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Review

Vaccinations in patients with immune-mediated inflammatory diseases

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Abstract

Patients with immune-mediated inflammatory diseases (IMID) such as RA, IBD or psoriasis, are at increased risk of infection, partially because of the disease itself, but mostly because of treatment with immunomodulatory or immunosuppressive drugs. In spite of their elevated risk for vaccine-preventable disease, vaccination coverage in IMID patients is surprisingly low. This review summarizes current literature data on vaccine safety and efficacy in IMID patients treated with immunosuppressive or immunomodulatory drugs and formulates best-practice recommendations on vaccination in this population. Especially in the current era of biological therapies, including TNF-blocking agents, special consideration should be given to vaccination strategies in IMID patients. Clinical evidence indicates that immunization of IMID patients does not increase clinical or laboratory parameters of disease activity. Live vaccines are contraindicated in immunocompromized individuals, but non-live vaccines can safely be given. Although the reduced quality of the immune response in patients under immunotherapy may have a negative impact on vaccination efficacy in this population, adequate humoral response to vaccination in IMID patients has been demonstrated for hepatitis B, influenza and pneumococcal vaccination. Vaccination status is best checked and updated before the start of immunomodulatory therapy: live vaccines are not contraindicated at that time and inactivated vaccines elicit an optimal immune response in immunocompetent individuals.

Key words: Vaccination, Immune-mediated inflammatory disease, Infection, Vaccine-preventable disease, Rheumatoid arthritis, Inflammatory bowel disease, Psoriasis, Review.

REVIEW

Introduction

The term immune-mediated inflammatory disease (IMID) covers a group of apparently unrelated diseases affecting various organs and systems, such as RA, IBD and psoriasis. However, these disorders share some common genetic predispositions and inflammatory pathways, characterized by cytokine dysregulation. Hence, similar anti-inflammatory treatment strategies, including administration of immunosuppressive or immunomodulatory agents (hereafter named immunotherapy), are used to treat these disorders [1].

Vaccination is a proven and well-established strategy for prevention of infectious diseases in the general population and in patients with IMID, who have an increased risk of complications for some vaccine-preventable infections, due to both the nature of the disease and its immunomodulatory treatment. In this article, we aim (i) to summarize current scientific evidence about infection risk, vaccine safety and efficacy in patients with IMID and treatment-induced impaired immune competence and (ii) to provide clinicians with a conceptual framework and best practice recommendations on vaccine-preventable diseases in this patient population.

Literature search and selection

The Medline database was searched through PubMed, using the following key words, individually and in combination: ‘rheumatic disease’, ‘psoriasis’, ‘inflammatory

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bowel disease', 'vaccine safety', 'vaccine efficacy', 'immunization', 'vaccination', 'autoimmunity', 'infection' and 'guidelines'. Additional searches included the key words mentioned above in combination with the names of specific vaccines or drugs. Additionally, the European Centre for Disease Prevention and Control, the Centers for Disease control (CDC), the British Society of Rheumatology (BSR) and the World Health Organization (WHO) web sites and publications were consulted for recent papers and recommendations regarding immunocompromized patients and immunization. The reference lists of retrieved articles were handsearched for relevant publications.

Levels of evidence. The recommendations made in this article are graded (Levels A–D) according to the classification scheme of Shekelle *et al.* [2], depending on the level of evidence supporting the recommendation.

IMID patients are at increased risk of vaccine-preventable disease

Infectious disease is the net result of exposure to a pathogen and the subsequent reaction of the host's defence mechanisms. Since the immune response in patients with IMID may be subdued, due to immunological changes intrinsic to immune-mediated diseases and immunotherapy, IMID patients may be at increased risk of infection [3].

IMID and the directly linked infection risk

A comprehensive population-based retrospective study comparing RA patients with matched controls reported a nearly doubled incidence of documented infections in RA patients [4], although evidence allowing to distinguish between increased infection risk due to the disease and its treatment is sparse. RA-associated changes in cellular immunity may predispose RA patients to infection [5]. Early reports suggest that RA intrinsically entails an elevated susceptibility to infection [4, 6]. Predictive factors for serious infection episodes in RA patients include RA severity indices, such as presence of RF, increased sedimentation rate and extra-articular involvement, as well as corticosteroid use and the presence of comorbidities [7]. The excess mortality described in RA is partly attributable to infection, with reported standardized mortality rates due to infection in RA patients ranging from 4.2 to 14.9 [8].

In SLE, infectious complications occur in 25–45% of patients, and up to 50% of the mortality is attributed to infection. The increased infection rate in SLE patients is at least partly related to immunological defects such as complement deficiencies [9, 10].

In IBD, infections are over-represented as a cause of death [11, 12]. Whether infections are implicated in the onset of the disease is still a matter of debate [13]. Nevertheless, decreased intestinal barrier function, immune deficiencies (deficiency in the defensin system, macrophage immunodeficiency [14]) and malnutrition [15] may contribute to the higher susceptibility of IBD patients to certain infections. Abdominal sepsis may occur as a direct complication of the disease.

For psoriasis, one study suggests that psoriasis patients are at increased risk for pneumonia and systemic viral infections [16], whereas increased post-operative infection risk after orthopaedic surgery—as a surrogate marker of immune competence—is controversial in psoriasis patients [17]. Increased susceptibility to infection in psoriasis patients thus remains a matter of debate.

Effect of immunotherapy on the risk of infection in IMID

Treatment of IMID patients with corticosteroids, immunosuppressive drugs and targeted biological therapies such as TNF blockers are the most important factors leading to immunosuppression. IMID patients treated with immunotherapy must be regarded as immunocompromized individuals, although the extent to which immune competence is impaired depends on the type and dose of medication used, as well as the duration of therapy. Immunotherapy predominantly impairs cellular immunity, leaving the humoral immune response more or less intact. Experience in transplant medicine indicates that the risk of infection under immunotherapy varies with the degree of immunosuppression [18]. Unfortunately, up to now no clinical or laboratory measurements allow accurate assessment of the immune status in order to identify patients at increased risk of infectious complications. Cytokine profiling techniques may hold a promise for the future in this respect [19]. Table 1 gives an overview of the different classes of drugs used for treating IMID patients and their effect on the immune system.

The use of corticosteroids has long been known to increase the risk of infection. The degree of immunosuppression caused by corticosteroid therapy increases with the dose and duration of treatment. Treatment >2 weeks with >20 mg/day of prednisolone is commonly considered to induce clinically significant immunosuppression [20], whereas a meta-analysis showed that cumulative doses of <500 mg or mean daily doses of <10 mg are not associated with increased incidence of infectious complications and can be considered as not immunosuppressive [21].

In RA patients, corticosteroids significantly increase the risk of infection, with relative risks of 1.15 and 1.9 for mild and serious infections, respectively. The combined use of corticosteroids and conventional DMARDs yielded a comparably increased infection risk, whereas non-biological DMARD therapy alone was not associated with increased risk of infection [7, 22], although some of these compounds have well-known negative effects on the immune system.

Lacaille *et al.* [22] reported no elevated risk of infection under MTX, whereas a case–control study reported a small increase of the risk for pneumonia [23]. In the latter study, cyclophosphamide and corticosteroids were associated with the highest infection risk, whereas moderate risk was observed under AZA. HCQ,

Table 1 Immunomodulatory drugs commonly used to treat IMID

Drug class	Drug	Immunosuppressive effect [20]	Remarks
NSAIDs		–	
Corticosteroids		+	Immunosuppressive dose: >20 mg/day of prednisone or equivalent for >2 weeks [97] Not immunosuppressive doses: <10 mg/day or cumulative doses <500 mg [21]
DMARDs	SSZ; 5-ASA	–	Immunomodulator in arthritis and IBD
	Gold salts	–	Anti-inflammatory mechanism unclear [98]
	HCQ	–	Blocks Toll-like receptor on dendritic cells
	Cyclophosphamide	+	Alkylating agent
	MTX	+	Anti-metabolite, folate antagonist, immunomodulator
	LEF	+	Anti-proliferative agent, inhibits pyrimidine synthesis
	AZA	+	Anti-proliferative agent, purine synthesis inhibitor
	Ciclosporin	+	Calcineurin inhibitor, transplant-related immunosuppressive drug
Anti-psoriatic drugs	Acitretin	–	Second-generation retinoid
	Fumarate	–	Anti-inflammatory and anti-proliferative action
Anti-TNF-α agents	Infliximab	+	Chimaeric monoclonal anti-TNF antibody
	Adalimumab	+	Human monoclonal anti-TNF antibody
	Etanercept	+	TNF receptor–immunoglobin G fusion protein
	Certolizumab	+	PEGylated Fab fragment of a humanized anti-TNF monoclonal antibody
	Golimumab	+	Human monoclonal anti-TNF antibody
Other biologicals	Anakinra	+	IL-1 receptor antagonist, blocks IL-1 signalling
	Rituximab	+	Anti-CD-20, reduces B-cell number
	Abatacept	+	Anti-CTLA4, blocks T-cell co-stimulation
	Tocilizumab	+	Anti-IL-6 receptor
	Alefacept	+	LFA-3 immunoglobin G fusion protein, binds to CD2, reduces T cells number
	Efalizumab	+	Anti-CD-11, blocks leucocyte adhesion and T-cell activation
	Ustekinumab	+	Anti-p40 subunit of IL-12 and IL-23

5-ASA: 5-aminosalicylic acid; CD: cluster of differentiation; COX-2: cyclo-oxygenase-2; CTLA4: cytotoxic T-lymphocyte antigen 4; LFA-3: lymphocyte function-associated antigen-3.

chloroquine and SSZ did not increase the risk of serious infections [23].

Biologicals revolutionized the treatment of IMID, but the altered immune response to which they thank their therapeutic effect also leads to an increased risk of infection (reviewed in [24, 25]). In RA, TNF inhibitors are associated with an increased risk of infection *vs* conventional DMARDs [25]. A retrospective study of infection risk under anti-TNF therapy in clinical practice revealed infection rates [increasing from 3.4 (38.7) per 100 patient-years before to 10.5 (86.9) during anti-TNF-therapy] well above those reported in the registration trials for those products [26]. The limited data available on abatacept and rituximab suggest that the risk of infections and serious infections with these products may be more limited or similar to that of the TNF inhibitors [25]. A study comparing abatacept or infliximab with placebo suggested a more favourable safety profile of abatacept, with fewer serious infections in the abatacept group [27]. In Crohn's disease, both registries and clinical practice in large referral centres have only shown a slight increase of severe infection under immunotherapy [28–30]. Infections seem to be mostly attributed to steroids; combination of immunomodulatory treatments increases significantly the risk for infection [31, 32].

Vaccination strategy in patients with IMID

IMID patients, in particular those under immunotherapy, are at an increased risk for complications of some vaccine-preventable infections (Table 2). Hence, for this patient population the benefits of implementing a suitable vaccination protocol in daily clinical practice are potentially even greater than for the general population. When vaccination coverage in the population is high, herd immunity grants a certain extent of protection to non-vaccinated individuals by reducing the prevalence of the disease. The infection risk in non-vaccinated individuals is not negligible; however, a recent study demonstrated that non-vaccinated children in the USA have a 35 times increased risk of contracting measles in comparison with vaccinated children [33]. These findings stress the important task that clinicians have to advocate

Table 2 Recommendations for vaccination of IMID patients

Vaccination	Live vaccine	Severity of infection in IMID	Recommended in IMID patients				Remarks
			CDC [68]	BSR [99]	ECCO [95]	APF [100]	
Routine vaccinations							
Tetanus	No	=	✓	✓	✓	✓	Every 10 years
Diphteria	No	=	✓	✓	✓	✓	Every 10 years
Pertussis	No	=	✓	✓	✓	✓	One booster in adulthood
Poliomyelitis	No/Yes	=	✓	✓	✓	✓	Use inactivated vaccine in IMID patients and their household contacts. Live vaccine should not be given to immunocompromised hosts or their household contacts.
MMR	Yes	↑ (measles)	×	×	×	×	MMR vaccination is contraindicated in immunocompromised patients but not in household contacts. Test serology in case of exposure in patients that were immunized in childhood or before start of therapy [97].
Vaccination in selected groups							
Pneumococcal disease	No	↑ (↑ mortality)	✓	✓	✓		Initial dose followed by booster after 5 years
Influenza	No	↑ (↑ mortality)	✓	✓	✓	✓	Yearly
Others							
Human papilloma virus	No	↑ (↑ morbidity)			✓		
Varicella/zoster	Yes	↑ (↑ mortality)	✓	✓	✓		In rheumatology, low-dose immunomodulatory drugs[a] are not considered severely immunosuppressive and are not contraindications for the herpes zoster vaccine [94].
Hepatitis B	No	↑ (↑ morbidity)	(✓) CDC [20]	(✓) ACS [97]			
Travel-related vaccines							
Hepatitis A	No	=		✓			Recommended for mild to moderately immunosuppressed patients in/travelling to endemic countries; immunoglobulins are recommended for more severely immunocompromised patients travelling to high-risk destinations [97].
Typhoid fever	Yes/no	Unknown					Use the Vi capsular polysaccharide vaccine instead of the live vaccine in immunocompromised patients.
Yellow fever	Yes	Unknown	×	×			Contraindicated in immunocompromised individuals. For travel to some countries that require yellow fever vaccination, a waiver letter can be provided. In combination with rigorous mosquito protection measures.
Japanese encephalitis	No	=	✓	✓			
Meningococcal meningitis	No	Unknown	✓	✓			Quadrivalent conjugate vaccine
Tick-born encephalitis	No	Unknown					
Rage	No	=					Rarely indicated
TBC/BCG	Yes	↑	×	×			Contraindicated in immunocompromised individuals. No contra-indication for household contacts [68].
Cholera	Yes/no	Unknown					Rarely indicated; use the combined B subunit and killed whole-cell vaccine if necessary [97].

The risk associated with the infectious disease in IMID patients in comparison with controls is indicated as '=' (comparable) or '↑' (increased). [a]Low-dose immunomodulatory drugs include: MTX <0.4 mg/kg/week, AZA ⩽3.0 mg/kg/day, 6-mercaptopurine ⩽1.5 mg/kg/day [95]. ✓: recommended vaccination; ×: contraindicated vaccination; ACS: Advisory Committee Statement; APF: American Psoriasis Foundation; BCG: Bacillus Calmette-Guérin; ECCO: European Crohn and Colitis Organisation; MMR: measles mumps and rubella; TBC: Tuberculosis.

vaccination, especially for patients with increased risk of infectious complications.

However, vaccination coverage of IMID patients is surprisingly low. In RA patients, vaccination coverage rates rarely exceed those in the general population [34]. A survey in IBD patients revealed that only 45% of respondents recalled tetanus immunization within the past 10 years, only 28% reported yearly influenza vaccination, 9% reported having received pneumococcal vaccine and only approximately half the patients at risk were vaccinated against hepatitis B [35].

Possible explanations for under-vaccination of IMID patients are unawareness of the increased infection risk, and concerns about safety and efficacy of vaccination in this patient group. Factors to consider when evaluating the safety of a vaccine in IMID patients are the hypothetical risk for a flare of the IMID after vaccination and, for live vaccines, the risk of vaccine-induced infections. The reluctance of clinicians to vaccinate IMID patients may be due to fear of vaccine-induced disease flares, and to the concern whether the lower immune response observed in IMID patients treated with immunomodulatory drugs still provides sufficient protection against the disease.

Types of vaccines

Available vaccines can be categorized into inactivated or inert vaccines *vs* live vaccines (Table 3). Live vaccines have the advantage of providing good protection rates, as they reproduce the natural infection, with active virus replication and exposure of the vaccine to a large number of immunogenic epitopes, thereby inducing a fast antibody response and good immunological memory. Disadvantages of live vaccines include the risk for transmission and persistence of the virus, risk for back-mutation to a more virulent virus and more stringent transport and storage requirements.

Inactivated vaccines have indisputable advantages in terms of safety since they do not contain infectious agents and are easier to transport and store. However, they provide a less close imitation of natural infection (no replication, no intracellular penetration and limited number of epitopes in recombinant vaccines), and may therefore need adjuvants and repeated exposure (boosters) in order to induce an adequately protective immune response.

Vaccine safety: impact on disease activity in IMID patients

Part of clinicians' concerns about the safety of vaccination in IMID originated from a number of case reports suggesting an impact of vaccination on IMID disease onset or course [36, 37]. These publications led to a belief among some clinicians that vaccination might trigger a flare of the underlying IMID. Despite substantial research, a direct and causal relationship between vaccination and flare of disease has not been detected [36, 38, 40–59]. Live vaccines are generally contraindicated in immunocompromized individuals, so reports dealing with their effect on disease activity are rare. In a relatively small retrospective study, measles–mumps–rubella (MMR) booster vaccination in children with juvenile idiopathic arthritis (JIA) appeared safe, as vaccination did not induce infection, nor did it significantly increase disease activity or medication use [39, 40].

For non-live vaccines, substantial literature data (summarized in Table 4) supports the conclusion that

Table 3 Types of vaccines

Type of vaccine	Example	Description
Inactivated or inert vaccines		
Chemically or thermally inactivated	Salk poliomyelitis vaccine	Chemical inactivation with formaldehyde or β-propriolactone; physical inactivation by exposure to high temperature or UV irradiation
Split virion or subunit vaccine	Most influenza vaccines	Contains only part of the virion
Recombinant vaccine	Hepatitis B	Virus proteins produced with recombinant DNA technique
Virus-like particle vaccine	Human papillomavirus	Consists of virus proteins without nucleic acid assembled into a virion-like particle
Live vaccines		
Related non-human virus	Vaccinia Bovine rotavirus W3	
Attenuated virus	Measles	Attenuation is achieved by passaging in non-natural host cells or when the vaccine administration route is different from that of the natural infection
	Mumps Rubella Yellow fever Oral poliomyelitis Varicella zoster vaccine	
Temperature-sensitive mutant	Flumist influenza virus	This virus strain replicates at 25°C (intranasal administration) but not at 37°C (in the lungs)

Non-exhaustive table, illustrating the different vaccine types with one or more examples.

immunization of IMID patients does not increase clinical or laboratory parameters of disease activity. Most of this evidence comes from medium-sized controlled trials in which disease activity was mostly assessed by general clinical symptoms and pain scores. Some studies additionally used standardized clinical disease activity scores such as DAS or SLEDAI. Laboratory measurements minimally included sedimentation rate or CRP in some studies supplemented with more specialized disease activity markers. This evidence indicates that inactivated vaccines for hepatitis B, influenza and pneumococcal disease can be administered safely to IMID patients (evidence Level B, except for hepatitis B vaccination in SLE: Level C, influenza vaccination in RA: Level A).

Vaccine safety: induction of IMID

A particular concern that certainly contributes to the reticence of clinicians to actively promote vaccination in IMID patients are the reports of a temporal association between vaccination and new onset of autoimmune disease [41], suggesting that vaccination acts as a potential trigger of autoimmune disease.

In this context, it is important to distinguish autoimmunity, which is an abnormal immune response directed against host antigens, involving production of autoantibodies or the presence of autoreactive T cells, without clear symptoms of disease nor evolution towards an IMID, from autoimmune disease itself [41]. Autoimmunity results from complex interactions between genetic traits and environmental factors and can be triggered by a number of stimuli, including local inflammation as well as viral, bacterial and parasitic infections [42]. Vaccination could trigger autoimmunity through the same mechanisms as natural infection.

In 1976, a number of cases of Guillain–Barré syndrome occurred after swine flu vaccination [43]. This phenomenon was not repeated in subsequent influenza virus campaigns [44]. The risk for Guillain–Barré syndrome after influenza vaccination is now estimated to be lower than the risk resulting from severe influenza, and is not to be considered as an argument against influenza vaccination [45]. In the 1990s, extensive epidemiological research in France, where 25 million people (40% of the population) received hepatitis B vaccination in this period, did not observe an association between hepatitis B vaccination and multiple sclerosis [46] as suggested by earlier case reports [38, 41, 47].

The incidence of idiopathic thrombocytopenia following MMR vaccination is 1/30 000 in vaccinated children. However, the risk of developing thrombocytopenia after natural measles and rubella infection amounts to 1/3000 and 1/6000, respectively [48].

Incidence of joint symptoms after MMR vaccination is slightly increased, but still lower than that after natural rubella infection [49]. A transient increase in RF levels or arthritis symptoms has been reported after immunization against a number of agents (MMR, tetanus, paratyphoid, mumps, diphtheria, polio, smallpox and hepatitis B), but the incidence of RA among the vaccinated population was similar to non-vaccinated controls [50]. After extensive review of available studies, French pharmacovigilance [51] and the WHO advisory committee on Vaccine Safety [52] concluded that there is no convincing evidence of causal relationship between hepatitis B vaccination and a number of reported RA cases [37, 53–55].

In IBD, the observation that measles virus can persist in intestinal tissue [56], in combination with the epidemiological association of *in utero* [57] or perinatal [58] measles infection with subsequent Crohn's disease, led to the refractory 'measles hypothesis' of Crohn's disease. The elevated risk for development of IBD in subjects vaccinated against measles in a controversial study by Thompson *et al.* [59] was not confirmed in subsequent studies [60–62]. Available evidence does not support an association between measles-containing vaccines and risk of IBD [63]. A potential association between Bacille Calmette–Guérin (BCG) vaccination and Crohn's disease still needs further investigation [64, 65].

Extremely rare cases of psoriasis or psoriasis-like esions have been reported following BCG vaccination [66], and a case–control study reported rubella vaccination as a risk factor for PsA [67]. However, these data must also be seen in relationship with the well-known Köbner phenomenon that occurs in psoriasis, i.e. the development of new plaques at sites of skin injury. In this

Table 4 Effect of vaccination (non-live vaccines) on IMID disease activity

Vaccine	Disease activity	RA	JIA	SLE	IBD
Hepatitis B	=	Clin, Lab (CCT) [74]	Clin (CCT) [101]	Clin, Lab (UCT) [75]	
Pneumococcal vaccine	=	Clin, Lab (CCT) [77]		Clin, Lab (CCT) [77] Clin, Lab (UCT) [102]	
Influenza	=	Clin, Lab (RCT) [103] Clin, Lab (CCT) [84, 86, 88, 93]		Clin, Lab (CCT) [86] Clin (UCT) [87]	Clin (CCT) [89]

Summary of literature data on the effect of vaccination on IMID disease activity. '=' indicates no significant effect. Non-live vaccines are well-tolerated in IMID patients and do not increase either clinical (Clin) or laboratory (Lab) markers of disease activity. Study design is recorded in parentheses: CCT: controlled clinical trial; UCT: uncontrolled clinical trial; RCT: randomized controlled trial.

respect, the vaccination act itself could trigger exacerbation of psoriatic skin lesions [67].

Vaccine safety: infection with live vaccines

The main safety issue in vaccination of IMID patients concerns the use of live vaccines: like in other groups of immunocompromized individuals, the use of live vaccines is contraindicated in IMID patients treated with immunomodulatory drugs [68]. Immunocompromized individuals are not capable to mount an adequate immune response towards the vaccine virus and have an increased risk of enhanced virus replication, possibly leading to persistence of the virus or even to overt vaccine-associated disease. Caution should also be exerted when vaccinating household contacts of IMID patients with live vaccines, since virus replication after vaccination is often accompanied by shedding of the virus, with possible subsequent infection of patients. Transmission of vaccine virus to household contacts increases disease protection coverage beyond vaccination coverage in the general population, but for severely immunocompromized individuals this may pose a risk of developing infectious disease with the vaccine virus. Spreading of the vaccine virus to household contacts has been described after oral poliomyelitis vaccination [69], which is therefore contraindicated for household contacts of IMID patients [68], and after rotavirus vaccination [70]. MMR, varicella, zoster and BCG vaccination are not contraindicated for household contacts of IMID patients [68].

Vaccine efficacy in IMID patients

Vaccine efficacy is defined as percentual risk reduction for clinically significant infection in a vaccinated group *vs* a control group [71]. Efficacy of a vaccine is preferably demonstrated through well-conducted and well-controlled field efficacy trials, evaluating different possible end points (infection, hospitalization and death) in different settings and populations. However, field efficacy data are not always available. In that case, demonstration of B-cell-generated antibodies is often used as a surrogate marker for vaccination-induced protection, because most vaccines protect against infection or disease by inducing a B-cell antibody response. In addition to seroconversion, which indicates the presence of an antibody response, the antibody titre as well as the quality of the antibody response (in terms of binding avidity and bactericidal or neutralizing activity of antibodies) are important as predictors of protection. Although antibody production accounts for the largest part of the protective response, cellular immune response is very important for immunological memory, and contributes substantially to the protection induced by some vaccines such as the influenza, varicella zoster and BCG vaccines [72].

The reduced quality of the immune response in IMID patients, especially in those under immunotherapy, may thus have a negative effect on the efficacy of vaccination. Reduced seroconversion rates after vaccination in IMID patients may reduce the proportion of protected patients. Diminished quantity or quality of the antibody response may reduce the duration of protection provided by vaccination in individual patients, thus requiring shorter vaccination intervals or additional boosters.

Table 5 summarizes the current evidence on antibody response after vaccination in IMID patients for different vaccines and treatment options. In a normal population, a humoral immune response to hepatitis B vaccination is expected in >90% of vaccines, whereas lower immune response rates have been described in immunocompromized patients [73]. The percentage of RA and SLE patients producing HBsAg antibodies after hepatitis B vaccination was found to be in the normal range [74, 75]. Classical DMARDs do not have a negative influence on the response to hepatitis B vaccination (for RA and JIA: evidence Level B), but etanercept and the combination of etanercept and MTX significantly decrease response rates to hepatitis B vaccination (for RA, evidence Level B). The effect of the newer biologicals on the immune response after hepatitis B vaccination remains to be investigated.

For the polysaccharide pneumococcal vaccine, vaccine response rates in RA and SLE patients were similar to those in control populations. However, a subset of patients will remain unprotected after vaccination, since a small percentage of patients responded to none or only one of the seven polysaccharide antigens [76–78].

TNF-α inhibitors do not impair the response to pneumococcal vaccination, but MTX decreases the response rates to this vaccine [76, 77, 79]. A recent study by Melmed *et al.* [80] shows a normal pneumococcal vaccination response in IBD patients without immunosuppressive therapy and impaired vaccination responsiveness in patients treated with TNF blockers in combination with other immunomodulators (MTX, 6-mercaptopurine or AZA). The B-cell targeting antibody rituximab in combination with MTX significantly reduced the percentage of patients responding to pneumococcal vaccination with a 2-fold titre rise in comparison with patients treated with MTX alone [81]. Efalizumab had no negative influence on the responsiveness towards pneumococcal vaccination in psoriasis patients [82], whereas abatacept caused impaired responsiveness in healthy controls [83].

Influenza vaccination of RA patients generates a good humoral response [84], lower than [84] or comparable with [85, 86] healthy controls. The response to influenza vaccination was not affected by the use of prednisone or DMARDs [84]. Treatment with anti-TNF antibodies only modestly decreases the antibody response to influenza vaccination: anti-TNF treatment does not significantly decrease the proportion of IMID patients reaching a protective antibody titre after vaccination, but does lower the post-vaccination geometric mean antibody titres reached [85]. In SLE patients without prior vaccination, the percentage of seroconversions or 4-fold titre rises after influenza vaccination was lower in comparison with controls; vaccination response was not influenced by treatment with immunosuppressive agents (AZA, HCQ, prednisone) [87]. However, a seroconversion rate comparable with that in the control population was observed

Table 5 Efficacy of vaccines in IMID patients

Drug	Vaccine		
	Hepatitis B	Pneumococcal	Influenza
DMARDs			
AZA	= RA (CCT) [74]		= RA (RCT) [103], (CCT) [86] ↓ IBD (CCT) [89] ↓ SLE (UCT) [87]
CSA	= RA (CCT) [74] = JIA (CCT) [101]		= RA (RCT) [103] (CCT) [86]
MTX	= RA (CCT) [74, 104] = JIA (CCT) [101]	↓ RA (CCT) [76] ↓ PsA (RCT) [79] ↓ RA, SLE (CCT) [77]	= RA (RCT) [93, 103] = RA (CCT) [84, 86, 91]
Biologicals			
MTX + Anti-TNF-α agents	↓ RA (CCT) [104]	= RA (RCT) [105, 106], (CCT) [76] PsA (RCT) [79]	↓ RA (CCT) [91]
Anti-TNF-α agents	↓ RA (CCT) *ETA* [104]	↓ RA, SA (CCT) *ETA, IFX* [107] = PsA, (RCT) *ETA* [79]	= RA (RCT) *ADA* [105] ↓ RA (CCT) [88] ↓ RA (CCT) *IFX, ETA* [84] ↓ RA (CCT) [91] ↓ RA/IBD (PC) [85] ↓ IBD (PC) [90]
Rituximab		↓ RA (RCT) [81]	↓ RA (CCT) [92, 93]
Abatacept		↓ Healthy controls (RCT) [83]	
Efalizumab		= Psor (RCT) [82]	

Summary of the effect of different treatments on the response to vaccination. Vaccination response is indicated as '=' or '↓' as measured by the percentage of patients with seroconversion, by antibody titre or a combination of both. Study design is recorded in parentheses: CCT: controlled clinical trial; PC: prospective cohort study; UCT: uncontrolled clinical trial; RCT: randomized controlled trial. Italics indicate effect of individual TNF inhibitors. When no products are mentioned, the study did not distinguish between different TNF inhibitors. ETA: etanercept; IFX: infliximab; Psor: psoriasis.

when all SLE patients, including those with prior influenza vaccination, were taken into account. This finding clearly illustrates the importance of yearly repeated influenza vaccination [87]. Salemi *et al.* [88] recently reported year-to-year progressive increase in immune response in RA patients treated with TNF blockers.

Mamula *et al.* [89] observed a reduced seroconversion rate and geometric mean titre after influenza vaccination in IBD patients receiving immunotherapy (including biological therapy) compared with healthy controls, whereas vaccine response rates in patients without immunotherapy were similar to those in controls. A good seroconversion rate was observed in another study evaluating influenza vaccine in children with IBD [90]. Some studies observed an impaired immune response after influenza vaccination in patients treated with anti-TNF agents [89, 91], but all studies report a significant percentage of responders in anti-TNF-treated patients [85, 88, 91]. Rituximab significantly reduces seroconversion rates after influenza vaccination of RA patients [92, 93], and the immune responsiveness is only modestly restored after 6–10 months [93]. The effect of abatacept and efalizumab on the responsiveness to influenza vaccination is still unknown. Although the studies described here are heterogeneous in design, evaluated parameters of vaccine responsiveness and control groups, they all conclude that a considerable proportion of IMID patients are able to respond to hepatitis B, pneumococcal and influenza vaccination, so as to warrant the administration of these vaccines to IMID patients (evidence Level B).

Recommendations for vaccination of IMID patients

Except for live vaccines, the risk : benefit ratio for vaccination of IMID patients with reduced immune competence is favourable. For most vaccine-preventable diseases, IMID patients are at comparable or elevated risk of infection, and vaccination is generally able to elicit a protective humoral immune response in most patients (evidence Level B), although the fraction of protected patients, as well as the antibody titre and duration of protection may be lower in IMID patients, especially those under immunotherapy, in comparison with the general population.

General recommendations

A detailed overview of vaccination recommendations for IMID patients is given in Table 2. As in the general population, the immunization status of patients with IMID should be checked and vaccination considered for tetanus, diphtheria and pertussis (evidence Level B). Influenza, pneumococcal and hepatitis B vaccines are safe and generally sufficiently immunogenic in patients with IMID (evidence Level B).

Live vaccines (MMR, oral poliomyelitis vaccine, yellow fever and varicella zoster) are contraindicated in IMID patients under immunotherapy (evidence Level B). Although the varicella zoster vaccine is a live vaccine and is as such contraindicated in immunocompromized individuals, some consider the risk : benefit ratio for this vaccine beneficial for patients on low-dose immunotherapy [94], especially since rescue therapy with acyclovir is possible in case of virus persistence or infectious symptoms after varicella zoster vaccination [94].

Inactivated travel-related vaccines can be administered safely to IMID patients, although protection against disease cannot always be guaranteed (evidence Level B). Yellow fever vaccination is contraindicated in immunocompromized patients, since it is a live vaccine (evidence Level B). Vaccination for patients on immunotherapy travelling to countries or regions with increased infection pressure or frequently travelling around the world should be discussed with a specialist in travel medicine.

Timing of vaccination

Vaccination status is best checked and updated before the start of immunotherapy: live vaccines are not contraindicated at that time and inactivated vaccines elicit an optimal immune response in immunocompetent individuals. In IBD, it has even been suggested to vaccinate at the time of diagnosis, particularly in patients with risk factors for a rapid evolution towards severe disease requiring immunosuppressive therapies [95]. Inactivated vaccines can be administered safely to patients under immunotherapy, but live vaccines must be given 3–4 weeks before (re)start of therapy, to ensure that virus replication has ended before impairing the patient's immune competence [68] (evidence Level D).

The duration of therapy discontinuation needed in order to safely administer a live vaccine depends on the type, dose and duration of the therapy. As a rule of thumb, a period of 3 months is estimated for the immune status to be completely restored (evidence Level D), except for corticosteroid therapy, where a waiting period of 1 month is thought to be sufficient (evidence Level D).

Vaccination of household contacts

Close contacts of persons with altered immune competence can safely receive all age-appropriate vaccines (evidence Level B), with the exception of live oral poliomyelitis vaccine, which has been replaced by the injectable inactivated vaccine in industrialized countries. MMR, varicella and rotavirus vaccines should be administered when indicated. MMR vaccine viruses are not transmitted to contacts, and transmission of varicella vaccine is rare [68]. The risk of rotavirus transmission to immunocompromized household contacts is estimated to be much lower than the risk of contracting wild-type rotavirus infection [70]. However, to minimize potential rotavirus transmission, hand hygiene measures after contact with faeces of a rotavirus-vaccinated infant should last for at least 1 week [68, 96].

In summary, vaccination is a very valuable measure to prevent increased morbidity and mortality from vaccine-preventable disease in the IMID population that is at increased risk for a number of vaccine-preventable diseases. Vaccinations are best given to IMID patients before introduction of immunotherapy, since live vaccines

(MMR, BCG and yellow fever) are generally contraindicated during immunotherapy and vaccine response is optimal in immunocompetent individuals. Vaccination with inactive vaccines can be given normally in these patients, keeping in mind that—depending on the degree of immunosuppression—the response to the vaccine and potentially the period of protection are more limited in these patients. Vaccines for patients on immunotherapy travelling to endemic countries or frequently travelling around the world should be discussed with a travel medicine specialist.

Rheumatology key messages

- Patients with immune-mediated inflammatory disease are at increased risk for a number of vaccine-preventable diseases.
- Inactive vaccines are considered safe and generally effective in IMID patients.
- Live vaccines are contraindicated in IMID patients under immunosuppressive therapy.

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