

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

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ABSTRACT

Objectives To develop evidence-based European League Against Rheumatism (EULAR) recommendations for vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD).

Methods A EULAR task force was composed of experts representing 11 European countries, consisting of eight rheumatologists, four clinical immunologists, one rheumatologist/clinical immunologist, one infectious disease physician, one nephrologist, one paediatrician/rheumatologist and one clinical epidemiologist. Key questions were formulated and the eligible spectrum of AIIRD, immunosuppressive drugs and vaccines were defined in order to perform a systematic literature review. A search was made of Medline from 1966 to October 2009 as well as abstracts from the EULAR meetings of 2008 and 2009 and the American College of Rheumatology (ACR) meetings of 2007 and 2008. Evidence was graded in categories I–IV, the strength of recommendations was graded in categories A–D and Delphi voting was applied to determine the level of agreement between the experts of the task force.

Results Eight key questions and 13 recommendations addressing vaccination in patients with AIIRD were formulated. The strength of each recommendation was determined. Delphi voting revealed a very high level of agreement with the recommendations among the experts of the task force. Finally, a research agenda was proposed.

Conclusion Recommendations for vaccination in patients with AIIRD based on the currently available evidence and expert opinion were formulated. More research is needed, particularly regarding the incidence of vaccine-preventable infectious diseases and the safety of vaccination in patients with AIIRD.

Patients with autoimmune inflammatory rheumatic diseases (AIIRD) are at increased risk of contracting infections.^{1–10} The increased susceptibility to infection can be attributed to by any of the following: the immunosuppressive effect of the underlying AIIRD, the occurrence of a ‘locus minoris resistentiae’ as a sequel of the AIIRD and the use of immunomodulatory medication to treat the AIIRD. The possible contribution of biological agents to the risk of infection is of particular interest, especially since increasingly more indications are being recognised for their use, they are increasingly being used earlier in the course of AIIRD and newer agents are becoming available.^{11–23}

Vaccination is an attractive method to prevent certain infections. The efficacy of vaccinations in patients with AIIRD, however, may be reduced and there is a potential risk of flares of the underlying AIIRD following vaccination.

Our aim was to develop recommendations for vaccination in patients with AIIRD in line with the standard operating procedures of the European League Against Rheumatism (EULAR), combining evidence from clinical studies with expert opinion when sufficient evidence was lacking. Our recommendations target all physicians and nurses who are involved in the care for patients with AIIRD.

METHODS

Expert Committee

The committee consisted of eight rheumatologists (OE, MFD, MD, PE, PG, UML, LS, GV), four clinical immunologists (NAL, RC, CGMK, YS), one rheumatologist/clinical immunologist (MB), one infectious disease physician (SvA), one nephrologist (DRWJ), one paediatrician/rheumatologist (NMW) and one clinical epidemiologist (JPAI), representing 11 European countries.

Definitions

In these recommendations, the term ‘efficacy’ represents the capability of a vaccine to mount a protective immune response because vaccination studies in patients with AIIRD addressing clinical end points are scarce. Moreover, it should be acknowledged that in vitro immune responses may not always correlate well with clinical effectiveness. This should be taken into account when interpreting the available evidence for these recommendations.

Development of recommendations

The experts were invited to define the AIIRD, the vaccines and the immunosuppressive medications which were to be used as search terms for the systematic literature review. Furthermore, key questions regarding vaccination of patients with AIIRD were formulated.

Medline (via PubMed) was searched from 1966 to October 2009 as well as the abstracts from the meetings of EULAR 2008 and 2009 and of the American College of Rheumatology (ACR) 2007 and 2008. As search terms, the MESH terms for the defined AIIRD, immunosuppressive medications

and vaccines were combined. Only articles in English and concerning patients aged >16 years were included. Other papers that were considered relevant in the opinion of the experts could be added. The results of the systematic literature review (performed by SvA, MB, NAL, OE) were sent to the committee before the second meeting together with proposals for recommendations.

Thirteen recommendations were formulated. For each recommendation we used a widely-accepted hierarchy for categorising the available evidence and the strength of the recommendations (see table 1 in the online supplement). A Delphi exercise with closed voting followed. During this exercise the 13 recommendations were separately voted on and given a score from 0 (absolutely no agreement with the proposed recommendation) to 10 (maximal possible support for the recommendation). The means and SDs of the scores of the whole group were calculated to determine the level of agreement among the experts for each recommendation. Finally, a research agenda was created.

RESULTS

Twenty-seven eligible AIIRD, 17 immunosuppressive medications and 29 vaccines (table 1) were identified and eight key questions (box 1) were composed for the systematic literature review. The task force members agreed on 13 recommendations, reaching a high level of agreement according to the Delphi scores (table 2).

Recommendations

Each recommendation is followed in parenthesis with the grade of the evidence, the strength of the recommendation and the Delphi voting score.

(1) The vaccination status should be assessed in the initial work-up of patients with AIIRD (no grade of evidence possible; strength of recommendation D; Delphi vote 9.50)

In order to make recommendations for the individual patient with AIIRD, it is necessary to know which vaccines the patient received in the past according to box 2. Catch-up vaccination might be considered for missed vaccinations that are recommended for the general population. Also, adverse events and flares of the underlying AIIRD following former vaccinations should be queried since these might be (relative) contraindications for certain future vaccinations.

(2) Vaccination in patients with AIIRD should ideally be administered during stable disease (no grade of evidence possible; strength of recommendation D; Delphi vote 8.88)

No studies have been performed comparing efficacy and harms between patients with AIIRD with stable and unstable disease. Moreover, almost all vaccination studies in patients with AIIRD addressed patients with quiescent disease. Studies that also included patients with moderate or severe disease activity did not show more frequent side effects or disease flares, or decreased efficacy in patients with AIIRD compared with healthy controls.^{24–26} However, the numbers of patients in these studies were too small to conclude that vaccination during active disease is safe and efficacious. Therefore, based on theoretical risks of disease flare following vaccination in unstable patients with AIIRD, vaccination is preferentially administered during stable disease, according to expert opinion.

Table 1 AIIRD, immunomodulating agents and vaccines considered in the literature search and recommendations

AIIRD	Immunomodulating agents	Vaccines
Rheumatoid arthritis	Corticosteroids	BCG
Serum lupus erythematosus	Methotrexate	Cholera
Antiphospholipid syndrome	Sulfasalazine	Diphtheria
Adult Still disease	Leflunomide	Hepatitis A
Systemic sclerosis	Hydroxychloroquine	Hepatitis B
Sjögren syndrome	Azathioprine	<i>Haemophilus influenzae</i> b
Mixed connective tissue disease	Mycophenolic acid preparations	Human papillomavirus
Relapsing polychondritis	Ciclosporine	Influenza
Giant cell arteritis	Tacrolimus	Japanese encephalitis
Polymyalgia rheumatica	Cyclophosphamide	Measles*
Takayasu arteritis	Biologicals:	Mumps*
Polyarteritis nodosa	TNF α blocking agents	<i>Neisseria meningitidis</i> (A/C/Y/W135, C conjugated)
ANCA-associated vasculitis	Infliximab	Pertussis
Microscopic polyangiitis	Etanercept	Poliomyelitis (parenteral and oral*)
Wegener granulomatosis	Adalimumab	Rabies
Churg-Strauss syndrome	Rituximab	Rubella*
Behçet disease	Tocilizumab	<i>Streptococcus pneumoniae</i> (polysaccharide and conjugated)
Goodpasture disease	Abatacept	Tetanus toxoid
Cryoglobulinaemic syndrome	Anakinra	Tick-borne encephalitis
Polymyositis		Typhoid fever (parenteral and oral*)
Dermatomyositis		Varicella zoster*
Clinically amyopathic dermatomyositis		Yellow fever*
Sporadic inclusion body myositis		
Antisynthetase syndrome		
Eosinophilic myositis		
Eosinophilic fasciitis		
Spondylarthropathies		
Periodic fever syndromes		

*Live attenuated vaccines.

AIIRD, autoimmune inflammatory rheumatic diseases; BCG, Bacillus Calmette-Guérin.

Recommendation

(3) Live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD (grade of evidence IV; strength of recommendation D; Delphi vote 9.25)

Live attenuated vaccines (table 1) might lead to (severe) infections in immunosuppressed patients. It is not known what level

Box 1 Key questions

1. Is the risk of infections for which vaccines are available increased in patients with autoimmune inflammatory rheumatic diseases (AIIRD) in general, and specifically in those with active disease and in those using immunomodulating agents?
2. Do vaccines decrease the risk of infections in patients with AIIRD in general, and specifically in those with unstable disease and in those using immunomodulating agents?
3. Do vaccines cause any significant harm in patients with AIIRD in general, and specifically in those with unstable disease and in those using immunomodulating agents?
4. Does the timing of vaccination in relation to disease activity and receipt of immunomodulating agents affect the effectiveness of vaccination in patients with AIIRD?
5. Does the timing of vaccination in relation to disease activity and receipt of immunomodulating agents affect important harms of vaccination in patients with AIIRD?
6. Does revaccination with any vaccines increase the effectiveness in patients with AIIRD?
7. Does revaccination with any vaccine increase significant harms in patients with AIIRD?
8. Is vaccination in patients with AIIRD cost-effective?

of immunosuppression renders patients to be at risk for infections caused by these vaccines, and this risk should be balanced to the risk of (severe) infection the vaccine aims to prevent.

Measles, mumps and rubella (MMR) vaccine has been administered without subsequent infection to paediatric patients 2 years after bone marrow transplantation²⁷ and varicella vaccine has been administered without subsequent infection in HIV-infected children with a CD4 percentage $\geq 15\%$ or a CD4 count $\geq 200/\text{mm}^3$.²⁸ Studies are ongoing for herpes zoster vaccine in adult patients with HIV with a CD4 count $\geq 200/\text{mm}^3$ (<http://www.clinicaltrials.gov/ct2/show/NCT00851786?term=zostavax+hiv&rank=1>) and in older patients on treatment with prednisone 5–20 mg/day (<http://www.clinicaltrials.gov/ct2/show/NCT00546819?term=zostavax+corticosteroid&rank=1>). The Advisory Committee on Immunization Practices (ACIP) stated that herpes zoster vaccine may be administered to patients when treated with short-term corticosteroid therapy (<14 days); low to moderate doses of corticosteroids (<20 mg/day of prednisone or equivalent); intra-articular, bursal or tendon corticosteroids injections; long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids; therapy with methotrexate (MTX; <0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day) or 6-mercaptopurine (<1.5 mg/kg/day).²⁹ It must be emphasised that these recommendations are based on expert opinion only and require further investigation. The EULAR task force on vaccination recommends avoiding the use of live attenuated vaccines in immunosuppressed patients with AIIRD whenever possible. MMR, varicella and herpes zoster vaccine might be exceptions to this rule and may be considered in mildly immunosuppressed patients with AIIRD on a case-by-case basis. Temporary discontinuation of immunosuppressive medication before vaccination with live attenuated

Table 2 Recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases with level of evidence, strength of recommendations and results of Delphi voting per recommendation

Recommendation	Category of evidence			Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
	Increased incidence of VP infection	Efficacy of vaccination	Harms of vaccination		
The vaccination status should be assessed in the initial investigation of patients with AIIRD	–			D	9.50 (0.97)
Vaccination in patients with AIIRD should ideally be administered during stable disease	–			D	8.88 (1.26)
Live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD	IV			D	9.25 (1.13)
Vaccination in patients with AIIRD can be administered during the use of DMARDs and TNF α blocking agents, but should ideally be administered before starting B cell-depleting biological therapy	II			B	9.13 (1.02)
Influenza vaccination should be strongly considered for patients with AIIRD	III	Ib	Ib	B–C	9.00 (1.10)
23-valent polysaccharide pneumococcal vaccination should be strongly considered for patients with AIIRD	III	Ib	Ib	B–C	8.19 (1.38)
Patients with AIIRD should receive tetanus toxoid vaccination in accordance with recommendations for the general population. In case of major and/or contaminated wounds in patients who received rituximab within the last 24 weeks, passive immunisation with tetanus immunoglobulin should be administered	–	II	II	B–D	9.19 (1.11)
Herpes zoster vaccination may be considered in patients with AIIRD	III	–	IV	C–D	8.00 (1.59)
HPV vaccination should be considered in selected patients with AIIRD	III	–	–	C–D	8.44 (1.41)
In hyposplenic/asplenic patients with AIIRD, influenza, pneumococcal, <i>Haemophilus influenzae</i> b and meningococcal C vaccinations are recommended	IV			D	9.50 (0.82)
Hepatitis A and/or B vaccination is only recommended in patients with AIIRD at risk	–	II*	III*	D	9.13 (0.89)
Patients with AIIRD who plan to travel are recommended to receive their vaccinations according to general rules, except for live attenuated vaccines which should be avoided whenever possible in immunosuppressed patients with AIIRD	–			D	9.25 (1.24)
BCG vaccination is not recommended in patients with AIIRD	III	–	–	D	9.38 (1.09)

*For hepatitis B only

AIIRD, autoimmune inflammatory disease; BCG, Bacillus Calmette-Guérin; DMARD, disease-modifying antirheumatic drug; HPV, human papillomavirus; TNF, tumour necrosis factor; VAS, visual analogue scale; VP, vaccine-preventable.

Box 2 Vaccinations to be checked during the initial investigation (by history taking)

Haemophilus influenzae b
Hepatitis A
Hepatitis B
Human papillomavirus
Influenza
Neisseria meningitidis
Rubella (for women of childbearing age)
Streptococcus pneumoniae
Tetanus toxoid

vaccines might also be considered, but there are no studies to support this strategy.

(4) Vaccination in patients with AIIRD can be administered during the use of disease-modifying antirheumatic drugs and tumour necrosis factor α blocking agents but should ideally be administered before starting B cell depleting biological therapy (grade of evidence IIa; strength of recommendation B; Delphi vote 9.13)

The efficacy of vaccination during the use of disease-modifying antirheumatic drugs (DMARDs), glucocorticoids and/or tumour necrosis factor (TNF) α blocking agents has been studied in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ANCA-associated vasculitis (AAV) and systemic sclerosis (SSc). Influenza, pneumococcal, hepatitis B, tetanus toxoid and *Haemophilus influenzae* b vaccination were addressed. Most controlled studies showed responses in patients with AIIRD following vaccination comparable to those in healthy controls,^{24 25 30–62} while some showed slightly reduced efficacy.^{38 43 45 47 49 61 63–67} Of note, azathioprine hampered the response following influenza vaccination in patients with SLE but the majority of patients still develop protective levels of antibodies.^{63 68} The combination of TNF α blocking agents and MTX reduced the response to pneumococcal vaccination in patients with RA.^{45 67 69} Finally, humoral responses following influenza vaccination 1–3 months after treatment with rituximab^{41 70 78} as well as humoral responses following pneumococcal vaccination 28 weeks after treatment with rituximab⁷¹ are severely hampered. Tetanus toxoid vaccination led to adequate immune responses 24 weeks after rituximab administration.⁷¹ Vaccines should ideally be administered before B cell-depleting biological therapy is started or, when patients are on such a treatment already, at least 6 months after the start but 4 weeks before the next course.

(5) Inactivated influenza vaccination should be strongly considered for patients with AIIRD (grade of evidence Ib–III; strength of recommendation B–C; Delphi vote 9.00)

Although the exact incidence of influenza is unknown in patients with AIIRD, their risk of dying from pulmonary infections is increased.^{4 5 72} Influenza vaccination has been shown to reduce admissions for and mortality from influenza/pneumonia in elderly people with rheumatological diseases or vasculitis^{73 74} and is efficacious in patients with RA, SLE, AAV and SSc, even when treated with DMARDs, infliximab, etanercept or adalimumab,^{24–26 30–41 47–50 63 67 68 75–77} but with rituximab as an exception.^{41 70 78} Adverse events of influenza vaccination in patients with AIIRD seem comparable to those in healthy controls, although there are no studies that are sufficiently powered with regard to safety. This recommendation regards seasonal influenza vaccination as well as pandemic swine flu vaccination,

although no studies have been performed on efficacy and safety of swine flu vaccination in patients with AIIRD. Because some of the swine flu vaccines contain the adjuvant MF-59, an oil-in-water emulsion that potentiates the humoral response, it is reassuring that a large meta-analysis showed no difference in the occurrence of adverse events that were of autoimmune origin between persons vaccinated with influenza vaccine with and without MF-59.⁷⁹

(6) 23-valent polysaccharide pneumococcal vaccination (23-PPV) should be strongly considered for patients with AIIRD (grade of evidence Ib–III; strength of recommendation B–C; Delphi vote 8.19)

As stated above, patients with AIIRD are at increased risk of dying from pulmonary infections compared with the general population,^{2 4 5 72} with pneumococci being considered as one of the main causative pathogens. Pneumococcal vaccination induces an adequate to slightly reduced humoral response in patients with RA, SLE, psoriatic arthritis, ankylosing spondylitis and SSc, even when treated with immunosuppressive drugs.^{36 42–45 47 51–54 62 71 80} MTX, with or without TNF α blocking agents^{45 69} and, in particular, rituximab⁷¹ reduces the humoral response following pneumococcal vaccination. It is unknown if and when revaccination should take place and if the new conjugated pneumococcal vaccines, whether or not in combination with 23-PPV (so-called prime-and-boost strategy), induce more and/or more durable immunity to pneumococci in patients with AIIRD. Pneumococcal vaccination seems safe in patients with AIIRD, but again the available studies were not adequately powered for analysing safety.

(7) Patients with AIIRD should receive tetanus toxoid vaccination in accordance to recommendations for the general population. In case of major and/or contaminated wounds in patients who received rituximab within the last 24 weeks, passive immunisation with tetanus immunoglobulins should be administered (grade of evidence II; strength of recommendation B–D; Delphi vote 9.19)

In patients with RA and SLE, efficacy for tetanus toxoid vaccination has been demonstrated to be comparable with healthy controls.^{30 46 58 59} This also holds true for patients with RA on immunosuppressive drugs, including those who have been treated with rituximab 24 weeks earlier.⁷¹ However, since no data are available regarding the efficacy of tetanus toxoid vaccine within 24 weeks after treatment with rituximab,⁷¹ we recommend that patients with AIIRD who are treated with rituximab less than 24 weeks earlier be passively immunised with tetanus immunoglobulins in case of a serious risk of contracting tetanus (ie, in case of major and/or contaminated wounds).

(8) Herpes zoster vaccination may be considered in patients with AIIRD (grade of evidence III–IV; strength of recommendation C–D; Delphi vote 8.00)

Compared with the general population, patients with RA, SLE, AAV and polymyositis/dermatomyositis (PM/DM) have an increased risk of developing herpes zoster.^{81–99} RA is in itself a risk factor, and the risk of developing herpes zoster is further increased in patients with AIIRD treated with corticosteroids, TNF α blocking agents and non-biological DMARDs, particularly cyclophosphamide, azathioprine and leflunomide^{82–85 90 91 98} but not MTX.¹⁰⁰ One study found an increased risk of herpes zoster in patients with SLE when treated with rituximab.¹⁰¹ Lupus disease activity is not a risk factor for herpes zoster.⁸⁸ Herpes zoster vaccine has been shown to reduce herpes zoster and post-herpetic neuralgia in patients over 60 years,¹⁰² but no studies have been performed in patients with AIIRD. Because of the high burden of herpes zoster in patients with AIIRD,

herpes zoster vaccination may be considered in these patients, but only when less severely immunosuppressed. The ACIP suggested criteria for immunosuppressed patients who can receive herpes zoster vaccine; however, it must be emphasised that these recommendations are not validated but are based on expert opinion and require further investigation.²⁹ It seems prudent to administer herpes zoster vaccine only to patients with AIIRD who are seropositive for varicella zoster antibodies in order to prevent primary varicella infection with the vaccine strain.

(9) Human papillomavirus vaccination should be considered in selected patients with AIIRD (grade of evidence III; strength of recommendation C–D; Delphi vote 8.44)

It has been shown that human papillomavirus (HPV) infection occurs more often in patients with SLE, also with the high-risk (oncogenic) subtypes of the virus.^{103–105} A lower percentage of these infections (31.8%) is spontaneously cleared by patients with SLE,¹⁰⁶ leading to an increased risk of developing cervical cancer. The risk factors for contracting HPV infection are the same in patients with SLE as in the general population.^{103–105} The efficacy of HPV vaccination has not been investigated in patients with AIIRD. HPV vaccination is recommended for young women in many countries and should be considered for women with SLE until the age of 25 years. The quadrivalent (q) HPV vaccine has been associated with venous thromboembolic events (VTE). However, of the 31 cases (0.2/100.000 doses of qHPV vaccine) with objectified VTE, 90% had a known risk factor for VTE (antiphospholipid syndrome in two cases).¹⁰⁷

(10) In hyposplenic/asplenic patients with AIIRD influenza, pneumococcal, *Haemophilus influenzae* b and meningococcal C vaccinations are recommended (grade of evidence IV; strength of recommendation D; Delphi vote 9.50)

Hypsplenic/asplenic patients are at risk of contracting a so-called ‘overwhelming post-splenectomy infection (OPSI)’. OPSI is caused by encapsulated bacteria (eg, *Streptococcus pneumoniae*, *H influenzae* b, *Neisseria meningitidis*) and the mortality of OPSI is up to 70%.^{108–112} OPSI can occur as a secondary infection after infection with influenza. No studies have addressed the efficacy of vaccination to prevent OPSI in patients who are hyposplenic/asplenic, but the general consensus is to vaccinate these patients against influenza, *S pneumoniae*, *H influenzae* b and *N meningitidis* C.¹¹³ When hyposplenic/asplenic patients with AIIRD plan to travel to or live in areas where other meningococcal strains are endemic (A, Y, W135), vaccination for these meningococcal subtypes is also indicated.¹¹⁴ Prophylactic or on-demand antibiotics and preventive measures for malaria and babesiosis are beyond the scope of these recommendations.

(11) Hepatitis A and/or B vaccination is only recommended in patients with AIIRD at risk (grade of evidence II–III; strength of recommendation B–D; Delphi vote 9.13)

Data on the incidence of hepatitis A and B infection in patients with AIIRD are lacking. Reactivation of hepatitis B infection in patients with AIIRD has been described following treatment with immunosuppressive medication or immediately after discontinuing immunosuppressive medication (including TNF α blocking agents). However, no comparative studies have been published so it is impossible to distinguish whether the immunosuppressive treatment, the disease activity of the AIIRD or the natural course of chronic hepatitis B infection was the cause of the hepatitis flare. Hepatitis B vaccination is efficacious in most patients with AIIRD.^{55–57} Vaccination for hepatitis A and/or B is only recommended when the risk of

contracting these infections is increased (travel to or residence in endemic countries for hepatitis A and/or B); increased risk of exposure or proven exposure to hepatitis A and/or B (eg, because of medical profession, infected family member or contacts), only when protective antibodies against hepatitis A and/or B are absent.

(12) Patients with AIIRD who plan to travel are recommended to receive their vaccinations according to general rules, except for live attenuated vaccines which should be avoided whenever possible in immunosuppressed patients with AIIRD (no grade of evidence; strength of recommendation D; Delphi vote 9.25)

It is unknown whether patients with AIIRD have an increased risk of contracting travel-related vaccine-preventable infections (VPI). In patients with RA and SLE, the risk of tuberculosis (TB) is increased (also see recommendation 13).^{115–129} However, the majority of these TB cases represent reactivations from earlier contracted latent TB infection and Bacillus Calmette-Guérin (BCG) vaccination has not been clearly shown to prevent TB in adults. Influenza is endemic in subtropical and tropical climates during the entire year and is the most frequent VPI among travellers to subtropical and tropical countries.^{130–131} The incidence of influenza in patients with AIIRD is not known. Also the incidence of cholera, diphtheria, hepatitis A, meningococcal infection, poliomyelitis, rabies, tetanus, tick-borne encephalitis, typhoid fever and yellow fever is unknown. Studies addressing the efficacy of influenza vaccination (in patients with RA, SLE, SSc and AAV)^{24–26 30–41 47–50 63 67 68 75–77} and tetanus toxoid vaccination (in patients with RA and SLE)^{30 46 58 59} generally showed responses comparable to those in healthy controls. To protect patients with AIIRD from contracting travel-related VPI, they should receive the vaccinations that are recommended to the general population. Exceptions are vaccinations with BCG vaccine, oral poliomyelitis vaccine, oral typhoid fever vaccine and yellow fever vaccine which contain live attenuated microorganisms and therefore might lead to life-threatening infection in immunosuppressed patients with AIIRD.

(13) BCG vaccination is not recommended in patients with AIIRD (grade of evidence III; strength of recommendation C–D; Delphi vote 9.38)

The incidence of TB is increased in patients with AIIRD, in particular when treated with immunosuppressive drugs (DMARDs, corticosteroids),^{115–119 121–124 127–129} especially TNF α blocking agents.^{116–119 122 127–129} The large majority of these cases of active TB are reactivations of earlier contracted latent TB infections which cannot be prevented by vaccination. Moreover, BCG vaccination has not been clearly demonstrated to be efficacious in preventing TB in adults. Finally, BCG vaccine contains attenuated mycobacteria and vaccination with BCG vaccine has been shown to induce BCG-itis in immunosuppressed patients.^{132–134}

Research agenda

The EULAR Task Force for vaccination in patients with AIIRD agreed on the research agenda as shown in table 2 in the online supplement.

DISCUSSION

The recommendations for vaccination in patients with AIIRD, as presented above, are based on the current evidence resulting from the systematic literature review and the opinion of selected experts in the fields of rheumatology, clinical immunology, nephrology, paediatric rheumatology/

immunology and infectious diseases from 11 European countries. Unfortunately, no randomised controlled studies were available that addressed the efficacy of vaccination in patients with AIIRD on clinical end points. The highest strength of these recommendations is therefore B (see table 1 in online supplement). We did not systematically review the literature on vaccines in the general population without AIIRD, but the experts did take into account their knowledge of this wider literature in formulating the recommendations. In general, it should be noted that, even for the general population, conceptions about the efficiency and efficacy of vaccination have varied over time. There is strong evidence that adequate immune responses are achieved with vaccines, especially for influenza and pneumococcal vaccines, but this may not always translate into equally high efficiency at the clinical protection level.^{135–137}

Other infection-preventive measures than vaccination are not addressed in these recommendations, and we suggest a new EULAR task force should be set up to recommend on important issues such as general hygienic measures and antibiotic prophylaxis for patients with AIIRD to further reduce infection-related morbidity and mortality in patients with AIIRD.

Our literature search focused essentially on three important aspects of vaccination in patients with AIIRD: the incidence of infectious diseases for which vaccines are available; the efficacy of vaccinations that are indicated; and the harms of vaccination. We should acknowledge that the grading of the available evidence can differ between the three aforementioned aspects: often little evidence is available for the incidence of VPI and most studies are underpowered with regard to adverse events, while efficacy is best studied for most vaccines. The results of the Delphi voting to the traditional level of evidence are therefore of particular importance since they represent the overall interpretation of the evidence on all aforementioned aspects of vaccination in patients with AIIRD by the panel of experts.

The morbidity and mortality for most VPI increase in patients who are more severely immunosuppressed—for example, when treated with a more intensive immunosuppressive regimen. We therefore stress that the recommendations regarding vaccination in patients with AIIRD should be followed more stringently for more immunosuppressed patients. However, because efficacy can be reduced by immunosuppressive treatment, offering vaccination before starting (intensive) immunosuppressive treatment, in particular rituximab, is advisable.

A note of caution is warranted with regard to the safety of vaccination in patients with AIIRD. Although many case reports have been published demonstrating flares of AIIRD or new-onset autoimmune diseases following vaccination, these adverse events remain rare and a causal relationship has not been proved. Moreover, several controlled studies show no difference in the occurrence of flares of AIIRD after vaccination, although these studies have not been powered to address specific adverse events, but efficacy. Because of the lack of sufficiently powered studies focusing on harms, these issues remain an important item on the research agenda.

Finally, different vaccination schemes have been developed and proposed in different European countries. The exact implementation of the current recommendations may need to take into account local differences in specific countries and settings. Moreover, the recommendations need to be updated on a regular basis (every 3 years), since new evidence will become available with regard to current and new vaccines and current and new immunomodulating treatments.

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