Digestive and Liver Disease xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Screening, prophylaxis and counselling before the start of biological therapies: A practical approach focused on IBD patients

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ARTICLE INFO

Article history:
Received 14 July 2017
Received in revised form 3 September 2017
Accepted 4 September 2017
Available online xxx

Keywords:
Biologics (IBD)
Immunosuppression
Inflammatory bowel diseases
Microbiology
Screening

ABSTRACT

The standard of care in the management of immune-mediated inflammatory conditions relies on immunomodulators, glucocorticoids, and biologicals (including anti-tumour necrosis factor –α and other monoclonal antibodies). These agents have an overall favourable benefit/risk ratio; however, they modulate the immune response as part of their mechanisms of action, and therefore they may increase the risk of developing infections, particularly in older patients or in patients with concomitant corticosteroids. Some of these infections may be preventable by immunization, chemoprophylaxis or counselling. AIM: screening for and monitoring infections throughout these therapies is so mandatory to ensure patients' safety. Still, standardized guidelines focused on these procedures have yet to be established. This review aims to fill such a gap. The authors searched for articles published in English from 2009 until 2017 using PUBMED, with the terms "immunomodulators", "biological drugs", "anti-TNF α", "inflammatory bowel diseases", "immunomediated inflammatory diseases", "risk of infection", "infection prevention", "screening", "immunization", "tuberculosis", "latent tuberculosis", "listeriosis", "endemic mycosis", "*Pneumocystis jiroveci* pneumonia", "granulomatous infection", "varicella", "herpes virus", "hepatitis B", "hepatitis A", "hepatitis C" and identified the journal articles. Based on the literature and in their own experience the authors established recommendations and a practical guide for infections' screening, monitoring and prevention before and during immunomodulatory and biological therapies.

1. Introduction

The current therapeutic strategies employed in the management of immune-mediated inflammatory conditions include medication with immunomodulators, glucocorticoids and, more recently, biologicals (monoclonal antibodies, namely anti-tumour necrosis factor α [anti-TNFα]). These agents have an overall favourable benefit/risk ratio; however, they do impose a high risk of infections development [1–4]. In fact, and according to current guidelines [5], patients on glucocorticoids (prednisolone 20 mg/day or equivalent for two weeks or more), immunomodulatory drugs and biological agents should be considered immunocompromised.

Due to the infectious risk, screening for infection and monitoring, as well as prevention based on immunizations practices and counselling, are important issues related to the treatment of inflammatory immunomediated patients.

Despite the importance of a rigorous baseline assessment and routine-based monitoring, standardized guidelines focused on these procedures have yet to be established.

This review gathers together screening, prophylactic and monitoring procedures that can be used as a practical guide by those who treat immune-mediated inflammatory diseases' patients in order to reduce the infection risk before and during immunomodulatory and biological therapies.

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http://dx.doi.org/10.1016/j.dld.2017.09.002
1590-8658/

Table 1
Checklist for the medical interview.

Medical history	Check
Tuberculosis or tuberculosis exposition	
Respiratory disorders	
Hepatic disorders	
Cardiovascular disorders	
Joint symptoms	
Neurologic diseases and symptoms	
Hematologic disorders	
Diabetes mellitus	
HIV infection	
Other sexual transmitted diseases	
Immunizations	**Check**
BCG (data)	
Hepatitis A	
Hepatitis B (data) anti HBs quantified >10 UI/mL	
Measles/MMR	
Pertussis Booster of Tdap[a]	
Pneumococcal:conjugate –Polissacharidea – (data)	
Influenza (annual)	
Papilomavirus	
Varicella	
Others	**Check**
Malignancies (type, data, treatment)	
Cancer screenings (according to age and sex)	
Pregnancy issues	

[a] Booster of *Tetanus diphteria* and acellular *Pertussis*.

1.1. Search strategy and selection criteria

We searched for articles published in English from 2009 until 2017 using PUBMED. A search with the terms "immunomodulators", "biological drugs", "anti-TNF α", "inflammatory bowel diseases", "immunomediated inflammatory diseases" and "infection", "risk of infection", "infection prevention", "screening", "immunization", "tuberculosis", "latent tuberculosis", "listeriosis", "endemic mycosis", "*Pneumocystis jiroveci* pneumonia", "granulomatous infection", "varicella", "herpes virus", "hepatitis B", "hepatitis A", "hepatitis C" and identified the journal articles. We also read some other papers cited in these articles.

2. The clinical interview

A detailed clinical interview focused on the patient's medical history should be carried out before the prescription of immunomodulatory drugs and/or biologicals—a checklist for such an interview is depicted on Table 1. One should keep in mind that the utilization of immunosuppressive drugs in the past may carry and additional risk of infection [6,7]. Moreover, patients afflicted with diabetes or chronic pulmonary obstructive syndrome are particularly prone to suffer infections [8], as are patients with renal insufficiency. Tuberculosis (TB) is a key issue in the field: patients should disclose whether they were previously diagnosed with latent or active TB, and should depict any known contact with TB patients. Moreover, patients should also disclose whether and when they had TB screening tests in the past – either tuberculin skin tests, interferon gamma release assays (IGRAs) or pulmonary X-rays – as well as the result(s) obtained. Previous surgeries should also be disclosed, as well any places were the patient has lived in or travelled to where there is an intermediate or high risk for TB, or where endemic mycosis (histoplasmosis, coccidoidomicosis) or *Strongyloides stercoralis* infections are reported. Previous allergic reactions should also be inquired during this interview, as well as the gynaecologic and obstetric history of female patients. Sexual risk behaviours and sexual-transmitted diseases (STDs) must also be disclosed. Regarding patients' personal habits, smoking and alcohol intake should be taken into consideration. Finally, patients' immunization history should be carefully checked.

3. Patients' counselling

3.1. General counselling

All risks and alarm signs should be carefully explained to the patient during his/her first appointment. Patients should be instructed to seek medical care should any of the following symptoms occur: weight loss, excessive sweating, asthenia (in the absence of a known cause), fever, respiratory signs, and neurologic, cutaneous or articular signals developed during the treatment. Contact with TB-diagnosed patients during their contagious phase and activities such as revolving the ground in mycosis-endemic areas should be avoided [9]. Moreover, and to prevent the occurrence of *Listeria* sp. and *Salmonella* sp. infections, patients should not consume raw eggs, unpasteurized milk products, hot dogs or deli meats (unless reheated at high temperatures), and uncooked meat/fish [9]. *Clostridium difficile* associated colitis is a risk for immunosuppressed patients and the IBD patient; a minority of cases are acquired from other patients, so enteric precautions should apply in the case of colonized or ill patients with the bacteria, especially for inpatients [10]. Unpasteurized milk products should also be avoided in areas where there it the risk of brucellosis. Persons whom are not immune to varicella (*i.e.*, have not been vaccinated and never had the disease) should avoid contact with varicella patients. The establishment of a close and confidence-based relationship between the patient and the medical team is a fundamental step at this point.

3.2. Travel-related counselling

Whenever a patient who is about to start or already on biological therapy has plans to travel to tropical areas (where yellow fever, malaria and other infectious risks are a concern), he/she should have an appointment at a travel medicine clinic, ideally with an IBD-dedicated infeciologist, at least four weeks before travelling. With the exception of the attenuated vaccines, all the other prophylactic measures usually applied to non-immunocompromised patients should be applied to patients on immunosuppressive drugs. Special care should be taken to check for drug-to-drug interactions between prophylactic measures and immunosuppressive medication. High risk destinations and adverse live conditions that, according to the IBD-dedicated gastroenterologist, may worse the disease, should best be avoided.

4. Tests to be performed before therapy and their rationale

Before starting biological drugs, patients should go through a battery of screening and diagnosis tests, which are described below and listed in Table 2. A blood analysis – including a complete blood count, liver transaminases, serum creatinine levels and serological tests to some infectious agents – is required at this point. STDs, such as syphilis, HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), *herpes simplex virus* type 2 (HSV2), should also be screened for. Moreover, and given the increasing number of adults who are not immune to the hepatitis A virus (HAV), the presence of anti-HAV IgG should also be evaluated. The presence of antibodies to the common herpesvirus, such as *Epstein–Barr virus* (EBV), *cytomegalovirus* (CMV), *herpes simplex virus* type 1 (HSV1) and *varicella-zoster virus* (VZV), should also be assessed. In the absence of measles vaccination or previous infection, anti-measles IgG antibodies should also be assayed.

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Table 2
Laboratorial work-up before immunosuppressive prescription.

Analytical data	Observations	Check
Hepatitis B virus		
- Anti-HBs quantified*	*For those vaccinated	
- HBs antigen, anti-HBs and	**For all the others (see text)	
- Anti-HBc**		
Hepatitis C virus (anti-Hepatitis C)		
Human immunodeficiency virus (anti-HIV)		
Hepatitis A virus (anti-HAV IgG)		
Epstein–Barr virus (anti-EBV)	anti VCA (IgG, IgM), EBNA, EA-D	
Citomegalovirus (anti-CMV IgG and IgM)		
Herpes virus (anti-HSV 1 and 2: IgG and IgM)		
Varicella-zoster virus (anti VVZ IgG)		
Syphilis (VDRL or TPPA)		
In particular circumstances		
Anti-measles Ig G	If not vaccinated and without past measles disease	
Anti-JC virus	Before natalizumab prescription	

VCA—viral capsid antigen; EBNA—Epstein Barr nuclear antigen; EA-D—early antigen D; VDRL—venereal disease research laboratory; TPPA—*Treponema pallidum* antigen; JC—John Cunningham virus.

5. Dealing with test' results

5.1. Lymphopenia and neutropenia

Neutropenia or neutrophils' functional abnormalities – which are related to innate immunity – are known to increase the patients' risk of suffering a number of infections, namely from enteric Gram-negative bacteria, *Staphylococcus* sp. and fungi (*Candida* spp., *Aspergillus* spp., *Mucor* spp.) [11]. On the other hand, lymphopenia – especially if prolonged in time – and abnormal T cells may increase the patients' risk of suffering infections from herpes virus, progressive multifocal leukoencephalopathy associated to John Cunningham (JC) virus, and infections from *Mycobacterium* spp, *Nocardia* spp., *Listeria* sp., *Cryptococcus* spp., *Histoplasma capsulatum*, *Toxoplasma gondii* and *Strongyloides stercoralis* [11]. Moreover, an absolute lymphocyte count below 500 lymphocytes/μL is a risk factor for severe infections [12] and a contra-indication for tofacitinib (used in the treatment of rheumatoid arthritis). Patients' haematological profile should be routinely monitored (the suggestion is each two weeks if lymphocytes are close to 500/μL, and at least each two weeks for the first four weeks of a drug prescription that may frequently cause leukopenia) as its variations may contribute to increase the risk of developing infections among those on immunosuppressive drugs.

5.2. Syphilis

If a patient has a positive VDRL (venereal disease research laboratory) test but no symptoms, he/she should be diagnosed with latent syphilis. The appropriate treatment is a single intramuscular penicillin injection if the patient has at least one negative VDRL result in the previous 12 months; otherwise, latent syphilis should be treated with three weekly injections of penicillin [13]. All sexual partners should be screened for syphilis and treated accordingly.

5.3. HIV

An HIV test should always be requested when in the presence of a sexual transmitted disease (STD), and treatment must be started upon a positive result. It should be stressed that HIV infection is not a contraindication for biological therapy – namely with anti-TNFα agents – when the patient is being treated and his/her clinical situation is stable [14].

5.4. HBV and HCV

Patients who have not been vaccinated against HBV should be screened using hepatitis B surface antigen (HBsAg) antibody (anti HBs quantified) and anti-hepatitis B core (anti-HBc) IgG before being placed on immunosuppressive drugs. Following a positive HBV serological test, a sensitive HBV DNA assay should be performed. HBsAg-positive patients with HBV-DNA above 2000 UI/mL should be treated according to the current guidelines (which can be found at the European Association for the Study of the Liver [EASL] [15], Asian–Pacific Association for the Study of the Liver [APASL] [16] and American Association for the Study of Liver Diseases [AASLD]) [17]. HBsAg-positive patients with HBV-DNA below 2000 UI/mL, or HBsAg-negative patients with a positive result for anti-HBc IgG, are also at risk of HBV reactivation during immunosuppressive therapies [18]. This risk depends on the serological profile of the patient, his/her medical condition and which immunosuppressive drugs are to be used. The risk is higher for patients on anti-CD20 therapies, like rituximab and ofalumumab, mostly used for the treatment of haematological and rheumatic diseases, but is still considerable for patients on anti-TNFα, other biological drugs, antracyclines and glucocorticoids. Therefore, routine monitoring and application of prophylactic measures is mandatory for HBs antigen-positive and/or anti-HBc-positive patients who will be placed on immunosuppressive drugs or chemotherapy [19]. Table 3 depicts the procedures advocated by EASL, ECCO (European Crohn and Colitis Organization), APASL and AASLD in these situations. Accordingly, the American Gastroenterology Association (AGA) 2015 recommendations state that anti-HBc IgG positive patients, irrespective of their HBs Ag status, should receive prophylactic treatment before being placed on any biological therapy and anthracyclines derivatives (*e.g.*, doxorubicin, epirubicin). Moreover, those that are to be placed on systemic glucocorticoids for a period longer than four weeks should be treated if they are HBs Ag positive or if they are supposed to receive a dosage higher than 10 mg per day of prednisolone or equivalent [18].

The antiviral drug used in the prophylaxis should have a high genetic barrier, should be started before the immunosuppressive drugs' therapy and should be maintained for a minimum period of six months after the immunosuppressive drugs' discontinuation, or for a minimum period of 12 months if B cell-depleting agents were used. AGA do not recommend the use of this routine-based antiviral prophylaxis in patients whose risk for HBV reactivation is low (*i.e.*, less than 1%): patients on traditional immunosuppressive agents (*e.g.*, azathioprine, 6-mercaptopurine, methotrexate) on intra-articular steroids, on oral glucocorticoids for a short period (less than one week), or on less than 10 mg prednisolone or equivalent if the patient is HBsAg negative and anti-HBc positive. Moreover, and against former recommendations, AGA does not recommend HBV DNA monitoring for the decision of preemptive therapy as an alternative to antiviral prophylaxis [18].

Concerning hepatitis C, HCV-RNA should be assayed whenever HCV antibodies are detected. Should the patient have a positive result occurs in the former, he/she should be treated for HCV. As far as the current knowledge goes, there is no known risk of HCV reactivation with immunosuppressive drugs, and therefore a positive result in HCV testing is not a contra-indication for immunosuppres-

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Table 3
Screening, monitoring and prophylactic antiviral therapy concerning HBV status according to different guidelines.

	AASLD, 2009	ECCO, 2013	APASL, 2015	EASL, 2017
Screening a) before IST	HBs Ag and anti-Hbc for high risk of HBV infection	Hbs Ag, anti-HBc, anti-HBs for all; HBV-DNA if HBsAg positive	HBs Ag and anti-HBc for all	HBs Ag, HBs atc and anti-Hbc for all; HBV-DNA if isolated anti-HBc positive
b) during IST (each 1–6 month)		HBV serology and HBV DNA every 1–3 months	Monitoring ALT and HBV-DNA	Anti Hbc positive: monitoring HBV-DNA/ALT 1–3 months
Prophylactic-anti viral therapy	HBs Ag positive	HBs Ag positive; anti Hbc positive and HBV-DNA positive:	HBs Ag positive; anti Hbc positive and HBV-DNA positive:	HBs Ag positive; anti Hbc positive and HBV-DNA positive; anti-HBc positive: if high risk of HBV reactivation (>10%) consider also if: long duration of IST, limited compliance to monitoring or unknown risk of viral reactivation for new biologicals
Timing	From onset to 6 months after stopping IST	Best start 2 weeks before IST to at least 12 months after stopping IST	From onset to 12 months after stop IST	From onset to 12 to 18 months after stop IST
Nuc(s)	Lamivudine; preferred ETV/TDF particularly for those treated >12 months	Nucleoside/nucleotide analogues with high barrier to resistance (ETV/TDF)	lamivudine; ETV/TDF/TAF	ETV/TDF/TAF Lamivudine may be used although few cases of HBV exacerbation due to LAM resistance have been reported.

AASLD—American Association for the study of Liver Diseases; ECCO—European Crohn and Colitis Organization; EASL—European Association for the Study of Liver. APASL—Asian Pacific Association for the study of liver. IST—immunosuppressive therapy. Nuc(s)—nucleoside(s). ETV—entecavir; TDF—tenofovir; TAF—tenofovir alafenamide.

sive therapy [20]. Still, and as HCV is a treatable and curable disease, its screening should definitively be done.

Finally, biological agents should not be prescribed to patients who have liver dysfunction classified as Child–Pugh class B and higher [21].

5.5. Herpesvirus (EBV, CMV, HSV, VVZ)

The prescription of thiopurines has been associated to fatal early post-mononucleosis lymphoproliferative diseases in young men (less than 35 years-old) seronegative for EBV [22,23]. In fact, a Crohn's disease patient on azathioprine was reported to have an EBV primoinfection which developed into infectious mononucleosis, haemophagocytic lymphohistiocytosis (HLH) and a B-cell lymphoproliferative disorder [3]. Accordingly, HLH has been associated to EBV in medically-immunosuppressed patients [24]. Therefore, thiopurines' alternatives should be considered for EBV-negative patients [20].

CMV primoinfection or reactivation can occur in patients on immunosuppressive drugs, and may cause retinitis, pneumonia, encephalitis, and other invasive infections [25]. Accordingly, a prospective case-control report has described an association between severe steroid-refractory inflammatory bowel disease and CMV infection [25,26]. The knowledge of the CMV sero-status before the treatment of the immune-mediated inflammatory disease is thus a useful tool in the differential diagnosis.

VZV has been associated to significant morbidity and mortality in immunocompromised patients. After an acute infection (varicella), VZV persists in a latent state in autonomic ganglia, dorsal nerve roots and cranial nerves [27], and might later reactivate as zoster. Severe forms of VZV infection with retinian necrosis have been described in patients treated with fingolimod [28] and natalizumab [29]. Moreover, severe forms of varicella have been associated to anti-TNFα therapy [30–32]. Therefore, all patients who have not been vaccinated and who do not have a previous definitive diagnosis of chickenpox should be assayed for the presence of VZV antibodies before initiating immunosuppressive drugs; in the presence of a negative test, vaccination should be offered and completed at least four weeks before initiating immunosuppressive drugs [33]. For persons 60 years old or older without a history of chickenpox there is no need to check VZV antibodies and shingles vaccine should be offered in the absence of a medical contra-indication [34].

5.6. Measles

Patients who test negative for measles' antibodies should be vaccinated before initiating immunomodulation. If the vaccine is somehow contraindicated, and if the patient has contact with a person with measles, immunoglobulin should be administered within six days of exposure, as it may provide some protection or modify the clinical course of the disease [35].

5.7. TB

5.7.1. Screening

Patients should be screened for latent tuberculosis (LTB) before starting immunosuppression. TB reactivation is a risk not only for patients on anti-TNFα, but also for patients on glucocorticoids, leflunomide, teriflunomide, mitoxantrone and alemtuzumab (anti-CD52). Before vedolizumab and ustekinumab Food and Drug Administration (FDA) suggests TB screening, until the risk is clearly settled. Currently, there are no gold standard tests for TB screening. In this context, several guidelines (ECCO [5], National Institute for Health and Care Excellence [NICE] [36], World Health Organization [WHO] [37], and also national recommendations concerning LTB diagnosis) advocate the use of a tuberculin skin test (TST) and/or an IGRA test (Quantiferon or TB-spot.TB), and a pulmonary X-ray. The performance of TST and an IGRA test raises the diagnosis sensitivity and has been the authors' choice [38]. For immunocompromised patients, a single positive result in any of these tests supports an LTB diagnosis, as in the context of immunosuppression missing an LTB diagnosis poses a greater risk than the potential hepatotoxicity resulting from the prophylactic TB therapy. Concerning results of IGRA tests that remain indeterminate, should probably be better to proceed as they were positive.

Screening for LTB during biological therapy is controversial. Still, and having into account the serious risk posed by an active TB in immunocompromised individuals, some authors advocate a routine-based TB surveillance during and after anti-TNFαtherapy [39]. Conversely, other authors believe that TB screening should tailored-based and adjusted to the risk of developing TB [40]. What-

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ever the option is, TB screening should undoubtedly take place whenever a contact with a TB patient occurs.

5.7.2. LTB treatment

The WHO guidelines suggest different alternatives – considered to be equivalent – for LTB treatment: six-months isoniazid, nine-months isoniazid, or three-months of weekly rifapentine plus isoniazid. Other options include three to four months' isoniazid plus rifampicin, or three to four months' rifampicin alone [41]. NICE recommendations, on the other hand, recommends as treatment three-months isoniazid (with pyridoxine) and rifampicin, or six months isoniazid (with pyridoxine) [36]. Patients should be closely monitored throughout the treatment as there is the risk of hepatotoxicity. After one month of LTB therapy is generally considered safe to start biological therapy [5,42].

6. Immunizations

Upon the diagnosis of an immune-mediated inflammatory condition, the patients' previous immunizations should the carefully reviewed, and any missing vaccine should be promptly updated [43]. Adult patients should be protected against common agents, which are briefly mentioned in Table 4. Current evidence suggests the absence of a relationship between vaccines and immune-mediated disease flares [5].

Vaccination should ideally precede the onset of therapy with immunosuppressive drugs to ensure efficacy: inactivated vaccines should be administered at least two weeks before immunomodulatory therapies, and attenuated vaccines at least four weeks before. Still, and should that fails to occur, immunization using inactivated vaccines can be carried out while the patient is on immunosuppressive drugs, as some protection is expected to be achieved, and, whenever possible, the quantification of antibodies should be performed after the vaccination. Attenuated live vaccines, on the other hand, should not be administered during immunosuppression or biological therapies given the risk of reactivation of the vaccines' attenuated virus. Physicians should keep in mind that immunizations' recommendations may change over time, and should ensure they are updated with the latest indications.

Overall, vaccination should be applied outside periods of exacerbation of the immune-mediated disease (four to six weeks after a relapse in the case of multiple sclerosis), more than three months after immunoglobulin usage, and ideally more than six months after anti-CD20 agents like rituximab [44].

6.1. Inactivated vaccines

6.1.1. Pneumococcal

Streptococcus pneumoniae is the most common bacterial cause of pneumoniae and may also be responsible for invasive diseases such as bacteraemia and meningitis. Vaccination against this agent is recommended for children, persons who are 65 years or older, and patients on immunosuppressive agents, among others. Concerning the latter (immunocompromised patients over 19 years of age), the Advisory Committee on Immunization Practices (ACIP) guidelines recommends the following: patients who are naïve to pneumococcal vaccine should receive the conjugated vaccine (PCV13) and, at least eight weeks later, the polysaccharide vaccine (PPSV23) [45]; those who had been previously vaccinated with PPSV23 should receive, one dosage of PCV13, at least one year after PPSV23 [46]. The PPSV23 should be re-inoculated once within five years in patients who have been vaccinated for the first time before 65, and in patients turning 65 and for whom more than 5 years had elapsed since the last dose [45].

6.1.2. Influenza

Influenza infection might be followed by serious complications, especially in immunocompromised individuals. As so, the ACIP recommends that these individuals should be vaccinated against influenza once a year [47]. The inactive influenza vaccine (two influenza A and one influenza B strains) is known to be safe and effective both in children and adults with chronic diseases [48]. An inactivated influenza vaccine with four antigens (two influenza A and two influenza B strains) may become available in the near future. Rituximab-treated patients are known to have a weak response (in terms of antibodies production) to the influenza vaccine; still, these patients should nevertheless be vaccinated [49].

6.1.3. HBV and HAV

All patients who have a seronegative result concerning HBV (*i.e.*, a negative or low-titer HBsAb result) should be vaccinated against this agent. The HBV vaccine is safe, but its response may be significantly reduced in those on immunosuppressive drugs, and therefore an intensified vaccination protocol may be required. Protection is considered to be achieved if a concentration of anti-HBs higher than 10 mUI/mL is detected one to two months after vaccination. Patients who have not quantified the anti-HBs after vaccine administration, should do it; vaccine should be repeated if the anti-HBs concentration falls below 10 mUI/mL. According to several opinions expressed in the current literature, the re-inoculation can be done in one, two or three doses (20 μg) [50,51]. Alternative vaccination schedules (at 0, 1, and 4 months or 0, 2, and 4 months) have been approved and are known to elicit dose-specific and final rates of seroprotection similar to those obtained with a classical schedule [52].

The vaccine against HAV should be applied in two doses, separated by six to 18 months. Alternatively, individuals over 16 years may be inoculated with a combined HAV/HBV vaccine (Twinrix®) using one of the following schedules: 0, 1 and 6 months, or 0, 7, 21–30 days and 12 months (approved by FDA) [53]. Seroconversion is elicited in virtually everyone after the second dose, and antibodies to HAV can remain for more than 25 years in adults [54]. The absolute lower limit of anti-HAV required to prevent HAV infection has not been defined and, accordingly, neither has the vaccine's protective value. Antibodies quantification is not recommended as the sensitivity of the current tests is known to be variable.

6.1.4. Papillomavirus

The human papillomavirus (HPV) has been associated with cervical, vulvar and vaginal cancer in females, penile cancer in males, and anal cancer and oropharyngeal cancer in both genders [55]. Moreover, HPV is known to be related with cervical pre-cancers, including cervical intraepithelial neoplasia grade 2 or 3 and adenocarcinoma *in situ* (≥CIN2). Immunosuppressive drugs have been associated to an increased incidence of HPV-associated warts or condylomata [56]. Importantly, HPV infection can be prevented with a highly efficacious conjugated vaccine, although its application does not exclude the need of regular screening for cervical cancer in women.

Routine HPV vaccination (quadrivalent [4vHPV], bivalent [2vHPV] and the nonovalent [9vHPV]), is usually administered to 11- to 12-years-old infants in two doses at least six months apart. When HPV vaccination is started later (between the ages of 15 and 26), three doses are needed to achieve seroprotection [57]. The 9vHPV, 4vHPV or 2vHPV vaccines can be administered up to the age of 26 years; ACIP recommends the administration of three doses of either 9vHPV or 4vHPV vaccine in those who have not been vaccinated previously and are immunocompromised (including those with HIV infection) [58].

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Table 4
Vaccination in adults suffering from immuno-mediated inflammatory diseases.[d]

Vaccine	At diagnosis	Under immunosuppression (IS)	Routine vaccination schedule
Common vaccines			
Hepatitis A	√	√	2 doses: 0–6 to 12 month
Hepatitis B	√	√	3 doses: 0–1 and 6 month or 0–7 and 21 days and one year (same schedule applies to HAV/HBV vaccine)
Td, Tdap	√	√	1 dose every 10 years[#] one of this vaccine should be Tdap
Human papillomavirus	√ (11–26 years)	√ (11–26 years)	at diagnosis if 9–14 years: 2 doses at 0–6 month Under IS: 3 doses at 0, 1 and 6 month
Influenza-inactivated	√	√	1 dose every year
Influenza-live attenuated	√	**X**	–
Measles, mumps, rubella (MMR)—live*	√	**X**	2 doses: 0–4 weeks
Pneumococcal conjugate (PCV13)	√	√	1 dose: ideally before PPSV23; if after PPSV23: ≥1 year
Pneumococcal polysaccharide (PPSV23)	√	√	Before 65 years: 1 dose repeated 5 years after and at 65 of age, if an interval of at least 5 years from the last dose; after 65 years: 1 dose Timeline after PCV13 shot: ≥8 weeks after if under IS >6–12 months if without IS
Polio-inactivated (salk)	√	√	3 doses: 0–1 and 12 month or separated by ≥ 4weeks
Varicella—live	√	**X**	2 doses: 0–4 weeks
Zoster—live	√ (50–59 years)[b] √ (≥60)	**X**[a]	1 dose
Travel related vaccines			
Cholera, oral (inactivated)	√	√	>6 years: 2 doses 0–1 week Repeat each 2 years if needed
Japonese encephalitis (inactivated)	√	√	2 doses: 0–4 weeks; if booster needed: one dose >1 year after the initial one
Meningococcal, conjugate (A,C,Y,W135) (MCV4)	√ (2–55 years)[c]	√ (2–55 years)[c]	1 dose; repeated after 5 years if protection is still needed
Polio, inactivated (salk)	√	√	1 dose (if >10 years after a complete schedule vaccination); same as above if not vaccinated before
Tick borne encephalitis, inactivated (FSME-IMMUN®)	√	√	3 doses (0, 1–3 month, 6–15 month) first booster if needed at 3 years
Typhoid, inactivated	√	√	1 dose; each 2 to 3 year if needed
Yellow fever	√	**X**	1 dose is enough for life-long protection (WHO,2016)

√—administer if patient is not current with recommendations for adult immunocompetent persons in same risk and age categories.
[#]Portuguese recommendations state Td booster at 10, 25, 45 and 65 and then each 10 years.
X—contra-indicated.
*If not vaccinated previously.
[a]Zoster vaccine is admitted for ACIP if low level immunosuppression (treatment with prednisone <2 mg/kg with a maximum of ≤20 mg/day; methotrexate ≤0.4 mg/kg/week; azathioprine ≤3 mg/kg/day; or 6-mercaptopurine ≤1.5 mg/kg/day).
[b]Recommended by IDSA guidelines; contraindicated by ACIP recommendations.
[c]More than 55 years: meningococcal polysaccharide vaccine (A,C, Y, W135) (MPV4).
[d] Adapted from the protocol of Immunomodulation and risk of Infection Consultation (IRIC), Centro Hospitalar S João-Porto, Portugal.

6.2. Live vaccines

6.2.1. Varicella

Varicella vaccination consists of two doses of an attenuated vaccine administered four to eight weeks apart. For patients with immune-mediated inflammatory diseases, vaccination should be considered at least one month before being placed on immunosuppressive drugs, one month after discontinuing steroids, or three months after discontinuing other immunosuppressive drugs (including anti-TNFα therapy) [5]. Some authors [59] have reported a good response (in terms of tolerance) to the VZV vaccine in children with IBD on 6-mercaptopurine or infliximab. Still, a throughout knowledge of the risks and benefits of the varicella vaccine in patients on immunosuppressive drugs awaits larger prospective studies; until then, patients should be to tested for VZV as early as possible after diagnosis, and those previously unexposed to VZV should be vaccinated according to the timeline depicted above. Patients exposed to varicella who do not have anti-VZV antibodies and for whom the vaccine is contra-indicated should be treated with varicella zoster immunoglobulin (VZIG) within 10 days of the exposure [60]. These patients should also be carefully observed during the following four weeks, and antiviral therapy should be started immediately should varicella develops [5].

6.2.2. Zoster

The administration of a zoster vaccine has been approved for patients who are VZV-positive and at risk of developing herpes zoster (*i.e.*, the elderly, 60 years of age or older or, according to Infectious Diseases Society of America [IDSA], 50 years or older). This vaccine consists on a single dose; patients should be inoculated at least four weeks before being placed on immunosuppressive drugs [34]. Moreover, this vaccine should not be administered within one

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month after discontinuing immunosuppressive drugs [34]. However, and according to ACIP, it can be administered to patients on low doses of immunosuppressive drugs, such as azatioprine, metothrexate and steroids (Table 4).

Zoster vaccine seroprotection is fallible for those older than 70 years; still, it remains effective against this disease-associated pain [61]. Recently, a new vaccine against zoster – a subunit-inactivated vaccine – has been developed. This vaccine is now on its phase three trial, which is being conducted in adults aged 70 years or older, and its administration is made in two doses two months apart. This vaccine's efficacy against herpes zoster has been settled at 91.3%, whereas efficacy against post-herpetic neuralgia has been settled at 88% [62].

6.2.3. Measles, mumps and rubella (MMR)

Patients with immune-mediated inflammatory diseases who are not naturally immunized nor have been vaccinated while children against measles, mumps and rubella, should be inoculated twice with four weeks apart. This inoculation should not be made while the patient is on immunosuppressive drugs. If an unprotected patient has contact with a measles-infected person, he/she should be placed on immunoglobin within six days of the contact [35]. Moreover, susceptible close contacts should be vaccinated ("cocooning" strategy) [63]. The MMR vaccine should be postponed if the person has been recent (*i.e.*, in the previous 11 months) receipt of an antibody-containing blood product, has moderate or severe illness with or without fever, has history of thrombocytopenia or thrombocytopenic purpura, and performed a tuberculin skin testing. Concerning the latter, a tuberculin test should be done before, simultaneously with, or at least four to six weeks after MMR vaccination, as this vaccine can cause false negatives in the test [35].

7. Other prophylactic treatments: *Pneumocystis jiroveci pneumonia* (*Pjp*)

Pjp is a severe disease and its mortality is greater among HIV-uninfected individuals. Risk factors for Pjp development are known to include glucocorticoid therapy, lymphopenia (total lymphocyte count, <600 cells/mm^3),age greater than 55 years [64], and defects in cell-mediated immunity [65]. ECCO recommends prophylactic treatment in patients on three immunomodulators, or two when one is a calcineurin-inhibitor; the first-line agent for Pjp prophylaxis is Cotrimoxazole (960 mg administered three times a week) [66]. All the other prophylactic treatments are second-line alternatives, and include Atovaquone (1500 mg once a day, should be taken with fatty food) or Dapsone (100 mg a day). One should keep in mind that cotrimoxazole intolerance often predicts dapsone intolerance [65]. The optimal moment to discontinue prophylaxis is also yet to be established: whereas some authors advocate discontinuation one month after stopping immunosuppressive drugs [67], others prefer to prolong prophylaxis for up to three months, as there is a remaining risk for Pjp during immune reconstitution phase.

8. Conclusions

The new and more aggressive therapeutic strategies employed in immune-mediated inflammatory diseases – which include an earlier and more prolonged use of biological drugs – are a challenge for clinicians. Patients should be carefully examined before being placed on immunosuppressive drugs: risk factors for developing infectious diseases, demographic and epidemiological variables, past medical history and comorbidities should be enquired and considered in detail. Moreover, a thought-out screening and a routinely-based surveillance can actually reduce the risk of reactivation of some infectious diseases (such as TB, herpetic infections and endemic mycosis), whereas vaccination and chemoprophylaxis can protect from others. It is important to stress that a detailed evaluation before immunomodulation may prevent later therapeutic interruptions. The treatment of latent tuberculosis and the prevention of hepatitis B virus reactivation, should be done before biologics whenever they apply. Other prophylaxis (such as herpes virus reactivation, meningococcal infection prevention) should be done according to the biologic prescribed (for instance alemtuzumab demands herpes virus prevention [68], eculizumab demands meningococcal immunization [69]). Considering *Pneumocystis jiroveci* infection prevention, it should be done according to the association of therapies prescribed (immunomodulators or immunomodulators and biologicals) that are considered a risk for the disease.

We hereby propose an evidence-based practical guide for clinicians that aims to standardize patients' monitoring before and during biological therapies. A multidisciplinary approach, involving MDs specialized in infectious diseases and pneumology, pharmacists, microbiologists, general practitioners and nurses, is a key asset. Patients should be clearly informed, committed to the treatment and should have easy access to the medical team. Patients' surveillance is crucial, as some drug-related risks become known long after the approval and prescription of a specific drug. An up-to-dated knowledge is of an utmost importance, as pharmacovigilance-implemented modifications to therapies and new guidelines for immunization are continuously being published. An attentive medical team working closely with informed and committed patients is thus very important for the success of these treatments.

Conflict of interest

FM served as speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratorios Vitoria, Ferring, Hospira and Biogen.

CA served as speaker and received honoraria from Pfizer, Janssen and Biogen.

AS has no conflict of interest to declare.

Acknowledgments

The authors would like to express their acknowledgment to Nurse Team of the Gastroenterology and Infectious Diseases Day Care Clinic for welcome the patients and for the tests performance as well as to Catarina L. Santos for scientific writing assistance.

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