitor, or the Janus kinase inhibitor Tofacitinib. Due to this, they are at increased risk for infectious diseases, many of which are possible to prevent by vaccination. This review focuses on recommended vaccinations in IBD patients and stresses special issues which have to be paid attention to. The aim of the review is to increase gastroenterologists' awareness of the importance of vaccination and to stress why especially the gastroenterologist should assess the vaccination status of the patient and initiate vaccination as soon as diagnosis is established.

Introduction

The term *inflammatory bowel disease* (IBD) refers to 2 main disease subtypes, Crohn's disease (CD) and ulcerative colitis (UC), which are immune-mediated diseases. Due to the immune-mediated nature of these diseases, a cornerstone for therapy is immunosuppressive medications. However, these may carry a higher risk for infections. A recent review comprising data of 14,590 IBD patients reported an elevated risk for any infection (OR 1.19, 95% CI 1.10–1.29) and for opportunistic infections in particular (OR 1.90, 95% CI 1.21–3.01). In this review, no elevated risk for serious infections was reported among patients treated with biologics (OR 0.89; 95% CI 0.71–1.12) [1]. However, a large prospective study, investigating serious infections in 6,273 patients with CD during a >5-year follow-up period, found an increased risk for serious infections among patients with infliximab (hazard ratio [HR] 1.43, 95% CI 1.11–1.84), as well as for patients with moderate to severe disease activity (HR 2.24, 95% CI 1.57–3.19), narcotic analgesic treatment (HR 1.98, 95% CI 1.44–2.73), and prednisone therapy (HR 1.57, 95% CI 1.17–

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2.10) [2]. A very recent nationwide population-based study by Kirchgesner et al. [3] investigated the risk of serious and opportunistic infections among IBD patients treated with monotherapy with thiopurine or anti-TNF or a combination therapy of both during 6 years. Among 190,694 IBD patients 8,561 serious infections and 674 opportunistic infections were observed. The risk for serious infections was the highest being on combination therapy when compared with anti-TNF monotherapy (HR 1.23, 95% CI 1.05–1.45). Besides it was elevated among patients on anti-TNF monotherapy when compared to thiopurine monotherapy (HR 1.71, 95% CI 1.56–1.88). Patients on anti-TNF monotherapy were at high risk for mycobacterial infection (HR 1.98, 95% CI 1.15–3.40) and bacterial infection (HR 2.38, 95% CI 1.23–4.58) but at lower risk for opportunistic viral infections (HR 0.57, 95% CI 0.38–0.87) when compared to thiopurine monotherapy [3].

Particularly the risk of vaccine-preventable diseases such as influenza, pneumococcal disease, or hepatitis B is increased among patients with IBD, and low rates of vaccination are reported [4]. A very recent retrospective cohort study investigated risk differences with regard to influenza infection between 140,480 IBD and non-IBD patients. Overall, IBD patients had a higher risk for influenza infection (incidence rate ratio [IRR] 1.54, 95% CI 1.49–1.63), and treatment with corticosteroids was identified as the only medication class independently associated with an increased influenza risk [5]. A study of Melmed et al. [4] among 169 patients with IBD reported that only 9 and 28% of patients were vaccinated against pneumococcal disease and influenza, respectively. Only 28% were vaccinated against hepatitis B [4]. Main reasons for nonimmunization included lacking awareness and concerns about potential side effects. These factors were also reported among patients and their treating physicians in a study by Yeung et al. [6]. The study detected that only 14.3% of questioned gastroenterologists took a vaccination history from their patients. Besides, 18.6% of gastroenterologists were not aware of the importance of an up-to-date vaccination status prior to starting an immunosuppressive therapy [6]. A study by Wasan et al. [7] found that 52% of gastroenterologists took a vaccination history from their IBD patients. However, one additional problem with regard to low vaccination rates seems to be a disagreement on responsibility for who is doing it. While the study by Wasan et al. [7] reported that 83% of gastroenterologists thought that vaccinations should be administered by the primary care physician (PCP), a study among PCPs found that 20% of them did not feel responsible for vaccine administration [8].

For 2 main reasons, the gastroenterologist should take the vaccination history and complete immunizations if necessary: (i) the indication for an immunosuppressive therapy is usually confirmed and started by a gastroenterologist and thus he or she can update the vaccination status even prior to starting therapy; (ii) IBD patients attend the gastroenterologist more frequently than a PCP, and therefore, the gastroenterologist has more chances of checking and completing the vaccination status. The gastroenterologist would also be the one asked for traveling recommendations with regard to vaccination. A recent study evaluated the proportion of patients with immune-mediated inflammatory diseases (IMID) seeking advice at a University Hospital Travel Clinic on the one hand and demographics, travel destinations, and vaccination patterns on the other hand. The study found that almost 2% of travelers seeking advice were patients with an IMID and 34% were on immunomodulatory or -suppressive medication. They did not differ with regard to reasons for travel or destination and therefore similar vaccinations were required compared to non-IMID travelers [9].

As a consequence of the mentioned reasons, knowledge on generally recommended vaccinations as well as travel recommendations, familiarity with specifically relevant immunizations in IBD patients, and the awareness on contraindicated vaccinations in immunosuppressed individuals are crucial for the practicing gastroenterologist. This review therefore summarizes the literature and vaccination recommendations for IBD patients.

Vaccination Recommendations

Key messages regarding vaccination in IBD patients:

1. Vaccinations neither do not cause gastroenterological or other (auto-) immune diseases nor do they induce exacerbation of the disease.

2. In IBD patients without immunosuppressive therapy, there are no specific contraindications for vaccination with inactivated or live vaccines.

3. As in a majority of patients an immunosuppressive therapy will be started, the vaccination status of the patient should be determined at time of diagnosis, and recommended vaccinations should be administered. Independent of history and vaccination status, serologies regarding measles and varicella should be performed to check for antibody protection. The same approach applies to yellow fever serology in a person under immunosuppressive therapy who intends to travel to a yellow fe-

ver endemic area and who received the yellow fever vaccination in the past.

4. Due to higher efficacy, vaccinations should be administered during remission of disease.

5. Vaccinations should preferentially be administered before the start of an immunosuppressive therapy – ideally at least 4 weeks before starting the immunosuppressive therapy.

6. If an immunosuppressive therapy has already been started, vaccinations should be administered when immunosuppressive therapy is at the lowest possible dose.

7. If an immunosuppressive therapy has already been started, it is generally safe to use inactivated vaccines in these patients; however, the immunogenicity may be reduced.

8. If an immunosuppressive therapy has already been started live vaccinations should be avoided as there is a risk of replication of the attenuated microorganisms and invasive infections. However, live vaccines may be used with caution in selected immunosuppressed patients. Depending on the drug used, different intervals for administration of a live vaccine after immunosuppressive therapy are advised.

9. The immune response to a booster vaccine given during immunosuppressive therapy is less affected than the immune response to a primary vaccine dose.

10. Due to the induction of higher affinity antibody responses, longer lasting immune responses and memory responses conjugate vaccines should be used rather than polysaccharide vaccines.

11. General recommendations for basic vaccinations also apply to IBD patients.

12. There are several specific vaccination recommendations for IBD patients as they may require a more comprehensive protection. These include:

a. The annual seasonal inactivated influenza vaccination

b. Pneumococcal vaccinations

c. Vaccination against hepatitis B is recommended in all seronegative IBD patients

d. Vaccination against human papillomavirus (HPV) is recommended in young IBD patients

e. Herpes zoster (HZ) vaccination is recommended in patients aged 50 years and above. If available, the inactivated vaccine (Shingrix®) should be used. Among patients on immunosuppressive therapy only the inactivated vaccine is recommended.

13. In immunosuppressed patients, a serology should be performed after completion of a primary vaccination course if the respective serology is available.

14. In addition to checking the patient's vaccination status, the vaccination status of household members and other close contacts should be checked and they should also be vaccinated if indicated (especially against measles, mumps, rubella [MMR], varicella, and influenza).

15. If the immunocompromised IBD patient is not protected against measles and/or varicella, administration of immunoglobulins or antivirals has to be considered in case of exposure.

16. As a precaution, oral typhoid vaccination (Vivotif®) should be avoided in IBD patients under immunosuppressive therapy, although no published data on this topic exist.

When vaccinating immunosuppressed individuals, one has to differentiate between live vaccines and inactivated vaccines. Pertaining to live vaccines (MMR, varicella, HZ, yellow fever), there are different points of interest. Not only the class of immunosuppressive medication but also the dosage can play a role for decision making. Moreover, if an immunosuppressive therapy is paused or terminated, depending on the medication, different time intervals before administering a live vaccine are recommended. A detailed listing can be found in Table 1.

Inactivated vaccines can be addressed differently. As there are no safety concerns, they can be used in IBD patients with and without immunosuppressive therapy without restrictions. There are no limitations for any medication group or dose of immunosuppressive therapy. They may, however, be less immunogenic and there are some vaccine-specific recommendations. A summary of recommendations of different societies for inactivated as well as for live vaccines is shown in Table 2.

Inactivated Vaccinations

Influenza

The risk for influenza infection and influenza-associated hospitalization is elevated among patients with IBD [5]. A study focusing on the risk for hospitalization due to vaccine preventable pneumonias among IBD patients revealed an increased risk for hospitalization due to influenza-associated pneumonia among UC patients with a low income (OR 1.86; 95% CI 1.46–2.37) [10]. Safety, efficacy, as well as adverse events of influenza vaccination among IBD patients have been evaluated in several studies [11–15]. Overall, response to vaccination was appropriate. However, there have been several studies reporting a reduced immune response among patients on immunosuppression [14, 16–20]. Still, due to an increased risk of infection, even a suboptimal protection by vaccination is found to be beneficial [21]. Therefore, the

Table 1. Time interval between cessation or pausing of an immunosuppressive agent and live vaccination (modified from [81])

Medication	Time interval
Corticosteroids – Systemic: only short term (<2 weeks) or low dose (<20 mg/day of prednisone or equivalent [adult] or <2 mg/kg/day [children]) – Maintenance physiologic doses (replacement therapy) – Non-systemic glucocorticoids (topical or injections) Balsalazide Budenoside (≤ 6 mg/day) Mesalazine Olsalazine Sulfasalazine Vedolizumab	No time lag needed
Corticosteroids – Systemic and high dose (≥20 mg per day of prednisone or equivalent [adult] or ≥2 mg/kg/day [children]) and ≥2 weeks	1 month
Ciclosporine A Cyclophosphamide Mycophenolate Tacrolimus	3 months
Azathioprine Methotrexate 6-Mercaptopurine 6-Thioguanine	3 months
Adalimumab Certolizumab Golimumab Infliximab Ustekinumab	3 months
Leflunomide	6 months

seasonal influenza vaccination is recommended in all guidelines and should be carried out annually [22–28]. The inactivated quadrivalent vaccine, which has been shown to be well tolerated, should be used. In addition to the patient himself/herself close contacts should be vaccinated. Contacts should receive the inactivated vaccine [28].

Pneumococcal Disease

IBD patients are at increased risk for pneumonia (IRR 1.82; 95% CI 1.75–1.88) [29]. Several medications as biologic medications, steroids, thiopurines, proton-pump inhibitors, and narcotics were shown to be associated with pneumonia [29]. Besides, among patients with pneumonia, there is an elevated risk for pneumonia-associated mortality (OR 3.6, 95% CI 2.9–4.5) [30]. A large recent Danish cohort study including almost 75,000 IBD patients revealed an increased risk of invasive pneumococcal disease [31]. The risk was especially increased before and after diagnosis of IBD, suggesting that the risk increase might be due to general alterations in the immune response of IBD patients. This is also underlined by the fact that IBD medication, even biologics, had a limited effect on the elevated risk [31]. Pneumococcal vaccination is recommended for IBD patients in all current guidelines [22–28]. The most common scheme recommended is pneumococcal conjugate vaccine once, followed by pneumococcal polysaccharide vaccine 23 (PPSV23) 8 weeks to 6 months after and a final booster dose of PPSV23 5–6 years later. However, some countries, such as Switzerland, recommend only the pneumococcal conjugate vaccine to avoid a phenomenon called "hyporesponsiveness," which may be induced by a PPSV23.

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Table 2. Vaccination recommendations in IBD patients (reprinted from [22] with permission from Elsevier)

	Professional society, country, year					
	ACIP, USA, 2010	ECCO, Europe, 2014	PHAC, Canada, 2014	ATAGI, Australia, 2015	HCSP, France, 2014	STIKO, Germany, 2010
Vaccine						
Live vaccines						
BCG	Not recommended Contraindicated during IT					
MMR	Recommended at least 6 weeks before starting IT	Recommended at least 3 weeks before starting IT	Not recommended Contraindicated during IT			Recommended at least 2 weeks before starting IT
Varicella zoster	Recommended at least 1–3 months before starting IT Contraindicated during IT	Recommended at least 3 weeks before starting IT Contraindicated during IT	Not recommended Contraindicated during IT			Recommended at least 2 weeks before starting IT Contraindicated during IT
Rotavirus	Not recommended Contraindicated during IT					
Yellow fever	Not recommended Contraindicated during IT					
Inactivated vaccines						
Tdap-polio	Administer vaccine if not given over the past 10 years or give Tdap if Td ≥2 years, with a booster dose every 10 years	Not recommended but possible during IT			Administer vaccine if not given over the past 10 years, with a booster dose every 10 years Possible during IT	
Haemophilus influenzae b	Not recommended but possible during IT					A single dose is recommended in patients with IT
Hepatitis B	Recommended (3 doses at 1, 1–2 and 4–6 months; if no response 1 month after finishing last dose then revaccinate with double dose) Possible during IT	Recommended (double dose at 0, 1 and 2 months; if no response 1 month after finishing last dose then revaccinate with double dose) Possible during IT	Not recommended but possible during IT			
Meningococcal vaccination	Not recommended but possible during IT					A single dose of Men ACWY is recommended in patients with IT
Pneumococcal vaccination	Recommended (PCV13 and PPSV23 8 weeks later; re-vaccinate with a single dose of PPSV23 5 years after) Possible during IT			Recommended (PCV13 and PPSV23 8 weeks later; second dose of PPSV23 5–10 years after, third dose at 65 years) Possible during IT	Recommended (PCV13 and PPSV23 8 weeks later; revaccinate with a single dose of PPSV23 5 years after) Possible during IT	Recommended (a single dose of PPSV23 with a second dose 5 years in case of IT) Possible during IT
HPV	Recommended through age 26 years (3 doses 0, 2 and 6 months with HPV4) Possible during IT		Not recommended but possible during IT	Recommended through age 18 years in patients with IT (3 doses 0, 2 and 6 months with HPV4) Possible during IT	Not recommended but possible during IT	
Influenza	Recommended (annual vaccine with the TIV) Possible during IT					
Hepatitis A	Recommended (2 doses at 0 and 6–12 months or 0 and 12–18 months with a booster dose >10 years) Possible during IT	Not recommended but possible during IT				

IBD, inflammatory bowel disease; ACIP, Advisory Committee on Immunisation Practices; ECCO, European Crohn's and Colitis Organization; PHAC, Public Health Agency of Canada; ATAGI, Australian Technical Advisory Group on Immunisation; HCSP, Haut Conseil de la Santé Publique; STIKO, Vaccination Committee of the State of Saxony; BCG, bacillus calmette-guérin; IT, immunosuppressive therapy; MMR, measles, mumps, rubella; Tdap, Tetanus-diphteria-acellular pertussis; PCV13, 13-quadrivalent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; HPV, human papillomavirus; MenACWY, quadrivalent meningococcal vaccination; HPV4, quadrivalent HPV vaccine; TIV, trivalent inactivated vaccine.

Tetanus/Diphtheria/Pertussis

There are several studies evaluating antibody response to vaccination against tetanus, diphtheria, or pertussis. The latest study evaluated the persistence of tetanus, diphtheria, and pertussis-specific antibodies among 90 IBD patients on therapy either with thiopurines, anti-TNF monotherapy, or combination of both. Compared to healthy controls, IBD patients showed significantly reduced antibody concentrations against pertussis and diphtheria, being the lowest among patients on anti-TNF therapies [32]. A prospective controlled study from 2015 investigated serological immune responses to tetanus and pertussis booster vaccination in 84 IBD patients. This study found a reduced response rate among immunosuppressed patients, the lowest among those on a combined biologic and immunomodulator therapy [33]. Tetanus, diphtheria, and pertussis vaccination should be given according to general country-specific vaccination guidelines. Booster doses are generally recommended every 10 years.

Hepatitis B

Patients with IBD are at increased risk for infections with hepatitis B for several reasons. On the one hand, there is an elevated risk due to surgical interventions and blood transfusions [34, 35]. Besides it is known that among patients under immunosuppressive therapy, a hepatitis B virus (HBV) reactivation can be induced and, in the worst case, result in acute liver failure [36–41]. This is why hepatitis B should be screened for prior to initiation of anti-TNF therapy. Nevertheless, a recent retrospective study in 3,357 IBD patients revealed that the overall screening rate for hepatitis B was low [42]. However, it increased from 8.1% in 2003 to 43.2% in 2011 [42]. Vaccination against hepatitis B for IBD patients is recommended in several guidelines. A recent systematic review and meta-analysis evaluated the response rate to HBV vaccination [41]. Thirteen studies with 1,688 patients were included. The pooled vaccination serological response rate, defined as anti-HBs antibody titers of >10 mlU/mL, was 61%. Factors predictive for a better immune response were young age and vaccination during remission (RR 1.62; 95% CI 1.15–2.29). Moreover, patients without immunosuppressive therapy had a higher chance of response compared with patients on immunomodulatory (RR 1.33; 95% CI 1.08–1.63) or anti-TNF therapy (RR 1.57; 95%-CI 1.19–2.08) [41]. Recently, 2 publications reporting on HBV seroprotection among children with IBD were published. deBruyn et al. [43] reported on vaccine coverage and seroprotection among 156 children with IBD. Brenner et al. [44] reported on seroprotection and revaccination among 159 children with IBD. While 71% (82/115) of patients reported on by deBruyn et al. [43] had HBV seroprotection, the seroprotection rate among patients reported on by Brenner et al. [44] was only 26% (41/159). One major reason for these differences, Brenner et al. [44] point out might be due to regional variations in vaccine timing, as well as the fact that among the patients included by deBruyn et al. [43], there were no patients on biologics while patients included by Brenner et al. [44] were all on biologics and therefore possibly more immunocompromised. Interestingly, among the patients included by Brenner et al. [44] giving one booster dose increased seroprotection to 79% (26/33) while a complete booster vaccination resulted in seroprotection among 98% (58/59) of patients.

Due to the low response rates, Marin et al. [45] evaluated different vaccination protocols. One included study by Gisbert et al. [46] reported an increase of protection from 41 to 75% when using a faster double-dose schedule compared to a single-dose protocol. The faster double-dose protocol consists of double dose of Engerix-B® at 0, 1, and 2 months. This schedule is therefore recommended by the ECCO guideline focusing on vaccination among IBD patients [24]. Moreover, antibody levels should be checked 1–3 months after completion of the vaccination schedule to ensure response [47].

Hepatitis A

While the American College of Gastroenterology (ACG) guideline recommends vaccination against hepatitis A among all IBD patients, the ECCO guideline only recommends it to patients before travel to endemic areas [24, 28]. Patients should receive 2 vaccinations at the time points 0 and 6 months. In 2014 a study by Park et al. [48] was published, focusing on the immunogenicity of hepatitis A vaccination. Among the 419 included IBD patients 97.6% showed a seroconversion after 2 hepatitis A vaccine doses; however, it was lower among patients on anti-TNF medication (92.4%). Furthermore, it was also lower among patients on therapy with ≥2 immunosuppressants.

Human Papillomavirus

It is known that a compromised immune system can increase the risk for dys- or neoplastic alterations of the cervix [49]. Besides it is known that smoking as well as an HPV infection is associated with cervical cancer [28, 50, 51]. It is still subject of discussion whether IBD itself is accompanied by an increased risk for cervical cancer

[49]. However, many studies have addressed the possible impact of immunosuppressive therapy on the development of cervical abnormalities among IBD patients. An extensive review by Hazenberg et al. [49] summarizes the literature published to date. The authors conclude that IBD itself, especially CD, might be associated with an increased risk of cervical abnormalities, but not of cervical cancer. The cumulative dose of thiopurines appears to be correlated with cervical high-grade dysplasia (HGD), especially among patients with CD. Patients treated with a combination therapy do not seem to have a higher risk for cervical HGD or cervical cancer; however, the authors emphasize that data have to be interpreted with caution as in the majority of the included studies information with regard to duration and dose of the immunosuppressive medication are missing. In 2015, Allegretti el al. [52] conducted a meta-analysis to assess the risk of HGD and cervical cancer among female IBD patients. Data of 77,116 IBD patients from 5 cohort studies, and 3 case–control studies were included. The meta-analysis revealed an elevated risk for cervical HGD or cancer among immunosuppressed IBD patients compared to healthy controls (OR 1.34; 95% CI 1.23–1.46). Although data are not homogeneous, it is beyond doubt that a correlation between immunosuppression among IBD patients, HPV infection, and cervical abnormalities exist. Therefore, regular gynecologic screening for cervical cancer is recommended for female IBD patients [24]. The American College of Obstetricians and Gynecologists even recommend annual screening for women with a history of chronic immunosuppressive therapy [53]. Although immunosuppressed women are at an increased risk for cervical anomalies rates of cervical testing are suboptimal. A study by Long et al. [54] revealed that only 70.4% of female IBD patients received cervical testing at least once every 3 years. In a recent study by Waszczuk et al. [55], among 150 female IBD patients, only 69% reported of regular cervical testing (30% annually, 32% every 2–3 years, 7% every 5 years). Moreover, only 10% of female IBD patients were aware of the existing HPV vaccination recommendation. In addition to regular gynecological checkups, HPV vaccination is the major mean for reducing the incidence of cervical dysplasia [49, 56]. Beside of increased risk for HPV-associated cervical neoplasic alterations, there is an increased risk of HPV-related anal carcinoma among CD patients with perianal disease involvement [57]. HPV vaccination is recommended to young patients (through 26 years) in most guidelines [22]. It is of note that not only female but also male patients should be vaccinated. Vaccination with a quadrivalent HPV vaccine (HPV-6, -11, -16, and -18) as well as by a bivalent vaccine (HPV-16 and -18) results in vaccination rates of 95–100% [45, 58]. Recently, a 9-valent HPV vaccine (HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58) has been introduced. In a prospective study including 37 female IBD patients on immunosuppressive therapy, antibody response to vaccination with the quadrivalent HPV vaccine Gardasil was evaluated. Seropositivity after 3 doses was 100% for types 6, 11, and 16 and 96% for type 18. Besides there were no serious adverse events reported [58].

Live/Inactivated Vaccine

Herpes Zoster

IBD patients are at increased risk of developing HZ, as has been shown in several large studies [59–62]. In 2013, Long et al. [59] compared the HZ risk among 108,000 IBD patients compared with 434,000 non-IBD individuals. The HZ risk was increased among IBD patients (IRR 1.68; 95% CI 1.60–1.76). The study also showed that anti-TNF medication (OR 1.81; 95% CI 1.48–2.21), corticosteroids (OR 1.73; 95% CI 1.51–1.99), thiopurines (OR 1.85; 95% CI 1.61–2.13), but especially a combination therapy with anti-TNF medication and thiopurines (OR 3.29; 95% CI 2.33–4.65) were independently linked to HZ infection [59]. A very recent study by Nugent et al. [63] assessed HZ infections among IBD and non-IBD individuals before and after introduction of HZ vaccination in 2009 in Manitoba. The authors found a higher risk of HZ infections among IBD patients compared to non-IBD individuals (incidence rate [IR] 9.2/100,000 vs. 7.2/100,000, $p < 0.0001$). The incidence of HZ infections increased during the study period despite an introduction of HZ vaccination [63]. Khan et al. [60] investigated the HZ risk among 13,000 IBD patients on therapy with 5-aminosalicylic acid compared to 35,500 non-IBD individuals. The authors found an increased HZ infection rate among IBD patients (HR 1.72; 95% CI 1.51–1.96). In a second study, the authors compared the HZ risk among the 5-aminosalicylic acid only therapy group to IBD patients with other medications. Again, the risk was highest among patients on a combination therapy with thiopurines and anti-TNF medication (HR 1.65; 95% CI 1.22–2.23), followed by thiopurines alone (HR 1.47; 95% CI 1.31–1.65). However, there was no risk increase among patients on anti-TNF medication alone (HR 1.15; 95% CI 0.96–1.38) [60]. Another group high at risk for HZ infections is patients treated with the Janus kinase inhibitor Tofacitinib. Winthrop et al. [64] evaluated HZ infections among patients in To-

facitinib phase II/III/ongoing, open-label, as well as long-term extension UC trials. HZ IR was 4.07 (3.14–5.19) in the overall cohort over a mean range of 509.1 days (1–1,606). The IR was highest among old patients aged ≥65 years (IR 9.55 [4.77–17.08]), Asians (IR 6.49 [3.55–10.89]), and patients with prior anti-TNF failure (IR 5.38 [3.86–7.29]). Although some data suggest that among IBD patients HZ infection is not only an infection of the older patient [61, 65, 66], most guidelines recommend the HZ vaccination only in patients aged 50 or 60 years and above. The ACG for example recommends an immunization against HZ among IBD patients over the age of 50 [28]. However, until the end of 2017, the only available vaccine was a live vaccine (Zostavax®, Merck). As mentioned before, usually live vaccines are not recommended in immunosuppressed individuals. However, the ACG guideline as well as the Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices recommended it in certain subgroups of immunosuppressed patients (low-dose therapy with methotrexate [<0.4 mg/kg/week], azathioprine [<3.0 mg/kg/day], or mercaptopurine [<1.5 mg/kg/day]) [28, 67]. These recommendations are in line with the recommendations by the Infectious Disease Society of America [47]. Besides, a recent study by Khan et al. [68] suggests that even among patients on anti-TNF medication vaccination with the live vaccine may be safe. However, only around 21% of patients eligible for vaccination were vaccinated, as a recent study by Khan et al. [69] showed.

With regard to the high risk for HZ among patients treated with Tofacitinib Pfizer in their Tofacitinib-containing Xeljanz® label (summary of product characteristics) recommends not to use live vaccines among patients under treatment with Tofacitinib [70].

However, since 2018 a new inactivated vaccine is available (Shingrix®, GlaxoSmithKline). The vaccine is administered at 2 time points, 0 and 2–6 months. The vaccine has shown to significantly reduce the risk of HZ by >90% [71]. Limited data in immunosuppressed patients (stem cell transplant recipients and HIV patients) suggest that Shingrix® was immunogenic and safe in these patient groups [72, 73]. As it is an inactivated and immunogenic vaccine, it is now recommended by the Advisory Committee on Immunization Practices [74].

Live Vaccines

Yellow Fever

There are no data on yellow fever vaccination in patients with IBD under immunosuppressive therapy except of one case report which reported of a patient treated with infliximab accidentally live vaccinated against yellow fever. No yellow fever viremia was detected and the patient developed antibodies [75].

Wilckens et al. [76] focused on the immunization status of patients with IBD. The authors found that beside of low vaccination rates against other infections among 102 IBD patients, of those patients who had traveled only 1% had been vaccinated for yellow fever [76].

Vaccination with the yellow fever live vaccine is contraindicated among patients under immunosuppressive therapy. An inactivated form of the vaccine does not exist. If a patient plans to travel to a yellow fever endemic region and has been vaccinated against yellow fever before an antibody measurement should be performed irrespective of time point of vaccination.

Varicella

Varicella virus is highly contagious and IBD patients, especially when treated with immunosuppressive therapy, are at increased risk of infection and complications [77, 78]. The ACG guideline recommends assessment for prior exposure and vaccination if naïve [28]. However, as the vaccine is a live vaccine, the vaccination has to be administered at least 1 month before initiation of immunosuppressive therapy according to ACH guidelines. This is in line with the ECCO guideline. In contrast to the ACG guideline, the ECCO recommends a minimum interval of 3 weeks between vaccination and start of immunosuppression [24]. Two vaccine doses, at least 1 month apart, should be administered.

Measles, Mumps, Rubella

There is only scarce data on measles, mumps, and rubella vaccination among IBD patients. Lately a study conducted by Caldera et al. [79] evaluated measles, mumps, and rubella antibody concentrations among IBD patients on immunosuppressive medication. The authors found no difference with regard to antibody concentrations among IBD patients compared to non-IBD patients. Results did not differ for various types of immunosuppressive medications.

Similarly to other live vaccines, the MMR vaccination should be administered before the start of an immunosuppressive therapy. Two vaccine doses, at least 1 month apart, should be given. According to the ACG guidelines MMR vaccination should be administered at least 6 weeks before starting immunosuppression; according to the ECCO guidelines 3 weeks are sufficient [24, 28].

Household Immunizations

Beside focusing on vaccination of the IBD patient, treating physicians should think of vaccinating close contacts as well. Especially the ACG guideline focuses on this fact [28]. It is, for example, known that around 90% of susceptible close contacts will get varicella after exposure to a person with disease [28].

Household members of immunosuppressed IBD patients should be vaccinated against influenza, HZ, mumps, measles, rubella, and varicella. Waszczuk et al. [80] speak of a "cocoon strategy" of vaccination, meaning that vaccinating close contacts will protect vulnerable patients from infectious diseases. If available inactivated vaccines should be preferred, however, live vaccines can safely be administered (MMR, varicella, zoster) [28]. Transmissions from an immunocompetent vaccinated person to an immunosuppressed person have not been demonstrated for MMR or HZ vaccine. Rare cases of varicella transmission after vaccination have been reported from vaccinees with skin lesions [47]. Thus, if skin lesions develop after varicella or live HZ vaccination, the vaccinated persons should avoid close contact with the immunosuppressed patient.

Conclusion

Patients with IBD are at increased risk of infections. This risk is increased even higher during immunosuppressive therapy. Therefore, the vaccination status should be assessed as soon as the disease is diagnosed and missing vaccinations should be administered, ideally before immunosuppressive therapy is started. However, not only the patient him-/herself but also treating physicians often lack knowledge on this subject area. As a majority of IBD patients is of young age and might therefore not otherwise consult a PCP and as IBD patients at the beginning of their disease will be at closest contact with the gastroenterologist, the gastroenterologist should be the doctor assessing and completing the vaccination status in IBD patients. IBD patients should not only complete the vaccination status for standard vaccination as those against dTaP, varicella or MMR but they should also receive vaccinations specifically recommended for IBD patients, such as influenza, pneumococcal, HPV, or HZ vaccination.

In addition to vaccinating the IBD patient, household members as well as close contacts should be vaccinated especially against highly contagious infectious diseases to avoid disease transmission to IBD patients.

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References

1 Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet Let al. Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis. Clin Gastroenterol Hepatol. 2016;14:1385–97.e10.

2 Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. Am J Gastroenterol. 2012 Sep;107(9):1409–22.

3 Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2018;155:337–46.e10.

4 Melmed GY, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. Am J Gastroenterol. 2006 Aug;101(8):1834–40.

5 Tinsley A, Navabi S, Williams ED, Liu G, Kong L, Coates MD, et al. Increased Risk of Influenza and Influenza-Related Complications Among 140,480 Patients With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019 Jan;25(2):369–76.

6 Yeung JH, Goodman KJ, Fedorak RN. Inadequate knowledge of immunization guidelines: a missed opportunity for preventing infection in immunocompromised IBD patients. Inflamm Bowel Dis. 2012 Jan;18(1):34–40.

7 Wasan SK, Coukos JA, Farraye FA. Vaccinating the inflammatory bowel disease patient: deficiencies in gastroenterologists knowledge. Inflamm Bowel Dis. 2011 Dec;17(12):2536–40.

8 Gurvits GE, Lan G, Tan A, Weissman A. Vaccination practices in patients with inflammatory bowel disease among general internal medicine physicians in the USA. Postgrad Med J. 2017 Jun;93(1100):333–7.

9 Jaeger VK, Rüegg R, Steffen R, Hatz C, Bühler S. Travelers with immune-mediated inflammatory diseases: are they different? J Travel Med. 2015 May-Jun;22(3):161–7.

10 Stobaugh DJ, Deepak P, Ehrenpreis ED. Hospitalizations for vaccine preventable pneumonias in patients with inflammatory bowel disease: a 6-year analysis of the Nationwide Inpatient Sample. Clin Exp Gastroenterol. 2013 May;6:43–9.

11 Agarwal N, Ollington K, Kaneshiro M, Frenck R, Melmed GY. Are immunosuppressive medications associated with decreased responses to routine immunizations? A systematic review. Vaccine. 2012 Feb;30(8):1413–24.

12 Lu Y, Jacobson DL, Ashworth LA, Grand RJ, Meyer AL, McNeal MM, et al. Immune response to influenza vaccine in children with inflammatory bowel disease. Am J Gastroenterol. 2009 Feb;104(2):444–53.
13 Gelinck LB, van der Bijl AE, Beyer WE, Visser LG, Huizinga TW, van Hogezand RA, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis. 2008 May;67(5):713–6.
14 Mamula P, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007 Jul;5(7):851–6.
15 Benchimol EI, Hawken S, Kwong JC, Wilson K. Safety and utilization of influenza immunization in children with inflammatory bowel disease. Pediatrics. 2013 Jun;131(6):e1811–20.
16 Andrisani G, Frasca D, Romero M, Armuzzi A, Felice C, Marzo M, et al. Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti TNF-α agents: effects of combined therapy with immunosuppressants. J Crohn's Colitis. 2013 May;7(4):301–7.
17 deBruyn J, Fonseca K, Ghosh S, Panaccione R, Gasia MF, Ueno A, et al. Immunogenicity of Influenza Vaccine for Patients with Inflammatory Bowel Disease on Maintenance Infliximab Therapy: A Randomized Trial. Inflamm Bowel Dis. 2016 Mar;22(3):638–47.
18 deBruyn JC, Hilsden R, Fonseca K, Russell ML, Kaplan GG, Vanderkooi O, et al. Immunogenicity and safety of influenza vaccination in children with inflammatory bowel disease. Inflamm Bowel Dis. 2012 Jan;18(1):25–33.
19 Romanowska M, Banaszkiewicz A, Nowak I, Radzikowski A, Brydak LB. Immunization against influenza during the 2005/2006 epidemic season and the humoral response in children with diagnosed inflammatory bowel disease (IBD). Med Sci Monit. 2010 Sep;16(9):CR433–9.
20 Hagihara Y, Ohfuji S, Watanabe K, Yamagami H, Fukushima W, Maeda K, et al. Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease. J Crohn's Colitis. 2014 Mar;8(3):223–33.
21 Melmed GY. Vaccinations while on thiopurines: some protection is better than none. Am J Gastroenterol. 2012 Jan;107(1):141–2.
22 Lopez A, Mariette X, Bachelez H, Belot A, Bonnotte B, Hachulla E, et al. Vaccination recommendations for the adult immunosuppressed patient: A systematic review and comprehensive field synopsis. J Autoimmun. 2017 Jun;80:10–27.
23 Wasan SK, Baker SE, Skolnik PR, Farraye FA. A practical guide to vaccinating the inflammatory bowel disease patient. Am J Gastroenterol. 2010 Jun;105(6):1231–8.
24 Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al.; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's Colitis. 2014 Jun;8(6):443–68.
25 Canadian Immunization Guide: Part 3 – Vaccination of Specific Populations.
26 The Australian Immunisation Handbook, Februrary 22, 2019.
27 Teich N, Klugmann T, Tiedemann A, Holler B, Mössner J, Liebetrau A, et al. Vaccination coverage in immunosuppressed patients: results of a regional health services research study. Dtsch Arztebl Int. 2011 Feb;108(7):105–11.
28 Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. Am J Gastroenterol. 2017 Feb;112(2):241–58.
29 Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of pneumonia among patients with inflammatory bowel disease. Am J Gastroenterol. 2013 Feb;108(2):240–8.
30 Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. J Crohn's Colitis. 2013 Mar;7(2):107–12.
31 Kantsø B, Simonsen J, Hoffmann S, Valentiner-Branth P, Petersen AM, Jess T. Inflammatory Bowel Disease Patients Are at Increased Risk of Invasive Pneumococcal Disease: A Nationwide Danish Cohort Study 1977-2013. Am J Gastroenterol. 2015 Nov;110(11):1582–7.
32 Caldera F, Saha S, Wald A, Garmoe CA, McCrone S, Megna B, et al. Lower Sustained Diphtheria and Pertussis Antibody Concentrations in Inflammatory Bowel Disease Patients. Dig Dis Sci. 2018 Jun;63(6):1532–40.
33 Dezfoli S, Horton HA, Thepyasuwan N, Berel D, Targan SR, Vasiliauskas EA, et al. Combined Immunosuppression Impairs Immunogenicity to Tetanus and Pertussis Vaccination Among Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015 Aug;21(8):1754–60.
34 Hou JK, Velayos F, Terrault N, Mahadevan U. Viral hepatitis and inflammatory bowel disease. Inflamm Bowel Dis. 2010 Jun;16(6):925–32.
35 Tolentino YF, Fogaca HS, Zaltman C, Ximenes LL, Coelho HS. Hepatitis B virus prevalence and transmission risk factors in inflammatory bowel disease patients at Clementino Fraga Filho university hospital. World J Gastroenterol. 2008 May;14(20):3201–6.
36 Poupardin C, Nahon S, Pariente A, Cadranel JF, Renou C; ANGH. Hepatitis B reactivation in patients with inflammatory bowel disease: A prospective survey on screening and prevention practices at general hospitals in France. Inflamm Bowel Dis. 2011 Feb;17(2):669–70.
37 Esteve M, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. Gut. 2004 Sep;53(9):1363–5.
38 Morisco F, Castiglione F, Rispo A, Stroffolini T, Sansone S, Vitale R, et al. Effect of immunosuppressive therapy on patients with inflammatory bowel diseases and hepatitis B or C virus infection. J Viral Hepat. 2013 Mar;20(3):200–8.
39 Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, et al.; BIOGEAS Study Group. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine (Baltimore). 2011 Nov;90(6):359–71.
40 Xunrong L, Yan AW, Liang R, Lau GK. Hepatitis B virus (HBV) reactivation after cytotoxic or immunosuppressive therapy—pathogenesis and management. Rev Med Virol. 2001 Sep-Oct;11(5):287–99.
41 Jiang HY, Wang SY, Deng M, Li YC, Ling ZX, Shao L, et al. Immune response to hepatitis B vaccination among people with inflammatory bowel diseases: A systematic review and meta-analysis. Vaccine. 2017 May;35(20):2633–41.
42 Shah R, Ho EY, Kramer JR, Richardson P, Sansgiry S, El-Serag HB, et al. Hepatitis B Virus Screening and Reactivation in a National VA Cohort of Patients with Inflammatory Bowel Disease Treated with Tumor Necrosis Factor Antagonists. Dig Dis Sci. 2018 Jun;63(6):1551–7.
43 deBruyn JC, Soon IS, Fonseca K, Feng S, Purtzki M, Goedhart C, et al. Serologic Status of Routine Childhood Vaccines, Cytomegalovirus, and Epstein-Barr Virus in Children With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019 Jun;25(7):1218–26.
44 Brenner EJ, Jhaveri R, Kappelman MD, Gulati AS. Evaluating Hepatitis B Seroprotection and Revaccination for Children With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019 Aug;25(9):e108.
45 Marín AC, Gisbert JP, Chaparro M. Immunogenicity and mechanisms impairing the response to vaccines in inflammatory bowel disease. World J Gastroenterol. 2015 Oct;21(40):11273–81.
46 Gisbert JP, Menchén L, García-Sánchez V, Marín I, Villagrasa JR, Chaparro M. Comparison of the effectiveness of two protocols for vaccination (standard and double dosage) against hepatitis B virus in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2012 Jun;35(12):1379–85.
47 Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al.; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014 Feb;58(3):309–18.

48 Park SH, Yang SK, Park SK, Kim JW, Yang DH, Jung KW, et al. Efficacy of hepatitis A vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2014 Jan; 20(1):69–74.
49 Hazenberg HM, de Boer NK, Mulder CJ, Mom SH, van Bodegraven AA, Tack Md PhD GJ. Neoplasia and Precursor Lesions of the Female Genital Tract in IBD: Epidemiology, Role of Immunosuppressants, and Clinical Implications. Inflamm Bowel Dis. 2018 Feb; 24(3):510–31.
50 Kjær SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. J Natl Cancer Inst. 2010 Oct;102(19): 1478–88.
51 McIntyre-Seltman K, Castle PE, Guido R, Schiffman M, Wheeler CM; ALTS Group. Smoking is a risk factor for cervical intraepithelial neoplasia grade 3 among oncogenic human papillomavirus DNA-positive women with equivocal or mildly abnormal cytology. Cancer Epidemiol Biomarkers Prev. 2005 May;14(5):1165–70.
52 Allegretti JR, Barnes EL, Cameron A. Are patients with inflammatory bowel disease on chronic immunosuppressive therapy at increased risk of cervical high-grade dysplasia/cancer? A meta-analysis. Inflamm Bowel Dis. 2015 May;21(5):1089–97.
53 Practice Bulletin No. Practice Bulletin No. 157: Cervical Cancer Screening and Prevention. Obstet Gynecol. 2016 Jan;127(1):e1–20.
54 Long MD, Porter CQ, Sandler RS, Kappelman MD. Suboptimal rates of cervical testing among women with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2009 May; 7(5):549–53.
55 Waszczuk E, Waszczuk K, Bohdanowicz-Pawlak A, Florjański J. Women with inflammatory bowel diseases have a suboptimal cervical cancer screening rate and are not aware of the recommended human papilloma virus vaccine. Gynecol Endocrinol. 2018 Aug; 34(8):656–8.
56 Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmerón J, et al.; VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet. 2014 Dec;384(9961):2213–27.
57 Wisniewski A, Fléjou JF, Siproudhis L, Abramowitz L, Svrcek M, Beaugerie L. Anal Neoplasia in Inflammatory Bowel Disease: Classification Proposal, Epidemiology, Carcinogenesis, and Risk Management Perspectives. J Crohn's Colitis. 2017 Aug;11(8):1011–8.
58 Jacobson DL, Bousvaros A, Ashworth L, Carey R, Shrier LA, Burchett SK, et al. Immunogenicity and tolerability to human papillomavirus-like particle vaccine in girls and young women with inflammatory bowel disease. Inflamm Bowel Dis. 2013 Jun;19(7):1441–9.
59 Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013 Feb; 37(4):420–9.
60 Khan N, Patel D, Trivedi C, Shah Y, Lichtenstein G, Lewis J, et al. Overall and Comparative Risk of Herpes Zoster With Pharmacotherapy for Inflammatory Bowel Diseases: A Nationwide Cohort Study. Clin Gastroenterol Hepatol. 2018;16:1919–27.e13.
61 Soh H, Chun J, Han K, Park S, Choi G, Kim JH, et al. Increased Risk of Herpes Zoster in Young and Metabolically Healthy Patients with Inflammatory Bowel Disease: A Nationwide Population-based Study. Gut Liver. 2019 May 15;13(3):333–41.
62 Cote-Daigneault J, Bessissow T, Nicolae MV, Nie R, Bitton A, Lakatos PL, et al. Herpes Zoster Incidence in Inflammatory Bowel Disease Patients: A Population-Based Study. Inflamm Bowel Dis. 2019 Apr;25(5):914–8.
63 Nugent Z, Singh H, Targownik LE, Bernstein CN. Herpes Zoster Infection and Herpes Zoster Vaccination in a Population-Based Sample of Persons With IBD: Is There Still an Unmet Need? Inflamm Bowel Dis. 2019 Feb; 25(3):532–40.
64 Winthrop KL, Melmed GY, Vermeire S, Long MD, Chan G, Pedersen RD, et al. Herpes Zoster Infection in Patients With Ulcerative Colitis Receiving Tofacitinib. Inflamm Bowel Dis. 2018 Sep;24(10):2258–65.
65 Yun H, Yang S, Chen L, Xie F, Winthrop K, Baddley JW, et al. Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases: implications for Vaccination. Arthritis Rheumatol. 2016 Sep;68(9):2328–37.
66 Gupta G, Lautenbach E, Lewis JD. Incidence and risk factors for herpes zoster among patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2006 Dec;4(12):1483–90.
67 Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2008 Jun;57 RR-5:1–30.
68 Khan N, Shah Y, Trivedi C, Lewis JD. Safety of herpes zoster vaccination among inflammatory bowel disease patients being treated with anti-TNF medications. Aliment Pharmacol Ther. 2017 Oct;46(7):668–72.
69 Khan N, Trivedi C, Kavani H, Lewis J, Yang YX. Frequency of Herpes Zoster Vaccination Among Inflammatory Bowel Disease Patients. Inflamm Bowel Dis. 2019 Jan;25(2): 345–51.
70 Pfizer Inc: XELJANZ summary of product characteristics.
71 James SF, Chahine EB, Sucher AJ, Hanna C. Shingrix: The New Adjuvanted Recombinant Herpes Zoster Vaccine. Ann Pharmacother. 2018;52(7):673–80.
72 Berkowitz EM, Moyle G, Stellbrink HJ, Schürmann D, Kegg S, Stoll M, et al.; Zoster-015 HZ/su Study Group. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis. 2015 Apr;211(8):1279–87.
73 Stadtmauer EA, Sullivan KM, Marty FM, Dadwal SS, Papanicolaou GA, Shea TC, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. Blood. 2014 Nov;124(19):2921–9.
74 Dooling KL, Guo A, Patel M, Lee GM, Moore K, Belongia EA, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. MMWR Morb Mortal Wkly Rep. 2018 Jan;67(3):103–8.
75 Rüddel J, Schleenvoigt BT, Schüler E, Schmidt C, Pletz MW, Stallmach A. Yellow fever vaccination during treatment with infliximab in a patient with ulcerative colitis: A case report. Z Gastroenterol. 2016 Sep;54(9):1081–4.
76 Wilckens V, Kannengiesser K, Hoxhold K, Frenkel C, Kucharzik T, Maaser C. The immunization status of patients with IBD is alarmingly poor before the introduction of specific guidelines. Scand J Gastroenterol. 2011 Jul;46(7-8):855–61.
77 Leung VS, Nguyen MT, Bush TM. Disseminated primary varicella after initiation of infliximab for Crohn's disease. Am J Gastroenterol. 2004 Dec;99(12):2503–4.
78 Deutsch DE, Olson AD, Kraker S, Dickinson CJ. Overwhelming varicella pneumonia in a patient with Crohn's disease treated with 6-mercaptopurine. J Pediatr Gastroenterol Nutr. 1995 Apr;20(3):351–3.
79 Caldera F, Misch EA, Saha S, Wald A, Zhang Y, Hubers J, et al. Immunosuppression Does Not Affect Antibody Concentrations to Measles, Mumps, and Rubella in Patients with Inflammatory Bowel Disease. Dig Dis Sci. 2019 Jan;64(1):189–95.
80 Waszczuk K, Waszczuk E, Mulak A, Szenborn L, Paradowski L. A 'cocoon immunization strategy' among patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2015 Mar;27(3):249–53.
81 Bundesamt für Gesundheit und und Eidgenössische Kommission für Impffragen. Impfprinzipien und Empfehlungen für Personen mit chronisch entzündlichen Darmerkrankungen oder anderen gastroenterologischen (Auto-)Immunerkrankungen. BAG-Bulletin. 2017;50:28–31.