

ORIGINAL ARTICLE

Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations

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To cite: Rondaan C, Furer V, Heijstek MW, *et al.* Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. *RMD Open* 2019;**5**:e001035. doi:10.1136/rmdopen-2019-001035

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2019-001035>).

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Received 20 June 2019
Revised 1 August 2019
Accepted 6 August 2019



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ABSTRACT

Aim To present a systematic literature review (SLR) on efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD), aiming to provide a basis for updating the EULAR evidence-based recommendations.

Methods An SLR was performed according to the standard operating procedures for EULAR-endorsed recommendations. Outcome was determined by efficacy, immunogenicity and safety of vaccination in adult patients with AIIRD, including those receiving immunomodulating therapy. Furthermore, a search was performed on the effect of vaccinating household members of patients with AIIRD on the occurrence of vaccine-preventable infections in patients and their household members (including newborns). The literature search was performed using Medline, Embase and the Cochrane Library (October 2009 to August 2018).

Results While most investigated vaccines were efficacious and/or immunogenic in patients with AIIRD, some were less efficacious than in healthy control subjects, and/or in patients receiving immunosuppressive agents. Adverse events of vaccination were generally mild and the rates were comparable to those in healthy persons. Vaccination did not seem to lead to an increase in activity of the underlying AIIRD, but insufficient power of most studies precluded arriving at definite conclusions. The number of studies investigating clinical efficacy of vaccination is still limited. No studies on the effect of vaccinating household members of patients with AIIRD were retrieved.

Conclusion Evidence on efficacy, immunogenicity and safety of vaccination in patients with AIIRD was systematically reviewed to provide a basis for updated recommendations.

Key messages

What is already known about this subject?

- Patients with autoimmune inflammatory rheumatic diseases (AIIRD) are at increased risk of vaccine-preventable infections and associated complications.
- Vaccination may be less efficacious in (subgroups of) patients with AIIRD and could potentially lead to exacerbation of underlying disease.
- Evidence-based recommendations of the EULAR for vaccination of adult patients with AIIRD were published in 2011.

What does this study add?

- This systematic literature review summarises available evidence on efficacy, immunogenicity and safety of vaccination in AIIRD since October 2009, providing a basis for updated EULAR recommendations.

How might this impact on clinical practice?

- The aim of the updated recommendations is to aid health professionals dealing with questions regarding vaccination in patients with AIIRD, whereby reducing infection-related morbidity and mortality.

INTRODUCTION

Infectious diseases and associated complications comprise an important cause of morbidity and mortality in patients with autoimmune inflammatory rheumatic diseases (AIIRD). Increased susceptibility to infectious diseases in these patients is most likely due to an immunomodulating effect of the disease itself and/or by use of immunosuppressive medications.¹

Vaccination is generally regarded as a safe, efficacious and low-cost method for preventing certain infections. However, vaccination may be less efficacious in (subgroups of) patients with AIIRD, as a result of their immunosuppressed state, and, moreover, could potentially lead to exacerbation of the underlying AIIRD.

In 2011, evidence-based recommendations for vaccination in patients with AIIRD were published. They were formulated by an EULAR task force to aid health professionals dealing with questions regarding vaccination in patients with AIIRD in daily clinical practice, with the aim of reducing infection-related morbidity and mortality in these patients.² The authors stated that the recommendations needed to be updated on a regular basis as new evidence becomes available.² Towards this end, the League commissioned another multidisciplinary task force with the purpose of formulating up-to-date recommendations for vaccination in patients with AIIRD.

The current report presents the results of an SLR on efficacy, immunogenicity and safety of vaccination in adult patients with AIIRD, including those using immunomodulating agents. Together with the results of an SLR on incidence and prevalence of VPIs in patients with AIIRD,¹ the current SLR provided the task force with a basis for updating the recommendations.³

METHODS

The work was performed in accordance with the 2014 EULAR standard operating procedures for EULAR-endorsed recommendations.⁴

The expert committee first formulated four main research questions (Box 1), based on the 2011 version of the recommendations. The current review reports on the SLR results of three of these four questions, which include the topics of efficacy, immunogenicity and safety of vaccination in adult patients with AIIRD (including those receiving immunosuppressive agents) and the effect of vaccinating their household members on the occurrence of VPIs in both patients and their household members (including newborns). The efficacy of vaccination was defined as the capacity to prevent infections, while the

immunogenicity of vaccination refers to the capacity to induce vaccine-specific humoral and/or cellular immune responses. Safety of vaccination in the AIIRD population was determined by the assessment of both the occurrence of adverse effects and the influence on the underlying disease.¹

Next, the research questions were adapted according to the PICO-method (population-intervention-comparison-outcome). Population, intervention, comparison and outcome definitions were combined and adapted to be used as search terms (table 1). Medline (via Pubmed), Embase and the Cochrane Library were searched from October 2009 to August 2018. Meta-analyses, randomised trials, cohort studies and case series with at least five participants were eligible. Only English articles on adult patients (≥ 18 years) were included. Papers with non-original data, case reports, case series with less than five patients, abstracts presented in scientific meetings, and papers included in the previous version of these recommendations were excluded. Papers that were not retrieved in the search, but were relevant in the opinion of the committee, could be added. See figure 1 for the flow chart displaying the search strategy for PICO 2 and 3. For some of the AIIRD, immunomodulating agents and vaccines (diphtheria, pertussis, measles, mumps, rubella, *Neisseria meningitidis*, *Haemophilus influenzae* B and typhoid fever vaccine) that were included in the literature search, no relevant articles were retrieved. No relevant articles were retrieved in the search on the effect of vaccinating household members of patients with AIIRD (research question 4).

Data analysis was performed by CR, VF, MH, SvA and OE. The following information was retrieved from all included articles: name of first author, year of publication, country where the study was performed, years of data inclusion, type of study, vaccine used, addition of adjuvant, type of AIIRD, number of participants, age and sex of participants, disease duration, time of follow-up, medication used and outcome of vaccination (efficacy, immunogenicity and/or safety). The articles were critically assessed (online supplementary file S6—included articles and critical appraisal) by applying tools from the Cochrane Library (online supplementary file S7—critical appraisal criteria) and given a level of evidence based on the Oxford Centre for Evidence-based Medicine approach (table 2). Discrepancies between reviewers were resolved by consensus. The final recommendations were graded according to the level of evidence of the underlying articles (table 3).⁵

RESULTS

Influenza vaccination

Efficacy—immunogenicity—safety

Up to the previous recommendations, one study addressed the issue of efficacy of influenza vaccination in patients with AIIRD.⁶ Immunogenicity of the vaccine had been evaluated in 26 studies, mainly including patients with rheumatoid arthritis (RA), systemic lupus

Box 1 Research questions

1. What is the incidence or prevalence of vaccine-preventable infections (VPI) in adult patients with AIIRD?*
2. What is the efficacy, immunogenicity and safety of available vaccines in adult patients with AIIRD?
3. Are vaccines efficacious and immunogenic in adult patients with AIIRD, treated with immunosuppressive agents and disease-modifying antirheumatic drugs?
4. What is the effect of vaccinating household contacts of patients with AIIRD on the occurrence of VPI in both patients and household members (including newborns)?

* The systematic literature review covering research question 1 has been submitted for publication separately.¹

AIIRD, autoimmune inflammatory rheumatic disease(s).

Table 1 Formulation of PICO-questions

Q2: What is the efficacy, immunogenicity and safety of available vaccines in adult patients with AIIRD?

Population: patients with AIIRD*

Intervention: immunisation/vaccination with vaccines suitable for adults**

Comparison: healthy controls, non-vaccinated patients with AIIRD or none

Outcome: efficacy (prevention of vaccine-preventable disease), immunogenicity (laboratory markers for vaccine efficacy, eg, seroprotection/seroconversion) and safety (effect on the underlying autoimmune disease or adverse effects from vaccination)

Q3: Are vaccines efficacious and immunogenic in adult patients with AIIRD, treated with immunosuppressive agents and disease-modifying antirheumatic drugs (DMARDs)?

Population: patients with AIIRD* using immunomodulating agents***

Intervention: immunisation/vaccination with vaccines suitable for adults**

Comparison: healthy controls, patients with AIIRD not using analysed agents or none

Outcome: efficacy (prevention of vaccine-preventable disease), immunogenicity (laboratory markers for vaccine efficacy, eg, seroprotection/seroconversion)

Q4: What is the effect of vaccinating household members of patients with AIIRD on the occurrence of VPI in both the patients and household members (including newborns)?

Population: patients with AIIRD*

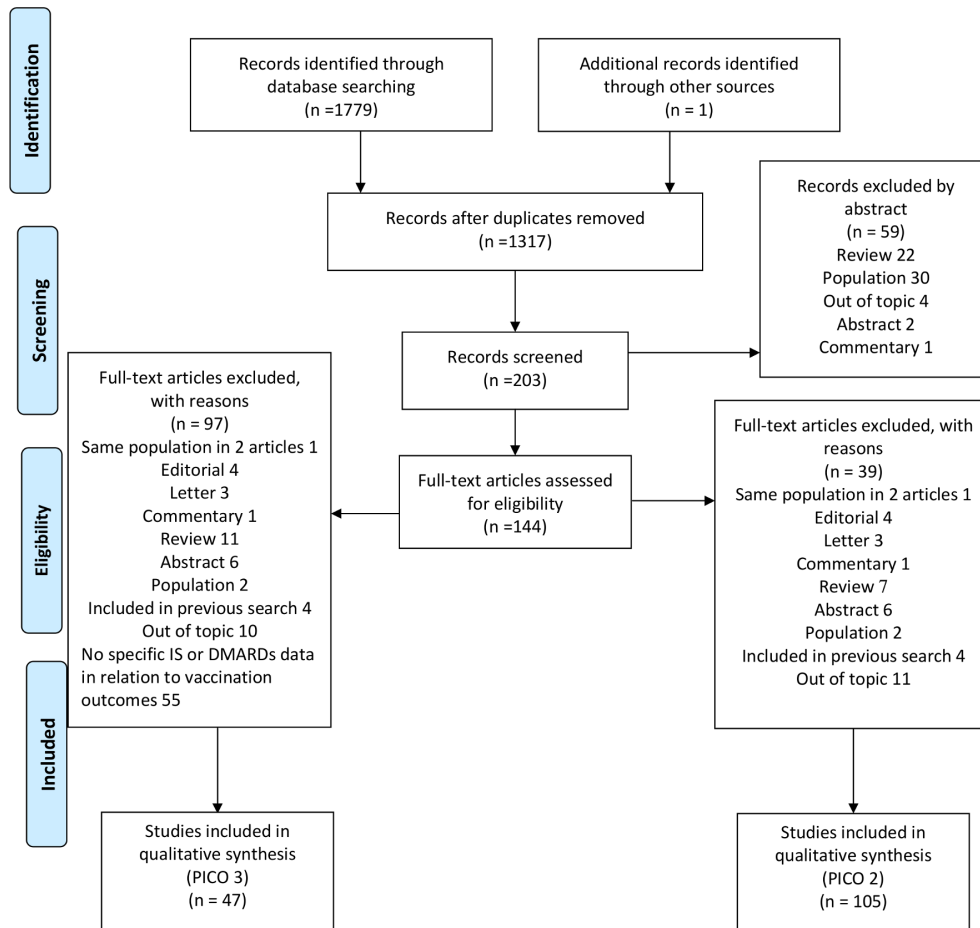
Intervention: immunisation/vaccination of household contacts of patients with AIIRD with vaccines suitable for children and adults**

Comparison: patients with AIIRD with non-vaccinated household members

Outcome: incidence of VPI in patients with AIIRD/safety of household vaccine for patients with AIIRD

* AIIRD	** Vaccines	*** Immunomodulating agents
Rheumatoid arthritis	Influenza	Glucocorticosteroids
Systemic lupus erythematosus	Tetanus toxoid	Methotrexate
Antiphospholipid syndrome	Diphtheria	Sulfasalazine
Adult Still's disease	Pertussis	Leflunomide
Systemic sclerosis	Measles	Hydroxychloroquine
Sjögren syndrome	Mumps	Azathioprine
Mixed connective tissue diseases	Rubella	Mycophenolic preparation
Relapsing polychondritis	Varicella-zoster virus	Ciclosporine
Giant cell arteritis	Human papillomavirus	Tacrolimus
Polymyalgia rheumatica	<i>Streptococcus pneumoniae</i>	Cyclophosphamide
Takayasu arteritis	Hepatitis A	Rituximab
Polyarteritis nodosa	Hepatitis B	Belimumab
ANCA-associated vasculitis	<i>Neisseria meningitidis</i>	Abatacept
Microscopic polyangiitis	<i>Haemophilus influenzae B</i>	TNF α blocking agents
Granulomatosis with polyangiitis	Tickborne encephalitis	Infliximab
Eosinophilic granulomatosis with polyangiitis	Typhoid fever	Etanercept
Behçet's disease	Yellow fever	Adalimumab
Anti-GBM disease		Certolizumab
Cryoglobulinaemic syndrome		Golimumab
Polymyositis		Anti-IL-6 agents
Dermatomyositis		Tocilizumab
Clinically amyotrophic dermatomyositis		Sarilumab
Inclusion body myositis		Anti-IL-17 agents
Antisynthetase syndrome		Secukinumab
Eosinophilic myositis		Ixekizumab
Eosinophilic fasciitis		Anti-IL-1 agents
Spondyloarthropathies		Canakinumab
Periodic fever syndromes		Anakinra
Familial Mediterranean fever		Riloncept
TNF-receptor associated syndrome (TRAPS)		Apremilast
Cryopyrin associated periodic syndrome (CAPS)		Tofacitinib
		Baricitinib

AIIRD, autoimmune inflammatory rheumatic disease(s); ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane; IL, interleukin; PICO, population-intervention-comparison-outcome; TNF, tumour necrosis factor; VPI, vaccine-preventable infection.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1 Flow chart displaying the search strategy for PICO 2 and 3. DMARDs, disease-modifying antirheumatic drugs; IS, immunosuppressives; PICO, population-intervention-comparison-outcome.

Table 2 Oxford Centre for Evidence-Based Medicine—levels of evidence

Level	
1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow CI)
1c	'All or none'
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low-quality RCT)
2c	'Outcomes' research, ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research of 'first principles'

RCT, randomised controlled trial.

erythematosus (SLE) and granulomatosis with polyangiitis (GPA).⁷⁻³² Most of these studies demonstrated similar rates of immunogenicity among patients and healthy controls (HC), except for the studies in patients treated with rituximab, whose responses were severely impaired.^{12 14 33}

From the previous recommendations up to August 2018, seven meta-analyses and 50 other studies have been published on efficacy, immunogenicity and safety of influenza vaccination, including the 2009 pandemic H1N1 influenza strain vaccine, in patients with AIIRD

Table 3 Grades of recommendation

Grade	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

(table 4 for seasonal trivalent and table 5 for monovalent pandemic influenza vaccination).

Five studies addressed the efficacy of influenza vaccination. Retrospective database analysis studies reported a reduced all-cause mortality rate and risk of hospitalisation for influenza-related complications in patients with RA³⁴ and SLE³⁵ who received trivalent seasonal subunit influenza vaccine. A prospective Japanese study following a total of 17 735 patients with RA during four influenza seasons, found that trivalent subunit influenza vaccination was associated with a lower self-reported rate of influenza infections (RR 0.83, 95% CI 0.71 to 0.95).³⁶ These findings are supported by two prospective cohort studies.^{6 37}

Most studies on influenza vaccination in patients with AIIRD, however, address immunogenicity, mainly by assessing the development of a protective level of antibodies (titre value ≥ 40 , as measured by the haemagglutination inhibition assay). For RA, most of these studies report similar responses in patients and HCs.^{7 9–15 20 38–41} A meta-analysis including a total of 886 patients with RA and 685 controls concluded that 60%, 68% and 61% of patients with RA reached seroprotective antibody levels following influenza vaccination for the H1N1, H3N2 and B strain, respectively. Only for the H1N1 influenza strain, the strain for which most data were available, responses were significantly lower in patients than in HCs.⁴²

For SLE most studies report similar, adequate immune responses using trivalent seasonal subunit influenza vaccine,^{17 22–25 43 44} although modestly lower responses compared with HCs were also reported.^{21 26–29} Two meta-analyses reported an adequate but lower response against influenza A strains (H1N1 and H3N2) but not against influenza B in patients with SLE as compared with HCs,^{45 46} while another meta-analysis reported a reduced immunogenicity in SLE for H1N1 and B strains, but not for H3N2.⁴⁷ Reported pooled seroprotection rates in patients with SLE are 66%–68%, 64%–76% and 60%–66% against H1N1, H3N2 and B strains, respectively.^{46 47}

Likewise, in other AIIRD, including patients with spondyloarthropathies, antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis and primary systemic sclerosis (pSS), adequate serological responses to influenza vaccination were found.^{30–32 48–53}

Regarding the pandemic monovalent subunit influenza vaccine, most larger studies report reduced immunogenicity in patients with AIIRD (mostly RA and SLE), although protective antibody levels were reached in the majority of patients.^{41 52 54–68} A second booster dose of vaccine, given 3–4 weeks after the first, improved immunogenicity, resulting in seroprotection levels comparable to those of HCs.^{55 62 69} This phenomenon has also been shown in patients with SLE who received seasonal influenza vaccine for the first time.⁷⁰ High disease activity levels did not preclude reaching seroprotection in a study that included 340 patients with RA, of which 14.5%

had a DAS 28 (Disease Activity Score in 28 joints) value above 5.1.⁵⁸

Influenza vaccination did not influence activity of the underlying AIIRD in patients with RA,^{78 121 141 538 394 254 555 771–73} SLE,^{6 19 21 26 28 37 43 45–47} ANCA-associated vasculitis^{30 31 48} or systemic sclerosis.^{32 49} Adverse events of influenza vaccination in patients with AIIRD were comparable to those in HCs in most studies,^{7 19 21 23 30 59 65} including a meta-analysis in patients with SLE.⁴⁶ In contrast, a meta-analysis including 13 studies in patients with RA concluded that local, mild adverse events occurred significantly more frequently in patients with RA.⁴²

Influence of immunomodulating agents

The influence of immunomodulating agents on influenza vaccine efficacy and immunogenicity is summarised in table 6. No influence of methotrexate (MTX) on influenza immunogenicity was found in most studies^{39 40 43 62 72 74} including one meta-analysis in patients with RA.⁷⁵ In some, a modest reduction in immunogenicity was observed.^{58–60 73 76} In another meta-analysis, results on the influence of MTX differed depending on whether response rates per influenza strain, or for at least two of the three strains, were analysed. In case of the latter approach, the negative impact of MTX was significant.⁷⁷ Interestingly, temporary discontinuation of MTX was shown to significantly improve immunogenicity of seasonal influenza vaccination in patients with RA in two studies by Park *et al.*^{78 79} Discontinuation of MTX for 2 weeks after influenza vaccination led to a 11%–16% (depending on influenza strain) higher seroprotection rate compared with patients with RA who continued the use of MTX. Flare rates tended to be higher in patients with RA who temporarily halted MTX use, but the increase in disease activity was transient.^{78 79}

Hydroxychloroquine does not influence the development of an adequate immune response to influenza vaccination.^{47 64 66} The same holds true for the use of TNF α -blocking agents in the majority of studies,^{11 13 20 41 80} including two meta-analyses in RA.^{75 77} Another meta-analysis reported a lower seroprotection, but not seroconversion rate in patients with RA on anti-TNF α , only for the H1N1 influenza strain.⁴² Four studies did report a modestly reduced response to influenza vaccination in patients using anti-TNF α .^{10 16 40 60}

B cell depleting therapy has been associated with hampered antibody responses following influenza vaccination in multiple studies. A negative influence of B cell depleting therapy was observed in two meta-analyses that pooled data from cohort studies. Patient numbers in analyses were low however, and CIs were wide.^{42 77} The interval between administration of rituximab and vaccination differed between studies. A study that included both patients with RA vaccinated 4–8 weeks (n=11) and 6–10 months after (n=12) the administration of rituximab demonstrated no response to influenza vaccination in the first, early group and a modestly restored response in the late group.¹⁴ The use of rituximab did not seem

Table 4 Efficacy, immunogenicity and safety of trivalent influenza vaccination in patients with AIIRD (October 2009–August 2018)

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	LoE			
							Influence of IS on eff./imm.	Eff.	Saf.	
Subesinghe ⁷⁵	2018	Meta-analysis	7 studies in RA	-	See column influence of IS	-	MTX and anti-TNF not associated with reduced immunogenicity	-	2a	-
Huang ⁴²	2017	Meta-analysis	13 studies in RA (also including pts <18 years)	-	Reduced immunogenicity RA compared with HCs for H1N1 strain, not for H3N2 and B Respective SP: 60%, 68%, 61% Lower response with non-adjuvanted vaccine	Disease activity not influenced by vaccination AE significantly more frequent in RA (RR 1.77; 95% CI 1.02 to 3.08)	GC: No influence Anti-TNF, RTX: Lower SP rate for H1N1, but not for SC or other strains Other biologics: Lower SP and SC for H1N1	-	2a	2a
Burmester ²⁰¹	2017	Meta-analysis	Total in analysis: 171 RA-anti-TNF vacc. 382 RA-anti-TNF- non-vacc. All using adalimumab	Influenza-related AE occurred in 5% of vaccinated pts versus 14% of non-vacc.	-	-	-	2a	-	-
Hua ⁷⁷	2014	Meta-analysis	7 studies in RA	-	See column influence of IS	-	RTX: reduced immunogenicity Anti-TNF: no influence For MTX, results differed depending on method of analysis	-	2a	-
Park ⁷⁹	2018	RCT	2 RA groups: ▲ 156 MTX-cont. ▲ 160 MTX hold for 2 weeks postvacc.	-	Better response for all strains in patients who hold MTX 2 weeks after vaccination (SP difference H1N1 11% (95% CI 2% to 19%), H3N2 16% (6% to 26%), B 14.7% (5% to 25%)	No SAE eight flares (5% in MTX-cont. and 17 (11%) in MTX-hold group (p=0.07)	-	-	1b-2b	2b
Park ⁷⁸	2017	RCT	4 RA groups on MTX: 1. 54 cont. 2. 44 hold 4 weeks pre, 3. 49 hold 2 weeks pre/2 weeks post 4. hold 4 weeks postvacc.	-	Adequate response Better results in pts who stopped MTX 2 weeks before and after vaccination	No SAE Flares tended to be more common in groups 2 and 3 (not significant)	-	-	1b-2b	2b
Kivitz ²⁰²	2014	RCT	107 RA-CZP 109 RA-PCB	-	No difference	No difference in AE: 62.3% in PCB versus 63.6% in CZP, mostly mild/moderate Disease activity NR	Reduced on MTX	-	1b-2b	4

Continued

Table 4 Continued

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	Influence of IS on			
							eff./imm.	LoE	Saf.	
Chen ³⁴	2018	Cohort (retrospective database)	3748 RA-vacc 3748 RA non-vacc	Reduced risk of morbidity and mortality in vaccinated pts	-	-	-	2b	-	-
Jain ³⁹	2017	Cohort	51 RA-MTX 51 RA-naïve 45 HCs	-	No difference	No influence on disease activity No difference in AE	See column immunogenicity	-	2b	4
Winthrop ⁸⁴ Part A	2016	Cohort	102 RA-TFC 98 RA-PCB	-	Similar proportions of satisfactory response	-	Reduced in TFC/ MTX	-	2b	-
Winthrop ⁸⁴ Part B	2016	Cohort	92 RA-TFC cont. 91 RA-TFC stop	-	No difference	No	No	-	2b	-
Alten ⁸³	2016	Cohort	184 RA ABT+MTX	-	Adequate response	-	See column immunogenicity	-	2b	-
Luque Ramos ²⁰³	2016	Cohort (retrospective database)	111482 RA 555410 HCs	Trend towards higher hospital admittance rates for pneumonia in areas with lower influenza and pneumococcal vaccine uptake	-	-	-	5	-	-
Kogure ⁷⁴	2014	Cohort	57 RA: 9 biologics 34 MTX 8 TAC 10 GC 14 SASP	-	Seroprotection: H1N1 63%, H3N2 81%, influenza B 26%	No change in disease activity, no AE.	Reduced on biologics	-	2b	4
Milanetti ⁴¹ Both seasonal and pandemic	2014	Cohort	30 RA 13 HCs	-	No difference	Milder AE in patients. No changes in disease activity	No effect of anti-TNF or ABT	-	2b	4
Kobashigawa ³⁶	2013	Cohort (prospective)	17735 RA in 4 seasons (12.2%–38.7% vacc)	Vaccination associated with reduced self-reported risk of influenza	-	-	No	2b	-	-
Milanovic ³⁷	2013	Cohort	19 SLE-vacc. 11 SLE 15 RA-vacc. 22 RA 13 SJS-vacc. 19 SJS	Lower incidence of influenza and bact. Complications among vaccinated pts	Sign. difference in GMT between vacc./unvacc. SLE; but not in RA and SJS.	No changes in disease activity	No	4	2b	4
Tsuru ⁸¹	2013	Cohort	38 TCZ (28 RA/10 CD) 39 RA anti-TNF/DMARD	-	No difference	-	No	-	2b	4
Mori ⁷³	2012	Cohort	62 RA-TCZ 65 RA-MTX 49 RA-TCZ +MTX 18 RA-DC	-	Adequate immune response, but lower on MTX	No systemic AE No flares	Reduced on MTX	-	2b	4

Continued

Table 4 Continued

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	Influence of IS on				
							eff./imm.	LoE Eff.	Imm.	Saf.	
Kogure ⁷²	2012	Cohort	RA treated with Japanese Kampo medicine: 24 RA+MTX 16 RA-DC	-	No difference Low response in general	No AE No influence on disease activity	No influence of MTX	-	4	4	4
Arad ³⁸	2011	Cohort	29 RA-RTX (16<5 mo, 13>5 mo) 17 RA-DC 16 HCs	-	Humoral immunity: reduced in RA-RTX Similar percentage of influenza-specific IFN-γ producing CD4+ cells in RA groups	No change in disease activity	Humoral immunity: Reduced on RTX Cellular immunity: No	-	2b	2b	4
Kobie ⁴⁰	2011	Cohort	61 RA-anti-TNF 70 RA-MTX 33 RA-DC 97 HCs	-	Reduced in RA-anti-TNF	-	Reduced on anti-TNF	-	2b	-	-
Rehnberg ¹⁰⁷	2010	Cohort	11 RA 6 mo post-RTX 8 RA 6 d pre-RTX 10 RA-DC	-	Lower frequency influenza-specific B cells in peripheral blood in post-RTX group 6 d after vacc. Lower humoral response 21 d after vacc. in post-RTX group	-	Reduced on RTX	-	4	-	-
Salemi ⁷¹	2010	Cohort	22 RA-anti-TNF 10 HCs	-	Lower in RA	No SAE No difference in AE No change in disease activity ANA appearance/increase similar RA and HCs	-	-	2b	-	4
Huang ⁴⁷	2016	Meta-analysis	15 studies in SLE (also including pts<18 years)	-	Reduced immunogenicity SLE compared with HCs for H1N1 and B, but not for H3N2 Respective SP: 66%, 64%, 60% Lower response with non-adjuvanted vaccine	Disease activity not influenced by vaccination No difference in AE between SLE and HCs	GC, AZA or IS in general: reduced immunogenicity HCsQ: No difference	-	2a	-	2a
Pugès ⁴⁵	2016	Meta-analysis	17 studies in SLE	-	Immunogenicity depends on viral strains: reduced against A and preserved for B	No influence on disease activity	-	-	2a	-	2a
Liao ⁴⁶	2016	Meta-analysis	18 studies in SLE	-	Reduced in SLE for H1N1 and H3N2, but not for B Respective SP: 68%, 76%, 66%	All side effects mild and transient Similar rate of AE in SLE and HCs 2 severe flares	-	-	2a	-	2a

Continued

Table 4 Continued

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	Influence of IS on			
							eff./imm.	Imm.	Saf.	
Chang ³⁵	2016	Cohort (retrospective database)	1765 SLE-vacc. 8360 SLE non-vacc.	Reduction of complications of influenza in vaccinated patients	-	-	-	2b	-	-
Launay ²⁰⁴	2013	Cohort	27 SLE		Percentages of responders at day 30 are 55.5%, 18.5% and 55.5%, for H1N1, H3N2 and influenza B, respectively	Increase in rheumatoid factor levels, after vacc. No flares.		4	4	4
Vista ²⁰⁵	2012	Cohort	101 SLE 101 HCs			Similar proportion new onset antinuclear antibodies		-	-	4
Crowe ⁴⁴	2011	Cohort	72 SLE 72 HCs		No difference. More high responses in African-American subjects.	19.4%/26.4% flare 6/12 weeks postvacc. More low responders with flare at 6 weeks.	Reduced on steroids	-	4	4
Wallin ⁴³	2009	Cohort	47 SLE: ▲ 23 GC ▲ 8 MTX ▲ 9 AZA 27 HCs		No difference in seroprotection	Overall stable disease	Reduced on steroids	-	2b	4
Jaeger ⁵³	2017	Cohort	107 injections influenza vaccine in 55 CAPS			AE in 7% of injections Fever in 2% No SAE		-	-	4
Caso ⁵¹	2016	Cohort	25 PsA-vacc. 25-PsA DC			Higher tender joint count and ESR after 1 month, more episodes mild symptoms in PsA- vacc.		-	-	4
Jeffer ⁴⁸	2015	Cohort	24 AAV-vacc. 67 AAV-non vacc. 53 HCs		Adequate, but lower response in AAV	No SAE Significant increase in local AE following vaccination only in HCs No change in disease activity		-	2b	2b
Polachek ⁵⁰	2015	Cohort	63 PsA 4 Pso 30 HCs		No difference	Increased CRP in patients 4-6 weeks postvacc.	No	-	2b	4
Litinsky ⁴⁹	2012	Cohort	26 SSC 16 HCs		Increased in SSC for H1N1 No difference for H3N2 and influenza B	Overall stable disease	Increased on combination iloprost and calcium channel blockers for H1N1 and influenza B	-	2b	4

Continued

Table 4 Continued

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	Influence of IS on			
							LoE eff./imm.	Imm.	Saf.	
Kostianovsky ⁸² Both seasonal and pandemic	2012	Cohort	74 systemic vasculitis 32 SSC 29 SLE 23 SJS 28 other AIIRD	-	No difference	19 flares	No	-	4	4

The table is structured as follows: First studies in RA, then SLE followed by other autoimmune inflammatory rheumatic diseases (AIIRD). Within this organisation, articles are clustered in study design (meta-analyses, RCT, cohort studies, case series) and presented in order of publication year.
 AAV, ANCA-associated vasculitis; ABT, abatacept; ANA, antinuclear antibodies; AZA, azathioprine; bact., bacterial; CAPS, cryopyrin associated periodic syndrome; CD, Castleman's disease; CD, cluster of differentiation; cont., continued; CRP, C reactive protein; CZP, certolizumab pegol; d, days; DC, disease control; DMARD, disease-modifying antirheumatic drug; eff., efficacy; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; GMT, geometrical mean titre; HC, healthy controls; HCC, hydroxychloroquine; IFN, interferon; imm, immunogenicity; IS, immunosuppressives; LoE, level of evidence; mo., months; MTX, methotrexate; No., number; NR, not reported; PCB, placebo; PsA, psoriatic arthritis; Pso, psoriasis; pts, patients; RA, rheumatoid arthritis; RCT, randomised controlled trial; ref., reference; RR, relative risk; RTX, rituximab; (S)AE, (serious) adverse event(s); saf., safety; SASP, salazosulfapyridine; SC, seroconversion; sign, significant; SJS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SP, seroprotection; SSC, systemic sclerosis; TAC, tacrolimus; TOZ, tocilizumab; TFC, tofacitinib; TNF, tumor necrosis factor; vacc., vaccinated; yrs., years.

to affect cell-mediated immune responses to influenza vaccination in a study with a limited number of patients.³⁸

Two studies demonstrated that patients with RA treated with tocilizumab, an IL-6 receptor blocking agent, were able to mount a satisfactory antibody response following influenza vaccination.^{73 81}

Controversial data have been published on the effect of abatacept on influenza vaccine immunogenicity. Most of the studies were small in patient numbers, but they reported a substantial negative effect.^{59 62 82} One relatively large but uncontrolled study, including 184 patients with RA, reported an adequate humoral response to influenza vaccination.⁸³

Only one study investigated the influence of tofacitinib on influenza vaccine immunogenicity in AIIRD. Tofacitinib alone did not seem to affect the immune response to the vaccine, but a combination of tofacitinib and methotrexate was associated with a lower response.⁸⁴

The effect of glucocorticoids on the immune response to influenza vaccine has mainly been studied in combination with other immunosuppressive agents. The antibody response is generally adequate in patients who were on glucocorticoids at the time of influenza vaccination,^{21–23 42 47} although some studies did find a mildly reduced response.^{17 43 44 64 69}

Summary and clinical implications

Seasonal trivalent influenza vaccination is associated with a reduced incidence of bacterial complications, hospital admissions and mortality in patients with RA and SLE. It has also been proven to be immunogenic in the majority of studies in patients with AIIRD, even when treated with immunosuppressive agents, with the exclusion of B cell depletion. Although studies that are sufficiently powered with regard to safety are lacking, in the majority of studies disease activity remained stable and only mild adverse events were reported, comparable with HCs. Therefore, the updated EULAR recommendation on influenza states that influenza vaccination should be strongly considered for the majority of patients with AIIRD.³

Pneumococcal vaccination

Efficacy—immunogenicity—safety

To date, 91 pneumococcal serotypes have been identified, 30 of them being responsible for up to 90% of all infections.⁸⁵ Although the pneumococcal polysaccharide vaccine that includes 23 serotypes (PPSV23) was found to prevent invasive pneumococcal infections in the general population, it did not generate immunity in children younger than 2 years of age and had a limited efficacy in reducing non-bacteraemic pneumonia.⁸⁶ Therefore, in 2000 a pneumococcal conjugate vaccine comprising seven antigens (PCV7) was developed and expanded to 13 serotypes (PCV13) which was licensed in 2010 based on immunogenicity outcome studies.^{87 88} In 2015, a randomised controlled study performed in the older healthy population demonstrated the capacity of PCV13 to prevent vaccine-type pneumococcal, bacteraemic and



Table 5 Efficacy, immunogenicity and safety of monovalent (H1N1) pandemic influenza vaccination in patients with AIIRD (October 2009–August 2018)

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	Influence of IS on eff./imm.			LoE
							Imm.	Eff.	Saf.	
Milanetti ⁴¹ Both seasonal and pandemic, adj. (MF59)	2014	Cohort	30 RA 13 HC	–	No difference	More mild AE in patients	No effect of anti-TNF or ABA	–	2b	4
Kapetanovic ⁶² Adj. (AS03)	2014	Cohort	50 RA-MTX 38 RA-anti-TNF 53 RA-anti-TNF+MTX 5 RA-ABA- 10 RA-RTX 2 RA TCZ 41 SpA-anti-TNF 51 SpA-anti-TNF+MTX Two doses in 58%	–	Reduced in RA-RTX Increased in SpA-anti-TNF Increased after two doses, except for RA-MTX and RA-RTX	One pneumonia 8.2% of patients reported that vaccination influenced their rheumatic disease	Reduced on RTX and ABA (only five pts)	–	2b	4
Ribeiro ⁸² Non-adj. Subanalysis of ⁶⁸	2013	Cohort	11 RA-ABA 33 RA-MTX DC 55 HC	–	Reduced in RA-ABA	No difference AE.	Reduced on ABA	–	2b	4
Adler ⁵⁹ AS03 adjuvanted	2012	Cohort	47 RA 59 SpA 15 vasculitis 28 CTD 40 HC	–	Reduced in patients (but not in SpA and CTD)	No difference in AE. Increase disease activity in 32 patients	Reduced on ABA, RTX (n=8) and MTX 2 responders in RTX group: 1 and 3 mo after RTX	–	2b	4
França ⁶⁰ Non-adj.	2012	Cohort	41 RA-anti-TNF 79 SpA-anti-TNF 41 RA-DC 75 SpA-DC 117 HC	–	Reduced in SpA-anti-TNF but not for etanercept	More mild systemic AE in patients on anti-TNF	Reduced on MTX (RA). Reduced on anti-TNF (SpA) (except etanercept)	–	2b	4
Iwamoto ⁶¹ Mostly non-adj.	2012	Cohort	89 RA 14 HC	–	Reduced (non-significant) in RA Seroprotection 55.1%	1 facial palsy	Lower (non-significant) on biologics	–	2b	5
Saad ⁵⁴ Non-adj.	2011	Cohort	1668 AIIRD* 234 HC	–	Reduced in AIIRD versus HC Reduced in SLE and RA	Overall stable disease	No	–	2b	4
Gabay ⁵⁵ Adj. (AS03)	2011	Cohort	82 RA 45 SpA 46 other AIIRD 138 HC	–	Reduced in patients No difference after two doses in patients (seroprotection after 1 and 2 doses 75% and 85%, respectively)	Overall stable disease	Reduced on DMARDs and within 3 mo. after B cell depletion	–	2b	4
Miraglia ⁵⁶ Non-adj.	2011	Cohort	1152 Immunocompromised: 260 RA 83 J/A	–	Seroprotection in 61.5% of patients with RA and in 85.5% of patients with J/A	Mild systemic AE in more than 20% of RA and J/A	–	–	2b	4
Elkayam ⁵⁷ Adj. (MF59)	2011	Cohort	41 RA 21 SLE 17 PsA 15 AS 25 HC	–	Reduced in patients with RA/PsA Seroprotection in 60%–76% of patients	Overall stable disease	Reduced on leflunomide and infliximab	–	2b	4
Ribeiro ⁵⁸ Non-adj.	2011	Cohort	340 RA 234 HC	–	Reduced in RA No influence of disease activity	More local AE in HC. More mild systemic AE in RA	Reduced on MTX	–	2b	2b
Müller ²⁰⁶ Adj. (AS03)	2013	Case series	16 RA+SJS	–	SC in B cell depleted: 22%, non-depleted: 57%	More influenza-like symptoms in B cell depleted patients	Low response with RTX	–	4	5

Continued

Table 5 Continued

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	Influence of IS on eff./imm.	LoE		
								Eff.	Imm.	Saf.
Borba ⁶⁴ Non-adj.	2012	Cohort	555 SLE 170 HC	-	Reduced in SLE with therapy (except for antimalarials) No difference in HC and SLE without therapy	Overall stable disease	Reduced for steroids and IS Restored when using concomitant antimalarials	-	2b	2b
Kostianovsky ⁵² Both seasonal and pandemic, non-adj.	2012	Cohort	74 systemic vasculitis 32 SSc 29 SLE 23 SJS 28 other AIIRD	-	No difference	19 flares	No	-	4	4
Lu ⁶³ Non-adj.	2011	Cohort	21 SLE 15 HC	-	No difference	Changes in autoantibody levels Overall stable clinical disease activity one flare	No	-	2b	4
Urowitz ²⁰⁷ Both adj. and non-adj.	2011	Cohort	103 SLE: 51 adj. 52 non-adj.	-	-	No difference Overall stable disease	-	-	-	2b
Mathian ⁶⁹ Non-adj.	2011	Cohort	111 SLE	-	Increased after booster vaccination (seroprotection after 1 and 2 doses 67% and 80%, respectively)	No severe AE Overall stable disease	Reduced on IS	-	2b	4
Brauner ⁶⁷	2017	Cohort	14 SJS 18 HC	-	Higher levels of influenza-specific IgG in patients, and higher avidity	Antibody titres to non-influenza (incl autoantigens Ro/SSA and La/SSB) antigen increased in patients, but not in HC.	-	-	4	4
Sampaio-Barros ⁶⁸	2017	Cohort	92 SSc 92 HC	-	Higher GMT SSc Comparable SP and SC	No difference in AE No SAE	No	-	2b	4
De Medeiros ²⁰⁸ Non-adj.	2014	Cohort	45 PAPS 33 HC	-	-	No change in overall frequencies of autoantibodies	-	-	-	2b
Miossi ⁶⁶ Non-adj.	2013	Cohort	69 MCTD 69 HC	-	No difference	Overall stable disease	No	-	2b	4
Shinjo ⁶⁵ Non-adj.	2012	Cohort	37 DM +21 PM 116 HC	-	No difference	No difference Overall stable disease	No	-	2b	4

The table is structured as follows: First studies in RA, then systemic lupus erythematosus (SLE) followed by other autoimmune inflammatory/rheumatic diseases (AIIRD). Within this organisation, presented in order of publication year.

*Group consisted of patients with SLE (n=572), RA (n=349), psoriatic arthritis (n=101), ankylosing spondylitis (n=152), Behçet's disease (n=85), dermatomyositis (n=45), systemic sclerosis (n=127), mixed connective tissue disease (n=69), primary antiphospholipid syndrome (n=54), primary Sjögren's syndrome (n=36), Takayasu's arteritis (n=30), polymyositis (n=28), granulomatosis with polyangiitis (n=26).

†Group consisted of patients with cancer (n=319), RA (n=260), HIV infection (n=256), kidney transplant recipients (n=85), juvenile idiopathic arthritis (n=83) and elderly persons (n=149).
 ABA, abatacept; adj., adjuvanted; AS, ankylosing spondylitis; AS, adjuvant system; DC, disease control; DM, dermatomyositis; DMARD, disease-modifying antirheumatic drug; eff., efficacy; GMT, geometrical mean titre; HC, healthy controls; imm, immunogenicity; IS, immunosuppressives; JIA, juvenile idiopathic arthritis; LoE, level of evidence; (M)CTD, (mixed) connective tissue disease; mo., months; MTX, methotrexate; No., number; PAPS, primary antiphospholipid syndrome; PM, polymyositis; PSA, psoriatic arthritis; RA, rheumatoid arthritis; ref., reference; RTX, rituximab; (S)AE, (serious) adverse event(s); saf., safety; SC, seroconversion; SJS, Sjögren's syndrome; SP, seroprotection; SpA, spondyloarthritis; SSc, systemic sclerosis; TCZ, tocilizumab; TNF, tumor necrosis factor.

Table 6 Influence of disease-modifying antirheumatic drugs on influenza and pneumococcal vaccine efficacy and immunogenicity

	Efficacy	Immunogenicity	LoE Immunogenicity	
			Influenza	Pneumococcal
MTX	No data	Adequate for influenza/reduced for pneumococcal	2a	2b
Other cs-DMARD	No data	Only for HCQ Adequate	4	4
Anti-TNF α	No data	Adequate	2a	2b
B cell depletion	No data	Reduced	2a	2b
Belimumab	No data	Pneumococcal: preserved	–	2b
Tocilizumab	No data	Preserved	2b	2b
Abatacept	No data	Controversial Probably mildly reduced	4	4
Tofacitinib	No data	Adequate for influenza, reduced for pneumococcal	2b	2b
Glucocorticoids (\pm other IS)	No data	Adequate for influenza, mildly reduced in high doses GC for pneumococcal	4	2b

cs-DMARD, conventional synthetic disease-modifying antirheumatic drugs; GC, glucocorticoids; HCQ, hydroxychloroquine; IS, immunosuppressives; LoE, level of evidence; MTX, methotrexate; TNF, tumour necrosis factor.

non-bacteraemic community-acquired pneumonia as well as vaccine-type invasive disease.⁸⁹

Up to the previous recommendations, 15 studies addressed the issue of immunogenicity and safety of PCV13 and PPSV23 in patients with AIIRD: 7 studies in RA,^{8 90–95} 8 in SLE,^{95–102} 2 in patients with spondyloarthritis (SpA)^{91 103} and 1 in pSS.¹⁰⁴ Adequate as well as reduced immunogenic responses compared with controls were reported in these studies. Treatment with rituximab, TNF α blockers and MTX seemed to impair the humoral response to the pneumococcal vaccine.^{16 90 92 93}

From the previous recommendations and up to August 2018, 34 studies^{53 76 81 83 84 105–133} and two meta-analyses^{45 77} have been published on the efficacy, immunogenicity and safety of PPSV23 and the conjugated vaccines PCV7 and PCV13, including evaluation of a combined strategy (tables 7 and 8).^{106 128 133}

Regarding efficacy of pneumococcal vaccination in AIIRD, a randomised double-blind trial on the clinical efficacy of PPSV23 in preventing pneumonia in patients with RA did not demonstrate an increased efficacy of the vaccine over placebo, emphasising the need for a more efficacious vaccine.¹²⁰ In contrast, a retrospective study on the long-term effect of PPSV23 in 180 patients with RA treated with MTX showed a relative risk of 9.7 to develop pneumonia among non-vaccinated patients.¹²¹ Vaccination with PCV7 tended to reduce the risk of pneumococcal infections in patients with RA and SpA.¹²² In this cohort, a direct correlation was shown between the postvaccination levels of antipneumococcal antibodies and the risk of pneumococcal infections: more robust antibody responses after vaccination with PCV7 were associated with lower risk of serious pneumococcal infections.¹²³ The humoral immunogenicity and safety

of PPSV23 were demonstrated in RA,^{76 81 109 112 113 119 124} SLE,^{116 125 134} and, to a limited extent, in SpA and other rheumatic diseases.¹¹⁵ The long-term immunogenicity of PPSV23 was evaluated in two studies in patients with RA, treated with MTX¹²¹ and biologics.¹³⁰ Both have shown a long-term duration of protective antibodies, up to 7 years.

Humoral immunogenicity of PCV7 is similar to that of PPSV23,¹¹¹ but was shown to decrease after 1.5 years.¹²⁷ A randomised controlled study in patients with SLE aiming at evaluating the immunogenicity of the combination of PCV7 and PPSV23 in comparison with PPSV23, showed an adequate and similar response in the two groups.¹²⁸ The immunogenicity of PCV7 is preserved in patients with ANCA-associated vasculitis on remission.¹⁰⁵

The immunogenicity of PCV13 has been evaluated in small groups of patients with RA,^{118 129} SLE¹¹⁴ and pSS.¹³¹ It induced an adequate humoral response.

Three studies evaluated the prime-boost strategy. In SLE, the combination of PCV7 and PPSV23 was not more immunogenic than PPSV23 alone.¹²⁸ Another randomised controlled study evaluated the serological response to PCV13 followed by PPSV23 after 16–24 weeks in patients with RA, with one of the arms including two doses of PCV13. This study demonstrated an adequate response in patients with RA (87% and 94% on biological disease-modifying antirheumatic drugs (DMARDs) and conventional synthetic DMARDs, respectively), without additional effect of two PCV13 injections.¹⁰⁶ An additional study has questioned the long-term effect of the prime boosting strategy using PCV13 and PPSV23, showing reduced levels of functional antibodies 2 years after vaccination.¹³³

No safety issues following pneumococcal vaccination in most of the AIIRDs were reported, independent of

Table 7 Efficacy, immunogenicity and safety of 23-valent pneumococcal polysaccharide vaccine (PPSV23) in patients with AIIRD (October 2009–August 2018)

First author +ref.	Year	Study design	No. cases	No. ST	Efficacy	Immunogenicity	Safety	LoE		
								Eff.	Imm.	Saf.
Izumi ¹²⁰	2017	RCT	464 RA–vaccinated 436 RA–placebo	NA	Similar efficacy in vaccinated versus placebo	–	No safety issue	1b-2b	–	–
Kivitz ⁷⁶	2014	RCT	110 RA–Certolizumab (68%+MTX) 114 RA–Placebo (68%+MTX)	6	–	No difference between certolizumab and placebo	–	–	1b-2b	–
Hesselstrand ¹³¹	2018	Cohort	44 SSC: ▲ 31 PPSV23 ▲ 13 PCV13 49 HC	2	–	Lower response in patients treated with DMARDs	No safety issue	–	2b	4
Jaeger ⁵³	2017	Cohort	16 patients with CAPS	NA	–	–	Significant side effects	–	4	–
Chatham ¹²⁵	2017	Cohort	34 SLE PPSV23 4 weeks before, and 45 SLE 24 weeks after belimumab	23	–	Adequate response, not affected by belimumab	No safety issue	–	2b	4
Broyde ¹³⁰	2016	Cohort (retrospective)	88 RA and SpA vaccinated 42 RA and SpA non-vaccinated	NA	–	Preserved immunogenicity after 7 years	–	–	2b	–
Winthrop ⁸⁴ Part A	2016	Cohort	102 RA–Tofacitinib 98 RA–Placebo	12	–	Reduced response in tofacitinib-treated patients	–	–	2b	–
Winthrop ⁸⁴ Part B	2016	Cohort	92 RA–Cont Tofacitinib 91 RA–Stop Tofacitinib	12	–	No difference between groups	–	–	2b	–
Alten ⁸³	2016	Cohort	125 RA ABA+MTX	5	–	Adequate response	No safety issue	–	2b	4
Rezende ¹¹⁶	2016	Cohort	54 SLE	7	–	Poor immunogenicity	–	–	2b	–
Migita ¹⁰⁹	2015	Cohort	35 RA–DMARDs 55 RA–MTX 21 RA–ABA +MTX	2	–	Reduced response in abatacept-treated patients	No safety issue	–	2b	4
Migita ¹²⁴	2015	Cohort	35 RA–DMARDs 55 RA–MTX 24 RA–Golimumab +MTX	2	–	Reduced response in golimumab-treated patients	No safety issue	–	2b	4
Migita ¹¹⁹	2015	Cohort	35 RA–DMARDs 55 RA–MTX 29 RA–Tacrolimus 14 RA–Tacrolimus +MTX	2	–	Higher response in tacrolimus-treated patients	No safety issue	–	2b	4
Bingham ¹¹²	2015	Cohort	27 RA–MTX 54 RA–MTX +TCZ	12	–	Similar response in patients treated with MTX or MTX +TCZ	No safety issue	–	2b	4
Fischer ¹¹⁵	2015	Cohort	57 vaccinated/122 non-vaccinated RA, SpA, vasc., CTD	NR	–	Adequate response	–	–	4	–
Tsuru ⁸¹	2014	Cohort	21 RA–TCZ	12	–	All TCZ-treated patients responded	–	–	2b	–

Continued

Table 7 Continued

First author +ref.	Year	Study design	No. cases	No. ST	Efficacy	Immunogenicity	Safety	LoE		
								Eff.	Imm.	Saf.
Mori ¹¹³	2013	Cohort	62 RA-MTX 54 RA-MTX+TCZ 50 RA-TCZ 24 RA-DMARDs	2	-	Better response in patients treated with TCZ	No safety issue	2b	4	4
Coulson ¹²¹	2011	Cohort (retrospective)	124 RA vaccinated 28 RA non-vaccinated	NA	Reduced rate of pneumonia in vaccinated	Preserved immunogenicity after 7 years	-	4	2b	2b
Rehberg ¹⁰⁷	2010	Cohort	11 RA-RTX 36 weeks 8 RA-Pre-RTX 1 week 10 RA-DC	NR	-	Reduced in patients treated with RTX	-	4	4	-

ABA, abatacept; CAPS, cryopyrin-associated periodic syndrome; cont., continued; CTD, connective tissue disease; DC, disease control; DMARD, disease-modifying antirheumatic drug; eff., efficacy; HC, healthy controls; imm., immunogenicity; LoE, level of evidence; MTX, methotrexate; No., number; NR, not reported; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; RA, rheumatoid arthritis; RCT, randomised controlled trial; Ref., reference; RTX, rituximab; saf., safety; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSC, systemic sclerosis; ST, serotypes; TCZ, tocilizumab; vasc., vasculitis.

vaccine type (see [tables 7 and 8](#)). In contrast, data from the b-CONFIDENT Study in patients with cryopyrin associated periodic syndrome (CAPS) and from a case series of seven patients with CAPS showed that PPSV23 might induce severe local reactions and systemic reactions in these patients (fever, headache, meningismus, nausea), necessitating hospitalisation.¹²⁶ All symptoms resolved within a period of 3–17 days.

Influence of immunomodulating agents

Humoral immunogenicity of PPSV23 has been shown to be reduced by MTX,¹¹⁹ abatacept,¹⁰⁹ golimumab,¹²⁴ tofacitinib⁸⁴ and rituximab,⁹⁰ but not to be affected by certolizumab⁷⁶ and belimumab.¹²⁵ Immunogenicity following PCV7 vaccination is reduced by the use of MTX,¹¹⁰ abatacept and rituximab,¹⁰⁸ but not by TNF α blockers.¹¹⁰ Additionally, the humoral response of PCV13 is reduced under MTX.¹¹⁸ A randomised controlled study in patients with RA that evaluated the serological response to PCV13 followed by PPSV23 after 16–24 weeks, showed a significantly decreased response in patients treated with rituximab. The prime-boost strategy with PCV13 did not improve the response¹⁰⁶ (see [table 6](#) for summary).

Summary and clinical implications

Stepwise pneumococcal vaccination, according to the prime-boost strategy (PCV13 followed by PPSV23, with an interval of at least 8 weeks between the two vaccinations) is currently recommended by the Centers for Disease Control and Prevention (CDC) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) for young children, adults above 65 years of age and patients at risk for pneumococcal disease.¹³⁵ This is mainly based on expert opinion, although studies conducted in the general population^{136,137} and in patients with HIV¹³⁸ did show an augmented immunogenic response following combined vaccination.

Pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD for the following considerations: (1) The increased risk of non-invasive and invasive pneumococcal disease in patients with AIIRD.¹ (2) Good efficacy, immunogenicity and a favourable safety profile of pneumococcal vaccines (with the exception of patients with CAPS). (3) In line with the present recommendations of the CDC^{87,139} and the ESCMID.¹³⁵ Given the insufficient evidence for the efficacy of the combination of PCV13 and PPSV23, the choice and sequence of pneumococcal vaccination should be in concordance with local guidelines.

Hepatitis A vaccination

Efficacy—immunogenicity—safety

Hepatitis A virus (HAV) vaccine, an inactivated vaccine, is very efficacious in preventing hepatitis A.^{140,141} There are however no studies on the efficacy of HAV vaccination in patients with AIIRD. All three studies on immunogenicity HAV vaccination in patients with AIIRD have

Table 8 Immunogenicity and safety of 7-valent and 13-valent pneumococcal conjugate vaccine (PCV7 and PCV13), including prime boosting with 23-valent pneumococcal polysaccharide vaccine (PPSV23), in patients with AIIRD (October 2009–August 2018)

First author +ref.	Year	Study design	No. cases	Strategy	No. ST	Immunogenicity	Safety	LoE	
								Imm.	Saf.
PCV7									
Grabat ¹²⁸	2017	RCT	46 SLE; 27 placebo +PPSV23 19 PCV7 +PPSV23	NA	7	Adequate immunogenicity No differences between groups	No safety issue	1b	4
David Morgan¹⁰⁵									
	2016	Cohort	92 AAV	NA	7	Preserved immunogenicity in patients on remission	–	2b	–
Nagel¹²³									
	2015	Cohort	248 RA 249 SpA	NA	2	Good correlation between levels of immunogenicity and incidence of pneumonia	–	2b	–
Kapetanovic¹⁰⁸									
	2013	Cohort	173 RA (TCZ, RTX, ABA, MTX) 86 SpA controls	NA	2	Reduced response in patients treated with ABA and RTX	No safety issue	2b	4
Kapetanovic¹²⁷									
	2013	Cohort	163 RA 139 SpA	NA	2	Reduced immunogenicity after 1.5 y	–	2b	–
Kapetanovic¹¹⁰									
	2011	Cohort	253 RA 252 SpA (MTX, anti-TNF)	NA	2	Reduced response in pts treated with MTX	No safety issue	2b	4
Kapetanovic¹¹¹									
	2011	Cohort	201 RA (PCV7) 201 RA (PPSV23)	NA	2	Similar immunogenicity for PCV7 and PPSV23	No safety issue	2b	4
PCV13, including prime boosting with PPSV23									
Nguyen¹⁰⁶									
	2017	RCT	98 RA 63 bDMARD 35 csDMARD-DC	PCV 13+PPSV23 PCV13 +PPSV23 PCV13 +PCV13+PPSV23	12	Adequate and similar response in the three arms	No safety issue	2b	4
Bahuaud¹³³									
	2018	Cohort	23 RA	PCV13 +PPSV23	10	Adequate short-term response Functional antibodies decreased after 2 years	–	2b	–
Kapetanovic¹¹⁸									
	2017	Cohort	10 RA-MTX 10 RA-DC	PCV13	2	Reduced response in MTX-treated patients	–	4	–
Nived¹¹⁷									
	2017	Cohort	49 vasculitis 49 HC	PCV13	2	Adequate response, similar in both groups	No safety issue	2b	4
Nagel¹¹⁴									
	2017	Cohort	47 SLE 21 HC	PCV13	12	Decreased response in IS-treated patients with SLE, preserved under HCQ and belimumab	No safety issue	2b	4
Rakoczi¹²⁹									
	2016	Cohort	22 RA 24 OA	PCV13	NR	Adequate immunogenicity, but lower in RA	No safety issue	2b	4
Groh¹³²									
	2017	Case series	19 AAV ▲ 9 induction ▲ 10 maintenance	PCV13/PCV 7±PPSV23	7	Decreased response on induction, preserved on maintenance therapy	–	4	–

AAV, ANCA-associated vasculitis; ABA, abatacept; ANCA, antineutrophil cytoplasmic antibodies; bDMARD, biological disease-modifying antirheumatic drug; (cs)DMARD, (conventional synthetic) DMARD; DC, disease control; HC, healthy controls; HCQ, hydroxychloroquine; imm., immunogenicity; IS, immunosuppressives; LoE, level of evidence; MTX, methotrexate; No., number; NR, not reported; OA, osteoarthritis; pts, patients; RA, rheumatoid arthritis; RCT, randomised controlled trial; ref., reference; RTX, rituximab; saf., safety; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; ST, serotypes; TCZ, tocilizumab; TNF, tumor necrosis factor; y, years.

been published after the 2011 version EULAR recommendations² and SLR¹⁴² (table 9).

In healthy persons, the HAV vaccine is highly immunogenic, resulting in seroprotection in $\geq 95\%$ only 1 month after the first vaccine dose.^{143 144} In patients with RA, it has been shown to be less immunogenic. The percentage of seroprotected patients with RA after 1 month varied between 10%¹⁴⁵ and 60%–68%¹⁴⁶ in two studies that used different methods. A three-dose schedule (0, 1 and 6 months or 0 (double dose) and 6 months) resulted in 99% seroconversion in patients with RA after 12 months.¹⁴⁶ A double dose of vaccine at baseline did not result in an improved seroconversion rate after 1 month, compared with the usual dose (68% vs 60%).¹⁴⁶

In terms of safety, there are no data on the influence of vaccination on activity of the underlying AIIRD. Adverse events were generally mild, and reported in up to 17% of patients.^{145 146} Askling *et al* reported one case of meningoenzephalitis which occurred in a patient with an RA 2.5 weeks after the second dose of HAV vaccine.¹⁴⁵

Influence of immunomodulating agents

Using a cut-off for seroprotection of anti-HAV ≥ 10 mIU/mL instead of 20 mIU/ml, significantly more patients with RA using only an anti-TNF α agent (73%, n=15) reached seroprotection than those using a combination of anti-TNF and MTX (15%, n=21) or MTX alone (6%, n=17).¹⁴⁵ In a study of 173 immunosuppressive-treated patients (31 anti-TNF, 123 classic DMARD and 19 other), the use of anti-TNF was associated with lower seroprotection rates in a multivariate logistic regression analysis (see table 9).¹⁴⁷

Summary and clinical implications

Since a single dose of HAV vaccine does not seem to afford sufficient protection in a substantial percentage of patients with AIIRD, it is recommended to administer a second dose of vaccine 6 months after the first and to determine postvaccination antibody titres. If this is not possible, as in the case of a last-minute traveller, it should be borne in mind that a patient with AIIRD may not be protected after a single dose of HAV vaccine. Passive immunisation for the specific journey may be considered.

Hepatitis B vaccination

Efficacy—immunogenicity—safety

The incidence of hepatitis B virus (HBV) infections has markedly decreased in countries where HBV vaccination is routinely implemented.¹⁴⁸ Although no antibody level gives complete protection against transient infection, there is a clear association between antibody level and risk of HBV infection.¹⁴⁹ In general, a level of antihepatitis B surface antigen ≥ 10 mIU/ml is considered protective.

Table 9 Efficacy, immunogenicity and safety of hepatitis A vaccination in patients with AIIRD

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	Influence of IS on eff./LoE			
							imm.	Eff.	Saf.	
Rosdahl ¹⁴⁶	2018	Cohort	69 RA 58 HC	-	Reduced in RA	No SAE Mild systemic AE in 17% (HC and RA combined)	-	-	4	
Askling ¹⁴⁵	2014	Cohort	53 RA: 15 anti-TNF 21 anti-TNF +MTX 17 MTX	-	Seroprotection in 10% after 1 month, 83% at month 7 (1 month after second dose)	One meningoencephalitis 2.5 weeks after second dose Mild AE in 2	Possibly reduced on MTX	2b	4	
Van den Bijlaardt ¹⁴⁷	2013	Cohort (retrospective)	173 IS-treated: 31 anti-TNF 123 DMARD 19 Other	-	-	-	Reduced imm. on anti- TNF in multivariate regression analysis	-	2b	-

AIIRD, autoimmune inflammatory rheumatic disease; DMARD, disease-modifying antirheumatic drug; eff., efficacy; HC, healthy control; imm., immunogenicity; IS, immunosuppressives; LoE, Level of evidence; MTX, methotrexate; No., number; RA, rheumatoid arthritis; ref., reference; (S)AE, (serious) adverse event; Saf., safety; TNF, tumor necrosis factor.

Up to the previous version of recommendations, a total of four studies reported on the immunogenicity of HBV vaccination in patients with RA,¹⁵⁰ SLE,¹⁵¹ AS¹⁵² and Behçet's disease.¹⁵³ One additional study in patients with RA had been published since then (online supplementary table S1).¹⁵⁴

This recent study, including 46 patients with RA and 9 HCs, reported a significantly lower percentage of patients versus HCs reaching seroprotective antibody levels (64% in patients vs 100% in HCs).¹⁵⁴ Another controlled study from 2005, with 13 patients with Behçet's disease and 15 HCs reported no difference in immunogenicity of the HBV vaccine.¹⁵³ A response to the vaccine was demonstrated in all remaining studies on HBV vaccination in patients with AIIRD that did not include a control group^{150–152} (online supplementary table S1).

The HBV vaccine did not lead to changes in overall disease activity in patients with RA and Behçet's disease.^{150 153 154}

Influence of immunomodulating agents

A severely hampered antibody response to HBV vaccination was noted in patients with AS treated with TNF-blocking agents.¹⁵²

Summary and clinical implications

HBV vaccine should be administered to patients with AIIRD at risk of infection, for example, medical personnel, patients having an infected family member, intravenous drug users, men who have sex with men, and patients travelling to or residents from endemic countries. It is advised to determine vaccination response. For non-responders several strategies are available to try to reach seroprotection. A booster vaccination or passive immunisation should be considered for an unvaccinated patient or a patient with insufficient response exposed to HBV. See recommendations of the CDC via <https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hepb.pdf>.

Tetanus toxoid vaccination

Efficacy—immunogenicity—safety

The efficacy of tetanus toxoid vaccination in the prevention of tetanus has never been studied in a vaccine trial. The incidence of tetanus has been shown to decrease dramatically in vaccinated populations,^{155 156} although this was not specified for the AIIRD population. The protective antibody level for tetanus is generally considered to be ≥ 0.1 IU/mL. Tetanus is extremely rare in fully immunised adults who received their last dose of vaccine within the preceding 10 years.

Reports on immunogenicity of tetanus toxoid vaccination in patients with RA showed satisfactory antibody responses.^{9 112 157} Most studies in patients with SLE reported adequate response rates.^{102 157–159} One small study from 1980 including nine patients with SLE and

nine HCs showed a diminished response in the patients with SLE, with a blunted response in three of them.¹⁶⁰

Most studies did not report on safety of tetanus toxoid vaccination. One randomised controlled trial (RCT) showed a higher incidence of mild/moderate adverse events after combined tetanus toxoid and pneumococcal vaccination in patients with RA on MTX who recently started the use of tocilizumab, compared with patients with RA on MTX only (online supplementary table S2).¹¹²

Influence of immunomodulating agents

Rituximab administered 24 weeks before vaccination did not affect response to the tetanus toxoid vaccine in patients with RA.⁹⁰ An RCT in 54 patients with RA on MTX who started tocilizumab 3 weeks before tetanus toxoid vaccination, and 27 RA MTX disease controls, showed no difference in immunogenicity of the tetanus toxoid vaccine between groups. However, there were only three patients in the tocilizumab + MTX group who did not have a seroprotective antibody level at baseline. Two out of these three patients reached a protective level 5 weeks after vaccination.¹¹²

An observational study on immunogenicity of pneumococcal, tetanus toxoid and *H. influenzae* type B vaccine in 73 patients with SLE reported a trend towards a lower response in patients on glucocorticoids and azathioprine, which was not specified for tetanus toxoid vaccination.¹⁰²

Summary and clinical implications

As satisfactory immune responses were observed in patients with AIIRD following tetanus toxoid vaccination, mostly similar to the response in HCs, and no serious adverse events have been reported, the updated EULAR recommendations conclude that patients with AIIRD should receive tetanus toxoid vaccination according to national recommendations for the general population. Since no data are available on efficacy or immunogenicity of tetanus toxoid vaccination in patients who received B cell depleting therapy within the preceding 6 months, passive immunisation with tetanus immunoglobulins should be considered in these patients in case of an event with high risk of acquiring tetanus, when the vaccine would otherwise be indicated, according to expert opinion.

Herpes zoster vaccination

Efficacy—immunogenicity—safety

Up to the previous recommendations, no data were available on herpes zoster vaccination in patients with AIIRD. Since 2010 seven relevant studies have been published (table 10).

Currently, two different vaccines are available for the prevention of herpes zoster in varicella-zoster virus (VZV)-seropositive healthy adults above the age of 50 years: one is a live-attenuated vaccine and the other is an adjuvanted subunit (non-live) vaccine. All studies on zoster vaccination in patients with AIIRD have been performed using the live-attenuated zoster vaccine. This vaccine has

Table 10 Efficacy, immunogenicity and safety of live-attenuated herpes zoster vaccination in patients with AIIRD

First author +ref.	Year	Study design	No. cases	Efficacy	Immunogenicity	Safety	Influence IS on eff./imm.		LoE	
							Imm.	Saf.	Eff.	Imm.
Winthrop ¹⁷⁰	2017	RCT	55 RA MTX+TFC* 57 RA MTX+PCB*	-	Similar CMI response. Trend towards higher humoral response MTX+TFC	3 SAE in MTX-TFC group versus 0 in MTX+PCB: one cholangitis, one bronchitis and one disseminated primary varicella in seronegative patient. Mild AE no difference.	See column immunogenicity.	-	2b	4
Russell ¹⁷³	2015	RCT	206 GC vacc. (25% PMR) 100 GC PCB-vacc (31% PMR) Mostly no AIIRD. > 10–20 mg: n=39	-	Higher postvacc. humoral response in vacc.	More injection-site AE and headache in vacc. Other systemic and serious AE: no difference.	No influence of limited daily GC dose	-	2b	4
Koh ¹⁶⁹	2018	Cohort	41 RA 28 OA	-	Lower CMI response in RA. Similar humoral response.	No SAE. Mild systemic AE in 11.6% of all participants. 6 RA flares during 12 weeks postvacc. Median Disease Activity Index unchanged.	-	-	2b	4
Zhang ¹⁶⁷ and Yun ¹⁶⁸	2012 2017	Cohort (retrospective database)	Total: 463 541 Vacc: 18 683 (4.0%) Vacc on biologics: 633 7780 vaccinated patients in analysis	Lower incidence of HZ in vacc. patients. Rapid decline difference incidence rate vacc. and unvacc. 6 years postvacc: no longer significant.	-	<42 of vacc: HZ incidence decreased, no cases of hospitalised meningitis or encephalitis, no HZ in patients using biologics	Lower HZ incidence in vacc. patients using biologics, DMARDs or GC alone	2b	-	4
Guthridge ¹⁷¹	2013	Cohort	10 SLE 10 HC	-	Similar proportion of subjects with 50% increase in CMI measures postvacc.	No difference. No flares.	-	-	2b	4

*Tofacitinib or placebo was started 2–3 weeks postvaccination.

†Patients with rheumatoid arthritis (n=292 169), psoriasis (n=89 565), psoriatic arthritis (n=11 030), ankylosing spondylitis (n=4026) and/or inflammatory bowel disease (n=66 751). AIIRD, auto-immune inflammatory rheumatic disease; CMI, cell-mediated immunity; DMARD, disease-modifying antirheumatic drug; eff., efficacy; GC, glucocorticoids; HC, healthy controls; HZ, herpes zoster; imm., immunogenicity; IS, immunosuppressives; LoE, Level of evidence; MTX, methotrexate; No., number; OA, osteoarthritis; PCB, placebo; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; RCT, randomised controlled trial; ref., reference; (S)AE, serious adverse event(s); Saf., safety; SLE, systemic lupus erythematosus; TFC, tofacitinib; vacc., vaccinated.

been shown to decrease the risk of herpes zoster in adults above the age of 50 years by 38%–70%,^{161 162} with lowest efficacy in those above 70 years.¹⁶¹ Of note, the AS01 adjuvanted subunit (non-live) vaccine has recently been shown to be safe and more efficacious than the live-attenuated vaccine in healthy adults above the age of 50 and 70 years.^{161 163 164} Vaccine efficacy ranged between 91% and 98% and did not significantly differ between age groups.^{163 164} Of note, safety of the adjuvant system AS01, which contributes to the generation of a particularly strong cellular immune response,^{165 166} has not yet been determined in patients with AIIRD.

Vaccination with the live-attenuated zoster vaccine was associated with a reduced incidence of herpes zoster in patients with immune-mediated diseases (RA, psoriatic arthritis, ankylosing spondylitis, psoriasis and inflammatory bowel diseases) over 60 years of age, as reported in a large retrospective database study by Zhang *et al*. In total, 7780 vaccinated and over 800 000 unvaccinated patients were included in their analysis.¹⁶⁷ A rapid decline in vaccine efficacy was observed in the same study population. Six years after vaccination, the difference in herpes zoster incidence between groups of vaccinated and unvaccinated subjects was no longer significant.¹⁶⁸

Immunogenicity of the live-attenuated zoster vaccine has been investigated in patients with RA^{169 170} and SLE.¹⁷¹ Both patient groups were able to mount cell-mediated immune responses to the vaccine,^{169–171} which is crucial for the protection against herpes zoster.¹⁷² However, live-attenuated zoster vaccination resulted in lower cell-mediated immunity in patients with RA (n=41) than in controls (n=28).¹⁶⁹ Because no correlate of protection for herpes zoster infection is known, and methods for assessing herpes zoster immunity are not uniform, interpretation and comparison of studies is difficult.

Disease activity of the underlying AIIRD did not seem to be affected by live zoster vaccination, but numbers of analysed patients are low.^{169–171} In a study in patients with RA, who were randomised to receive tofacitinib (n=55) or placebo (n=57) 2–3 weeks following vaccination, three serious adverse events were observed in the tofacitinib group versus none in the placebo group. Of note, one case of disseminated primary varicella occurred in a patient who was VZV-seronegative at baseline.¹⁷⁰ In the retrospective database study by Zhang *et al*, the zoster vaccine did not seem to induce infection within 42 days after vaccination. On the contrary: a reduced incidence of herpes zoster was seen in the vaccinated patients. No cases of hospitalised meningitis or encephalitis were identified in this period.¹⁶⁷

Influence of immunomodulating agents

The favourable effect of vaccination on herpes zoster incidence in patients with autoimmune diseases is present regardless of medication use, including biologics (used by 633 vaccinated patients), as reported in the same large database study by Zhang *et al*.¹⁶⁷ A daily dose of 5–20 mg of corticosteroids in a heterogeneous patient group

(206 patients received zoster vaccination, of whom 25% were patients with polymyalgia rheumatica) did not seem to affect humoral immune response to live-attenuated zoster vaccination. Unfortunately, effect on cell-mediated immune response was not reported.¹⁷³ Zoster vaccination resulted in a similar cell-mediated response in patients with RA who started the use of tofacitinib or placebo 2–3 weeks after vaccination (see table 10).¹⁷⁰

Summary and clinical implications

Although large prospective trials that are sufficiently powered for assessing safety are lacking, the safety and efficacy profile of the live-attenuated zoster vaccine seem to be favourable for VZV-seropositive patients with AIIRD. However, the vaccine contains live-attenuated virus and, therefore, should still be considered with caution in the immunocompromised patient. Before administering the zoster vaccine, it is advisable to affirm the VZV-seropositive status of the patient. In case of a VZV-seronegative patient, a less potent VZV vaccine approved for preventing primary varicella in children may be considered. Based on expert opinion, the zoster vaccine is preferably administered 4 weeks prior to initiation and not during treatment with biologics and targeted synthetic DMARDs.

As noted earlier, the novel non-live AS01 adjuvanted subunit vaccine has been shown to be more efficacious than the live-attenuated vaccine in healthy adults above the age of 50–70 years. Whether this also holds true for the AIIRD population and whether the adjuvant system AS01 is safe in this patient group, is most interesting and warrants further investigation.

Yellow fever vaccination

Efficacy—immunogenicity—safety

The yellow fever vaccine is a live-attenuated vaccine. Several cases of visceral dissemination of yellow fever of the vaccine type have been reported, with clinical features similar to wild type yellow fever, including high mortality.^{174–176} The vaccine is therefore generally contraindicated in immunocompromised patients^{177–180} (online supplementary table S3).

Only limited observational studies have been published on yellow fever vaccination in patients with AIIRD, mostly concerning revaccination (see online supplementary table S3 for details). The reported immunogenicity results are mainly adequate, and similar as in HC.^{177–180}

A study of 34 glucocorticoid-treated patients (among whom 9 were patients with RA and 14 with chronic inflammatory conditions, revaccination in 44%) and 68 HC, reported more moderate and severe local reactions in patients (12% vs 2%).¹⁷⁹ No serious systemic adverse events of yellow fever vaccination were reported in the previously mentioned studies in patients with AIIRD. As the vaccine has been contraindicated in immunocompromised patients for years, numbers of studies and included patients are however very low and, as stated, most patients were revaccinated. Of note, lethal outcomes of fellow

fever vaccination have been reported in immunocompromised patients, including a female patient with RA and SLE, who was possibly treated with glucocorticoids and MTX.¹⁸¹

Influence of immunomodulating agents

Due to the heterogeneous populations of the small studies on yellow fever vaccination in patients with AIIRD, it is difficult to discern the separate influences of different immunosuppressive agents. In a study of corticosteroid-treated patients, of whom 44% were vaccinated for yellow fever earlier in life, seroprotection against yellow fever was reached in all 20 analysed patients. A trend towards a lower yellow fever antibody response was observed in anti-TNF α -treated patients with RA (n=17) compared with HC (n=15).¹⁸⁰

Summary and clinical implications

Reported immunogenicity results of yellow fever revaccination among patients with AIIRD are mainly adequate and similar as in HC. However, the available data on the safety of yellow fever vaccination in this group are very limited, and potential sequelae are serious (including death). Patients with AIIRD under immunosuppression should, therefore, avoid yellow fever vaccination in general. Temporarily withholding immunosuppressive therapy may be considered for patients with AIIRD travelling to endemic countries.

Human papillomavirus vaccination

Efficacy—immunogenicity—safety

Data on the efficacy of human papillomavirus (HPV) vaccination originate from vaccine trials in HCs that investigate the capacity of HPV vaccination to prevent premalignant lesions. A vaccine efficacy of 66% to prevent cervical intraepithelial neoplasia grade III was reported in a bivalent (HPV types 16 and 18) HPV vaccine trial after 4.5–10 years of follow-up.¹⁸²

The correlation between the level of anti-HPV antibodies and protection against the development of cervical carcinoma is not known, since there are no reports on cervical carcinoma in vaccinated subjects. The level of seroprotection is based on comparison with naturally infected subjects.¹⁸³

To date, no studies on the efficacy of HPV vaccination to prevent malignancies or premalignant lesions in the AIIRD population have been published, but there are studies on HPV vaccine immunogenicity in patients with AIIRD, all published after 2010 (online supplementary table S4). All but one study, performed in patients with juvenile idiopathic arthritis (JIA),¹⁸⁴ include patients with SLE and used a quadrivalent (HPV types 6, 11, 16 and 18) vaccine.^{185–189} Seroconversion rates in patients were high and usually similar to those of healthy subjects, although two studies reported a lower geometrical mean titre for HPV 16 in patients with SLE after 5 years of follow-up,¹⁸⁵ and also for patients with JIA,¹⁸⁴ compared with HCs.

Rates of vaccine adverse events similar to HCs were reported for both patients with SLE¹⁸⁸ and patients with JIA.¹⁸⁴ Disease activity after vaccination was stable.^{184 186 188 189}

Influence of immunomodulating agents

Mok *et al* reported that anti-HPV titres were lower in vaccinated patients with SLE using immunosuppressive agents, especially in those receiving a combination of mycophenolate mofetil (MMF) and glucocorticoids.¹⁸⁸ After 5 years of follow-up it was noted that patients with SLE that no longer were anti-HPV seropositive received significantly longer and higher doses of glucocorticoids and MMF than those with persistent seropositivity.¹⁸⁵

Summary and clinical implications

Immunogenicity of HPV vaccination in the AIIRD population is high and, in the majority of studies, similar to that in HCs. The vaccine appears to be safe in patients with AIIRD. Therefore, the vaccine is recommended for patients with AIIRD, in accordance with recommendations for the general population. Patients with SLE, in particular, are advised to receive HPV vaccination, since they were shown to be at high risk of contracting a genital HPV infection, including the serotypes that are considered to be high risk for developing cervical dysplasia.^{190–194}

Tickborne encephalitis vaccination

Efficacy—immunogenicity—safety

The available tickborne encephalitis (TBE) vaccines are inactivated vaccines. The vaccine is highly immunogenic in the general adult population.¹⁹⁵ Excellent effectiveness of TBE vaccination in prevention of TBE was demonstrated in an Austrian study.¹⁹⁶ Nonetheless, cases of vaccine failure have been reported, which occurred mainly in older or immunocompromised persons.¹⁹⁷

To date, only one study on vaccination against TBE in patients with AIIRD has been published (online supplementary table S5). This Swedish study by Hertzell *et al* enrolled 65 patients with RA and 1 patient with AS on anti-TNF (n=16), a combination of MTX and anti-TNF (n=36) or MTX alone (n=14). Four doses of vaccine instead of three were offered to patients and HCs ≥ 60 years of age. One month after the last dose of vaccine, 39% of the patients and 79% of the HCs had developed protective levels of neutralising TBE antibodies. The difference was statistically significant. An extra dose of vaccine in patients with an undetectable antibody level at month 13 resulted in seroprotection in 4 out of 10 patients, all of whom were older than 60 years. No serious adverse events occurred.¹⁹⁸

Influence of immunomodulating agents

In the study by Hertzell *et al*, regarding only patients ≥ 60 years of age, it seemed that a lower percentage of those treated with a combination of MTX and anti-TNF reached seroprotective anti-TBE levels than those treated with MTX or anti-TNF alone (25% vs 38%–40%).¹⁹⁸

Summary and clinical implications

Although the updated recommendations do not specifically provide recommendations regarding TBE vaccination, an overarching principle states that non-live vaccines can be administered to patients with AIIRD, including during their use of glucocorticoids and DMARDs. The only available study on TBE vaccination in the AIIRD patient population showed a diminished immunogenicity response in these patients. As such, determining TBE-antibody levels after the last vaccine dose and, if necessary, giving an extra dose of vaccine may be considered.

DISCUSSION

This SLR summarises the available data on efficacy, immunogenicity and safety of vaccination in patients with AIIRD, including patients with AIIRD using immunomodulating agents. Since the first version of EULAR recommendations and accompanying SLR on vaccination of adult patients with AIIRD were published in 2011,^{2 142} there has been a large expansion in the amount of available evidence on this topic, necessitating an update. By defining four research questions, we were able to address incidence/prevalence of VPIs, efficacy, immunogenicity and safety of vaccination, as well as the influence of immunomodulating agents on vaccine efficacy/immunogenicity in patients with AIIRD. To enable the presentation of a clear overview of the large amount of available data, the evidence on the incidence and prevalence of VPI diseases in patients with AIIRD was presented in a separate SLR, which was submitted for publication simultaneously with this report. The literature search for the fourth research question, dealing with the effect of vaccinating household members of patients with AIIRD on the occurrence of VPI in these patients and household members (including newborns), did not result in finding any relevant studies. Therefore, the recommendation encouraging household members of patients with AIIRD to receive vaccines according to national guidelines with the exception of oral polio vaccine, as formulated in the updated recommendations, is based on expert opinion. This recommendation follows guidelines of international societies such as the Infectious Diseases Society of America.¹⁹⁹ Also the recommendation of avoiding live-attenuated vaccines during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy is based on expert opinion. This recommendation is in line with the EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation.²⁰⁰

One strength of our current approach, compared with the 2011 SLR, is the clear separation between efficacy and immunogenicity of vaccination, allowing a just interpretation of the data by readers. When assessing the different vaccines, evidence on efficacy, defined as the capacity of a vaccine to prevent infection, was

considered to be of higher quality than evidence on immunogenicity, which refers to the capacity of vaccines to induce humoral and/or cellular immune responses. Unfortunately, because of the necessarily large sample size, using a clinical end point was essentially infeasible for some groups of AIIRD and/or vaccines. Consequently, only a small number of studies used a clinical end point.

It is important to note that although a large number of articles was included, for certain AIIRDs, vaccines and immunomodulating treatments the number of publications was still very limited. The majority of studies was performed in patients with RA and SLE. Results in these patient groups cannot uncontestedly be extrapolated one on one to patients with other AIIRDs.

Regarding safety of vaccination in the AIIRD population, both the occurrence of adverse events and influence on underlying disease of vaccination were assessed. Although since 2011 the amount of available evidence has considerably grown, studying safety of vaccination in patients with AIIRD remains a challenge. While vaccination did not lead to significant harms in the large majority of the included studies, these studies were too small or not properly designed to be able to detect the occurrence of rare adverse events.

In conclusion, evidence on efficacy, immunogenicity and safety of vaccination in patients with AIIRD (including those using immunomodulation agents), from October 2009 to August 2018, was systematically reviewed to provide a basis for updated evidence-based recommendations for vaccination in patients with AIIRD,³ in order to aid physicians, nurses and other health professionals dealing with questions regarding vaccination in patients with AIIRD in daily clinical practice.

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Contributors CR, in collaboration with SvA, reviewed articles on efficacy, immunogenicity and safety of vaccination for influenza, hepatitis A, hepatitis B, tetanus toxoid, herpes zoster, yellow fever and tickborne encephalitis in patients with AIIRD, and drafted the first version of the manuscript. VF, in collaboration with OE, performed the literature search and reviewed articles on vaccination in patients with AIIRD on the various immunomodulating therapies. MH reviewed articles on efficacy, immunogenicity and safety of vaccination of human papillomavirus vaccination in patients with AIIRD. OE initiated the project, reviewed articles on efficacy, immunogenicity and safety of vaccination for pneumococcal disease in patients with AIIRD, and wrote the paragraphs on pneumococcal vaccination. All authors collaborated in discussions during two meetings, and read and approved the final manuscript.

Funding This project was supported by EULAR.

Competing interests KW reports personal fees from Pfizer, during the conduct of the study; grants and personal fees from Biotest, CSL Behring, personal fees from LFB, Grifols, Baxter, Roche, Octapharma, grants from BMS, outside the submitted work. AM reports grants and personal fees from ABBVIE, Pfizer, BMS, UCB, MERCK, during the conduct of the study. MD reports grants and personal fees from PFIZER, ABBVIE, UCB, NOVARTIS, LILLY, MERCK, ROCHE, grants from BMS, outside the submitted work. OE reports grants and personal fees from Pfizer, Abbvie, Roche, Janssen, personal fees from Novartis and Lilly. All other authors have no conflicts of interests to declare.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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