Review

Vaccinations in adults with rheumatoid arthritis in an era of new disease-modifying anti-rheumatic drugs

P.L. Meroni[1], D. Zavaglia[2], C. Girmenia[3]

[1]*Department of Clinical Sciences and Community Health, University of Milan, Department of Rheumatology, ASST-G. Pini, Immunorheumatology Research Laboratory, IRCCS Istituto Auxologico Italiano, Milan, Italy;*
[2]*Medical Department, Pfizer Italia, Rome;*
[3]*Department of Haematology, Oncology, and Dermatology, Azienda Policlinico Umberto I, Sapienza University, Rome, Italy.*

Pier Luigi Meroni, MD
Daniela Zavaglia, MD
Corrado Girmenia, MD

Please address correspondence to:
Dr Pier Luigi Meroni,
Divisione di Reumatologia,
ASST-Pini,
P.zza C. Ferrari 1,
20122 Milan, Italy.
E-mail: pierluigi.meroni@unimi.it

Received on June 22, 2017; accepted in revised form on September 18, 2017.

Clin Exp Rheumatol 2018; 36: 317-328.

Key words: rheumatoid arthritis, infections, vaccinations

Competing interests: Medical writing and editorial support was provided by CDM and was funded by Pfizer. C. Girmenia and P.L. Meroni received an honorarium from Pfizer in connection with the development of this manuscript. D. Zavaglia is a Pfizer employee.

ABSTRACT

Patients with rheumatoid arthritis are at greater risk of infectious morbidity and mortality due to disease-related abnormalities and use of immunosuppressive medications. Vaccinations are recommended by international guidelines among infection control strategies, but vaccination rates are reported to be still suboptimal in both America and Europe. Furthermore, with the increasing number of immunomodulatory medications used in RA patients, safety and efficacy of vaccinations in RA patients on such therapies have been questioned. This paper reviews current data about the safety of the most relevant vaccinations for RA adult patients and on the extent to which RA treatment can affect vaccine efficacy. Although it is recognised that immunological and pathological reactions can occur following vaccination, especially in genetically susceptible hosts, early data in RA patients under treatment with bDMARDs or tsDMARDs indicate that vaccines might be safer in the setting of immunosuppression than previously thought. Reviewing safety and immunogenicity data about influenza, pneumococcal, HZ, HPV, and HBV vaccines, we here try to summarise updated, practical suggestions for rheumatologists. Improving the knowledge of the vaccination practice both in patients and physicians is of crucial importance. In RA patients, vaccination status should be assessed in the initial patients' work-up and vaccination strategies should be planned and then implemented ideally during stable disease, as recommended by international guidelines.

Introduction

Patients with rheumatoid arthritis (RA) suffer greater infectious morbidity and mortality. They have a 1.5- to 2-fold higher risk of hospitalisation for infections compared to patients of similar age without RA, and also the risk of death from infection is greater (1, 2). This is attributable both to disease effects and to immunosuppressive medications used to treat RA (1-5). Serious infections (SI) have been reported to be more common in the lower respiratory tract followed by skin and soft-tissues, but other common infection sites are bone, joints and the urinary tract (2, 4). A systematic review and meta-analysis of interventional randomised controlled trials with bDMARDs and targeted synthetic disease-modifying anti-rheumatic drug (tsDMARDs) in RA was recently carried out in order to describe the epidemiological findings of SI in patients with moderate to severe active RA (3). Three summary measures were assessed for each bDMARDs and for tofacitinib (the first tsDMARD) across randomised controlled trials: incidence rate of SI for each agent, estimated relative risk (risk ratios) and risk differences for SI *versus* control. The main results of this analysis are summarised in Table I. The interpretation of these data may be difficult in relation to the apparent contradictions of the three epidemiological measures. If we consider the incidence rate it appears that tofacitinib is associated with a lower infectious risk compared to the bDMARDs, however, the other measures - risk ratio and risk difference *versus* placebo or *versus* methotrexate - seem to show different infectious risk correlations of the various DMARDs. Indeed, these apparent contradictions are dependent on the difficulty in comparing studies on different populations and enrolment criteria. In any case, these data show that, although infections represent relevant complications in RA, their frequency is relatively low

Table I. Incidence rates of serious infections (SI), risk ratios and risk differences *versus* placebo or *versus* methotrexate for bDMARDs and tsDMARD. Data are from a systematic review and meta-analysis of interventional randomised controlled trials with biologics in RA (3).

Drug	SI incidence rate, patients with events per 100 pt-years (N. of trials considered)	Risk ratio/difference of SI *versus* placebo (N. of trials considered)	Risk ratio/difference of SI *versus* methotrexate (N. of trials considered)
Abatacept	3.04 (11)	1.18/0.40 (4)	0.99/-0.02 (1)
Rituximab	3.72 (8)	0.99/-0.02 (5)	0.46/-2.78 (1)
Tocilizumab	5.45 (13)	1.82/1.51 (9)	1.97/0.68 (1)
Infliximab	6.11 (11)	0.83/-0.52 (3)	2.80/3.7 (2)
Etanercept	4.06 (17)	1.00/0 (1)	0.82/-0.79 (3)
Certolizumab pegol	7.59 (5)	2.18/1.96 (5)	/
Golimumab	5.31 (6)	1.30/0.68 (4)	0.68/-0.61 (4)
Adalimumab	5.04 (18)	2.27/1.16 (11)	1.43/1.07 (4)
Total TNFi	4.90 (57)	1.50/0.94 (24)	1.24/0.26 (11)
Tofacitinib, 5 mg BID	2.5 (6)	2.21/0.38 (9)	1.1/0.26 (1)
Tofacitinib, 10 mg BID	3.19 (6)	2.01/0.40 (9)	0.75/-0.67 (1)

over the prolonged period of DMARDs treatments.

These epidemiological findings are of crucial importance for the choice of the appropriate infection-control strategies that could be used in RA patients. Among the possible prevention strategies, primary prophylaxis with antimicrobials is generally not recommended considering the prolonged period at risk and the lack of the efficacy in RA patients. Conversely, vaccinations seem to be more appropriate and are recommended by the international guidelines (6-8). Unfortunately, vaccination rates are still suboptimal and a discrepancy between awareness of infectious complications risk and actual vaccination rates has been reported from several centres in America and Europe (9-15). Lack of physician recommendations appeared to be the most important factor for unvaccinated status, while patients' lack of knowledge or negative attitudes toward vaccinations play a minor role.

With the increase in the number of immunomodulatory medications available to treat RA, questions have arisen about safety and efficacy of vaccinations in RA patients on such therapies. In terms of safety, for example it has been stressed that live vaccines, such as the herpes zoster (HZ) vaccine, may be of particular concern due to the risk of severe infections following live vaccination of immunosuppressed patients on biologic drugs. However, it appears, from some observational studies, that they may be safer than previously thought, although trials specifically evaluating the risk of such vaccines in this setting are not currently available (16). Regarding efficacy of vaccinations in patients with RA, as well as in other systemic autoimmune conditions, it may be expected to be reduced. Since it is difficult to evaluate efficacy of vaccinations in clinical trials, rates of immunisation have been generally considered as a surrogate for efficacy (11). On the other hand, there is a potential risk of flares of the underlying autoimmune disease following vaccination, although evidence for any consistent relationship between adjuvant and autoimmune responses is scarce (17).

The European League against Rheumatism (EULAR) in 2011 (6), and the American College of Rheumatology (ACR) in 2015 (7) have issued recommendations about appropriate use of vaccines for adult RA patients (Tables II and III). An increasing number of vaccines are currently available to the rheumatologists that have a key role in the management of patient with RA. On the other hand, the number of RA drugs entering the market continues to increase, and this amplifies the gaps that still remain in our knowledge about vaccinations in RA. We here review current data about the safety of the most relevant vaccinations for RA adult patients and on the extent to which bDMARDs and tsDMARDs can affect vaccine efficacy. Vaccination specific data in patients treated with tsDMARDs are almost limited to tofacitinib, the first janus kinase inhibitor used for several years in RA treatment, while specific data available for the new tsDMARD baricitinib are very preliminar.

Vaccinations in adult patients with RA and effects of DMARDs

All vaccines may be important in RA, however, the most clinically relevant for all adult RA patients may be considered influenza and pneumococcal vaccines – recommended by the Centers for Disease Control and Prevention (CDC) – and HZ vaccines. Other important vaccinations for selected adult RA patients, bearing other specific risk factors, are those against human papilloma virus (HPV) and hepatitis B virus (HBV) (2, 16).

Influenza vaccination

Rates of seasonal influenza vaccination are suboptimal in this category of patients. The results of an observational, cross-sectional, multicentre, international study (COMORA cohort) were analysed with the objective to describe influenza and pneumococcus vaccine coverage in RA patients in the different countries and to identify factors associated with their usage (9). Vaccination coverage emerged to be low with great differences between countries: overall 25.3% of patients received influenza vaccination during the last year (from less than 1% in Morocco and Egypt to 66.2% in Japan). In particular, it was 26.3% in Italy.

Older age, higher education, comorbidities, lower disease activity, treatment with biotherapy and not with corticosteroids were predictive factors of vaccination, as identified in the countries with a higher vaccination coverage.

The constituents of the seasonal influenza vaccine generally change every year, based on the available data on the most prevalent circulating influenza strain. Live intranasal vaccines are contraindicated in RA patients – and are no longer available in Italy – and only intramuscular attenuated influenza vaccine formulations should be administered (18, 19). The intramuscular vaccine is traditionally a trivalent

Table II. 2011 recommendations regarding the use of vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD) of the European League Against Rheumatism (EULAR) (6).

Recommendations	Grade of the evidence
The vaccination status should be assessed in the initial work-up of patients with AIIRD	no grade of evidence possible; strength of recommendation D;
Vaccination in patients with AIIRD should ideally be administered during stable disease	no grade of evidence possible; strength of recommendation D
Live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD	grade of evidence IV; strength of recommendation D
Vaccination in patients with AIIRD can be administered during the use of disease-modifying anti-rheumatic 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
Inactivated influenza vaccination should be strongly considered for patients with AIIRD	grade of evidence Ib–III; strength of recommendation B–C
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
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
Herpes zoster vaccination may be considered in patients with AIIRD	grade of evidence III–IV; strength of recommendation C–D
Human papillomavirus vaccination should be considered in selected patients with AIIRD	grade of evidence III; strength of recommendation C–D
In hyposplenic/asplenic patients with AIIRD influenza, pneumococcal, *Haemophilus infl uenzae* b and meningococcal C vaccinations are recommended	grade of evidence IV; strength of recommendation D
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
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
BCG vaccination is not recommended in patients with AIIRD	grade of evidence III; strength of recommendation C–D;

Grade of evidence;
Ia: Meta-analysis of randomised controlled trials
Ib: Randomised controlled trial
II: Prospective controlled intervention study without randomisation
III: Descriptive/analytic study (including case-control, cross-sectional, case series)
IV: Expert committee reports or opinion or clinical experience of respected authorities or both

Strength of evidence based on
A: Category I evidence
B: Category II evidence or extrapolated recommendations from category I evidence
C: Category III evidence or extrapolated recommendations from category I or II evidence
D: Category IV evidence or extrapolated recommendations from category II or III evidence

vaccine protecting against 2 influenza A strains and 1 influenza B strain; however, recently a quadrivalent form became available that protects against an additional B strain (19). RA patients aged more than 65 should receive the high-dose vaccine, currently available only for the trivalent vaccine, which has been shown to be more effective than the standard dose (20, 21).

In view of the lack of controlled trials of efficacy, influenza vaccine immunogenicity is evaluated with haemagglutinin inhibition antibody titres (at least 1:40 is considered protective). The results of influenza vaccine immunogenicity in RA patients receiving different treatments are summarised in Table IV (22-32). The published studies generally demonstrated a reduction in influenza seroprotection and seroconversion in vaccinated RA patients compared to healthy controls. However, influenza virus vaccine anyhow generated a good humoral response in RA patients treated with most of DMARDs (*i.e.* methotrexate, infliximab, etanercept, tofacitinib, abatacept, tocilizumab, certulizumab pegol) with the exception of those treated with rituximab (22-32). Nevertheless, while humoral immunity against influenza was severely impaired in rituximab-treated patients, cellular immunity to influenza vaccination was similar to patients treated with other DMARDs and healthy controls. A preserved cellular immunity may account for the relatively low rate of infections among patients with B-cell depletion (25). Furthermore, the reduced response in rituximab-treated patients was dependent on the timing of the vaccine in relation to rituximab administration (22, 24, 25). In terms of safety, studies have demonstrated that the influenza vaccine is safe in patients with RA (33).

In summary, the intramuscular influenza vaccine was reported to be given annually to all RA patients, whether under treatment or not. In case of treatment with rituximab, it has been suggested that vaccine administration should be carried out prior rituximab

Table III. 2015 recommendations regarding the use of vaccines in patients with rheumatoid arthritis of the American College of Rheumatology (ACR) (7).

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal [1]	Influenza [2]	Hepatitis B [3]	Human papilloma	Herpes zoster
Before initiating therapy					
DMARD monotherapy	Recommended	Recommended	Recommended	Recommended	Recommended
Combination DMARD	Recommended	Recommended	Recommended	Recommended	Recommended
TNFi biologics	Recommended	Recommended	Recommended	Recommended	Recommended [4]
Non-TNF biologics	Recommended	Recommended	Recommended	Recommended	Recommended [4]
While already taking therapy					
DMARD monotherapy	Recommended	Recommended	Recommended	Recommended	Recommended
Combination DMARD	Recommended	Recommended	Recommended	Recommended	Recommended
TNFi biologics	Recommended	Recommended	Recommended	Recommended	Not recommended
Non-TNF biologics	Recommended	Recommended	Recommended	Recommended	Not recommended

[1]one-time pneumococcal revaccination after 5 years is recommended; [2] RA patients should use the intramuscular influenza vaccine, as the live intranasal vaccine is contraindicated. [3] If hepatitis B risk factors are present (*e.g.* intravenous drug abuse, multiple sex partners in the previous 6 months, health care personnel); [4] conditionally recommended giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA in both early or established RA patients ages ≥50 years. After giving the herpes zoster vaccine, there should be a 2-week waiting period before starting biologics.

therapy or that rituximab administration be delayed as long as the influenza season allows it, ideally 6 months (16).

Pneumococcal vaccination

Streptococcus pneumoniae is the main cause of bacterial community-acquired pneumonia and meningitis in western countries, and an important cause of children deaths in developing countries (34, 35). Immunocompromised adults are at greater risk for pneumococcal infection. In a retrospective cohort study (2006–2010) in 3 large and geographically diverse US populations the rates of pneumococcal disease in adults with chronic diseases or immunocompromising conditions were compared with rates in healthy adults (36). Rates of pneumococcal pneumonia (defined as a pulmonary infection confirmed by the isolation of *S. pneumoniae* from sputum) among persons with RA aged 18–49 years, 50–64 years, and ≥65 years were 4.4, 4.3, and 4.0 times the rates observed in age-matched healthy controls, respectively, while the rates of invasive pneumococcal disease (confirmed by *S. pneumoniae* isolation from blood or cerebrospinal fluid but not sputum) were 7.1, 21.1, and 33.3 times the rates in age-matched healthy counterparts, respectively.

Pneumococcal vaccination rates are suboptimal in RA patients as reported in several surveys conducted in the last years. The rate of any previous vaccination for pneumococcus in RA patients was 53.9% in a US single centre survey (15), 44% in a two-centre survey in UK (12) and 33% in a centre in Germany (11). According to the data of the above mentioned international COMORA cohort study, only 17.2% of patients received pneumococcal vaccination (from 0% in Morocco to 56.5% in France) (9). In particular, in Italy only 0.9% of patients have received pneumococcus vaccine in the last 5 years.

In Italy, two pneumococcal vaccines are currently available: a 23-valent pneumococcal polysaccharide vaccine (PPSV-23) and a 13-valent pneumococcal conjugate vaccine (PCV-13); 12 serotypes are shared between PCV-13 and PPSV-23. Conjugate vaccines provide stronger immune responses than polysaccharide vaccines, therefore, the CDC recommends PCV-13 for adult immunosuppressed patients, due to its potential to provide a more robust anti-pneumococcal serotype-specific antibody response.

A prospective, multicentre, double-blinded, randomised, placebo-controlled (1:1) trial was conducted across rheumatology departments in Japanese hospitals, in order to assess the efficacy of PPSV23 in preventing pneumonia in RA patients (37). Nine hundred RA patients, who had been previously treated with biologics or other immunosuppressives, were randomised to PPSV23 or placebo. Primary endpoints were the incidence of pneumococcal and all-cause pneumonia. The overall pneumonia rate was 21.8 per 1000 person-years, and there was no difference in the rates of all-cause pneumonia and pneumococcal pneumonia between the two study groups, showing that in RA patients at relative risk of infections, pneumonia is not prevented by PPSV23. A Swedish prospective study analysed the risk of pneumococcal infections in adult inflammatory arthritis patients treated with different anti-rheumatic drugs and immunised with the heptavalent pneumococcal conjugate vaccine (PCV7), comparing it with the risk in non-vaccinated arthritis patients (38). Four-hundred ninety-seven patients with RA or spondyloarthropathy on different anti-rheumatic treatments vaccinated with a single dose of PCV7 were included in the study and were compared with 1988 subjects (4 for each vaccinated patient) from the same geographical area and with no exposure to vaccination, individually matched for diagnosis, gender and age. In the Skåne Healthcare Register (SHR) all individuals seeking health care for possible pneumococcal infections occurring from 4 years before vaccination to 4.5 years after vaccination were identified. Pneumonia, other lower respiratory infections, meningitis, sepsis, and septic arthritis were considered SI. The results of this observational cohort study showed that, when compared to patients who had not been vaccinated, the use of vaccination with PCV7 has been as-

Table IV. Immunogenicity of influenza and pneumococcal vaccines in adult patients with RA receiving various DMARDs: review of the literature.

Vaccine (reference)	Type of RA treatment (number of patients)	Methods and endpoints	Results	Comments
Influenza, trivalent (22)	RTX (23) MTX (20) Healthy Controls (29)	Levels of antibodies against the 3 vaccine strains were measured before and 28 days after vaccination using haemagglutination inhibition assay.	Geometric mean titres of anti-influenza antibodies significantly increased for all influenza strains in the MTX-treated group and in healthy controls, but for no strains in the RTX-treated group. Seroconversion and seroprotection occurred less often in the RTX-treated group than in the MTX-treated group for the A/H3N2 and A/H1N1 strains, while seroprotection occurred less often in the RTX-treated group than in the healthy controls for the A/H1N1 strain. In the RTX-treated group, previously vaccinated patients had higher pre- and postvaccination geometric mean titres for the A/H1N1 strain compared with unvaccinated patients.	RTX reduces humoral responses following influenza vaccination in RA patients, with a modestly restored response 6–10 months after RTX administration. Previous influenza vaccination in RTX-treated patients increases pre- and post-vaccination titres. RA activity was not influenced.
Influenza, trivalent (24)	Post RTX (11) Pre RTX (8) RA controls (10)	Influenza vaccine was given 6 months after RTX or 6 days before RTX treatment. RA patients never exposed to RTX composed the control group. Vaccine-specific cellular responses were evaluated on day 6 after vaccination, and vaccine-specific humoral responses, on day 21	On day 6 after vaccination, formation of influenza-specific B cells was lower in post-RTX group as compared with the pre-RTX group and controls (p=0.04). Total absence of influenza-specific IgG production was observed in 55% of the post-RTX group.	RTX compromises cellular and humoral vaccine responses in RA patients. Repeated RTX treatment or previous anti-TNF treatment did not accentuate these defects.
Influenza, trivalent (25)	RTX (29) Other DMARDs (20) Healthy controls (16)	The objectives of this study were to comparatively assess cell mediated and humoral responses to influenza vaccination in RA patients with or without RTX-induced CD20 B-cell depletion. Peripheral blood mononuclear cells and sera were obtained immediately before and 4–6 weeks after vaccination. Cell-mediated response to influenza antigens was evaluated by flow cytometry for activated CD4 T-cells. Humoral response was evaluated by haemagglutination inhibition assay.	Cell-mediated responses were comparable in RTX-treated vs. DMARDs-treated patients. The recall post-vaccination $CD4^+$ cellular response was similar in RA patients and healthy controls. The antibody response rate was significantly impaired in the RTX group: being 26.4%, 68.4% and 47.1% in RTX-treated, DMARDs-treated and controls, respectively.	Cellular immunity to influenza vaccination in RTX-treated patients was similar to DMARDs treated patients and healthy controls, while humoral immunity was severely impaired. The preservation of cellular immunity may explain the relatively low rate of infection among B-cell depleted patients.
Influenza, trivalent (29)	MTX (20), RTX (23) healthy controls (28)	Before and 28 days after vaccination, H1N1- and H3N2-specific antibodies were measured by haemagglutinin inhibition and by IgM and IgG (subclass) enzyme-linked immunosorbent assay.	Vaccination induced a significant increase of IgM and IgG (IgG1 and IgG3) antibodies against both strains in the controls and MTX groups (all p<0·01), but not in the RTX group.	IgM- and IgG influenza-specific antibodies increase after vaccination in healthy controls and RA patients except in patients on RTX treatment.
Influenza trivalent (23)	Infliximab (38) Other DMARDs (23)	Patients treated with infliximab were divided into 2 groups: 22 were vaccinated on the day of administration of infliximab, while 16 received the vaccine 3 weeks after infliximab.	At baseline, RA patients and controls vaccinated on the day of infliximab administration had similar occurrence of protective levels of haemagglutination inhibition antibodies and geometric mean titres. In patients vaccinated 3 weeks after administration of infliximab the increase in geometric mean titre measured four weeks after infliximab administration was not significant for H1N1 (p=0.12) and H3 (p=0.06). The response was not affected by variables such as age, gender, MTX, or prednisone use.	Influenza virus vaccine generated a good humoral response in RA patients treated with infliximab. Vaccination was less effective when administered 3 weeks after start of infliximab.
Influenza, A/H1N1/2009 (26)	Various RA treatments (340) Healthy controls (234)	To evaluate the contribution of age, disease activity, medication and previous antibody levels to reduced response to pandemic A/H1N1/2009 vaccine. Patients were assessed before and 21 days after adjuvant-free influenza A/California/7/2009 (pH1N1) vaccine. Seroprotection, seroconversion and factor increase in geometric mean titre were calculated.	RA and controls showed similar prevaccination geometric mean titre (8.0 *vs*. 9.3) and seroprotection (10.8% *vs*. 11.5%). After vaccination, a significant reduction (p<0.001) was observed in all endpoints: geometric mean titre, seroprotection and seroconversion rates. Disease activity did not preclude seroconversion or seroprotection and remained unchanged in 97.4% of patients. MTX was the only disease-modifying anti-rheumatic drug associated with reduced responses (p=0.001).	The data confirmed both short-term anti-pH1N1 vaccine safety and, different from most studies with seasonal influenza, reduced seroprotection in RA patients, unrelated to disease activity and to most medications (except MTX).
Influenza, A/H1N1/2009 (27)	Various RA treatments (89) Healthy controls (14)	The seroprotection and seroresponse rates to vaccination with the pandemic influenza A/H1N1/2009 vaccine were analysed.	The seroprotection and seroresponse rates after the vaccination were 55.1 and 50.6% in the RA patients and 71.4 and 64.3% in the healthy volunteers, respectively.	Both the seroprotection and seroresponse rates obtained after the vaccination with the pandemic influenza A/H1N1/2009 vaccine were lower in Japanese patients with RA compared to healthy controls. A vaccination against this newly emerged influenza virus may protect only half of the Japanese patients with rheumatoid arthritis in a real world.

Vaccine (reference)	Type of RA treatment (number of patients)	Methods and endpoints	Results	Comments
Influenza, trivalent (28)	TCZ (62) TCZ + MTX (49) MTX (65) RA controls (18)	Antibody titres were measured, before and 4-6 weeks after. vaccination using the, haemagglutination inhibitory assay.	For the A/H1N1 and A/H3N2 strains, the TCZ and TCZ+MTX groups achieved fold increases of 9.9-14.5, postvaccination seroprotection rates greater than 70% and seroresponse rates greater than 40%. For the B/B1 strain, seroresponse rates were approximately 30%, but fold increases and seroprotection rates were 5.0-5.4 and greater than 70%, respectively, in these treatment groups. MTX had a negative impact on vaccination efficacy, but adequate responses for protection were nevertheless demonstrated in the MTX group. Neither severe adverse effects nor RA flares were observed.	TCZ does not hamper antibody response to influenza vaccine in RA patients. Influenza vaccination is considered effective in protecting RA patients receiving TCZ therapy with or without MTX.
Influenza, trivalent (30)	Certolizumab pegol (110) Placebo (114)	Influenza vaccine was administered at week 2. Satisfactory humoral immune response, defined as ≥4-fold titre increase in ≥2 of 3 influenza antigens, were assessed independently 4 weeks after vaccination.	Following influenza vaccination, 61.4% of placebo and 53.5% of certolizumab pegol patients without effective titres at baseline achieved a humoral response. In all patients, 54.1% of placebo and 50.5% of certulizumab pegol patients developed satisfactory influenza antibody titres. Vaccine response to influenza antigens was reduced with concomitant MTX use.	Humoral immune responses to influenza vaccination is not impaired when given during the loading phase of certulizumab pegol treatment in patients with RA.
Influenza. Trivalent (31)	Study A patients naïve at vaccination: Tofacitinib (102) Placebo (98) Study B patients already treated at vaccination: Tofacinib continuous (92) Tofacitinib withdrawn (91)	In study A, tofacitinib-naïve patients were randomised to tofacitinib 10 mg twice daily or placebo, stratified by background MTX and vaccinated 4 weeks later. In study B, patients already receiving tofacitinib 10 mg twice daily (with or without MTX) were randomised into two groups: those continuing ('continuous') or interrupting ('withdrawn') tofacitinib for 2 weeks, and then vaccinated 1 week after randomisation. In both studies, titres were measured 35 days after vaccination. Primary endpoints were the proportion of patients achieving a satisfactory response to influenza (four-fold or more titre increase against two or more of three influenza antigens).	In study A similar proportions of tofacitinib-treated and placebo-treated patients developed satisfactory influenza responses (56.9% and 62.2%, respectively), although fewer tofacitinib patients (76.5%) developed protective influenza titres (≥1:40 in two or more of three antigens) *versus* placebo (91.8%). In study B, similar proportions of continuous and withdrawn patients had satisfactory responses to influenza (66.3% and 63.7%, respectively).	Among patients starting tofacitinib, good responsiveness to influenza was observed. Among existing tofacitinib users, temporary drug discontinuation had limited effect upon influenza vaccine responses.
Influenza, trivalent (31)	Abatacept (191)	A pre-vaccination blood sample was taken, and after 28±3 days a final post-vaccination sample was collected. The primary endpoint was the proportion of patients achieving an immunologic response to the vaccine at Day 28 among patients without a protective antibody level to the vaccine antigens at baseline	61.3% of patients achieved an immunological response	Patients with RA receiving abatacept and background DMARDs were able to mount an appropriate immune response to influenza vaccine
Pneumococcus, PPSV23 (24)	Post RTX (11) Pre RTX (8) RA controls (10)	PPSV23 was given 6 months after RTX or 6 days before RTX treatment. RA patients never exposed to RTX composed the control group. Vaccine-specific cellular responses were evaluated on day 6 after vaccination, and vaccine-specific humoral responses, on day 21	On day 6 after vaccination, polysaccharide-specific B cells were found in 27% to 50%, being equally distributed between the groups.	RTX compromises cellular and humoral vaccine responses in RA patients. However, repeated RTX treatment or previous anti-tumor necrosis factor treatment did not accentuate these defects.
Pneumococcus, PPSV23 (39)	TCZ (50), TCZ + MTX (54). MTX (62), RA controls (24)	Serotype-specific IgG concentrations of pneumococcal serotypes 6B and 23F using ELISA and functional antibody activity using a multiplexed opsonophagocytic killing assay, reported as the opsonisation indices, before and 4–6 weeks after vaccination were measured.	IgG concentrations and opsonization indices were significantly increased in all treatment groups in response to vaccination. The TCZ group antibody response rates were comparable with those of the RA control group for each serotype. MTX had a negative impact on vaccine efficacy. Multivariate logistic analysis confirmed that TCZ is not associated with an inadequate antibody response to either serotype.	TCZ does not impair PPV23 immunogenicity in RA patients, whereas antibody responses may be reduced when TCZ is used as a combination therapy with MTX.
Pneumococcus, PPSV23 (30)	Certolizumab pegol (110) Placebo (114)	PPSV23 was administered at week 2. Satisfactory humoral immune response, defined as ≥2-fold titre increase in ≥3 of 6 pneumococcal antigens was assessed independently 4 weeks after vaccination.	Following pneumococcal vaccination, 62.5% of placebo patients and 54.5% of certolizumab pegol patients without effective titres at baseline achieved a humoral response. In all patients, 58.2% of placebo and 53.3% of CZP patients developed satisfactory pneumococcal titres. Vaccine response to pneumococcal antigens was reduced with concomitant MTX use.	Humoral immune response to pneumococcal vaccination is not impaired when given during the loading phase of certulizumab pegol treatment in patients with RA.

Vaccine (reference)	Type of RA treatment (number of patients)	Methods and endpoints	Results	Comments
Pneumococcus, PPSV23 (31)	Study A patients naïve at vaccination: Tofacitinib (102) Placebo (98) Study B patients already treated at vaccination: Tofacinib continuous (92) Tofacitinib withdrawn (91)	In study A, tofacitinib-naïve patients were randomised to tofacitinib 10 mg twice daily or placebo, stratified by background methotrexate and vaccinated 4 weeks later. In study B, patients already receiving tofacitinib 10 mg twice daily (with or without methotrexate) were randomised into two groups: those continuing ('continuous') or interrupting ('withdrawn') tofacitinib for 2 weeks, and then vaccinated 1 week after randomisation. In both studies, titres were measured 35 days after vaccination. Primary endpoints were the proportion of patients achieving a satisfactory response to pneumococcus.	In study A , fewer tofacitinib patients (45.1%) developed satisfactory pneumococcal responses *versus* placebo (68.4%), and pneumococcal titres were lower with tofacitinib (particularly with methotrexate). In study B (n=183), similar proportions of continuous and withdrawn patients had satisfactory responses to PPSV-23 (75.0% and 84.6%, respectively).	Among patients starting tofacitinib, diminished responsiveness to PPSV-23 was observed, particularly in those taking concomitant MTX. Among existing tofacitinib users, temporary drug discontinuation had limited effect upon PPSV-23 vaccine responses.
Pneumococcus, PPSV23 (40)	Tacrolimus (29), MTX (55), tacrolimus/MTX (14), RA controls (35)	The objective of the study was to evaluate the effects of tacrolimus on immune response following administration of PPSV23 in patients with established RA.	IgG concentrations and opsonisation indices were significantly increased in all treatment groups after PPSV23 vaccination. The tacrolimus treatment group appears to respond in a manner similar to that of the RA control group in terms of 6B and 23F serotype concentration and function. In contrast, the MTX group had the lowest immune response. Patients who received a combination of tacrolimus and MTX also had a diminished immune response compared with those who received tacrolimus alone.	Tacrolimus monotherapy does not appear to impair PPSV23 immunogenicity in patients with RA, whereas antibody production and function may be reduced when tacrolimus is used with MTX. Thus, PPSV23 administration during ongoing tacrolimus treatment should be encouraged for infection-prone tacrolimus-treated patients with rheumatic diseases.
Pneumococcus, PPSV23 (41)	Abatacept (21) MTX (55) RA controls (35)	Before and 4-6 weeks after vaccination, we measured the patients' concentrations of antibodies against pneumococcal serotypes 6B and 23F using an enzyme-linked immunosorbent assay and determined their antibody functionality using a multiplexed opsonophagocytic killing assay, reported as the opsonisation index (OI).	The pneumococcal serotype-specific IgG concentrations and OIs were both significantly increased in all treatment groups in response to PPSV23 vaccination. In the ABT group, the IgG responses for the 6B serotype were lower compared with those in the MTX alone or control groups, whereas the OI responses were similar to those in the other two groups.	OI responses indicate antibody functionality rather than simply their amount, so the similarity of these measurements between all three groups suggests that RA patients receiving abatacept still benefit from receiving the PPSV23 vaccination, even though they produce less IgG in response to it.
Pneumococcus, PPSV23 (32)	Abatacept (125)	The objective of the study was to evaluate proportion of patients achieving an immunologic response to the vaccine at Day 28 among patients without a protective antibody level to the vaccine antigens at baseline.	73.9% of patients achieved an immunological response	Patients with RA receiving abatacept and background DMARDs were able to mount an appropriate immune response to pneumococcal vaccine.
Pneumococcus, PPSV23 (42)	Golimumab + MTX (24) MTX (55) RA controls (35)	Before and 4-6 weeks after vaccination, we measured the patients' concentrations of antibodies against pneumococcal serotypes 6B and 23F using an enzyme-linked immunosorbent assay and determined their antibody functionality using a multiplexed opsonophagocytic killing assay, reported as the opsonisation index (OI).	The IgG concentrations and OIs were both significantly increased in all treatment groups in response to PPSV23 vaccination. In the golimumab+MTX group, the IgG responses were lower than those in the MTX alone or control groups, whereas the OI responses were similar to those in the other 2 groups.	OI responses indicate that antibody functionality rather than antibody quantity is important. The similarity of these measurements between all 3 groups suggests that RA patients receiving golimumab+MTX still benefit from receiving the PPSV23 vaccination, even though they produce less IgG in response to it.
Pneumococcus, PVC7 (43)	RA and spondyloarthropathy patients. MTX (85) anti-TNF + MTX (169) anti-TNF (158) non-steroid anti-inflammatory drugs (85)	Antibody levels of serotypes 6B and 23B were analysed before and 4 to 6 weeks after vaccination using standard enzyme-linked immunosorbent assay. Serious pneumococcal infections (pneumonia/lower respiratory tract infection, meningitis, sepsis, septic arthritis) occurring within 4.5 years after vaccination were identified.	Patients with serious infections after vaccination had significantly lower post-vaccination antibody titres for both 6B (p=0.04) and 23 F (p=0.04). Post-vaccination antibody levels of at least 1.29 mg/L and 1.01 mg/L for 6B and 23, respectively, were associated with better protection from serious infections. Higher age, concomitant prednisolone but not MTX or anti-TNF were associated with such infections.	Patients with more robust antibody responses after vaccination with pneumococcal conjugate vaccine were less likely to suffer from serious infections. High age and prednisolone at vaccination were associated with putative serious pneumococcal infections in this cohort.
Pneumococcus, PCV13 (44)	Etanercept (7) Etanercept + MTX (15) RA controls (24)	All subjects were vaccinated with a single dose of the PCV13. Pneumococcal antibody levels at baseline, 4 and 8 weeks were assessed. At least two-fold increase in antibody level, as the protective antibody response was an indicator of responsiveness (*i.e.*, ratio of postvaccination and prevaccination antibody levels). The antibody levels and their ratios were analysed in a variety of different ways, vaccine safety parameters (fever, infections, changes in regular antirheumatic treatments) were assessed at baseline, 4 and 8 weeks after vaccination.	Four weeks after vaccination, the anti-pneumococcal antibody levels significantly increased in both groups. At week 8, antibody levels somewhat decreased in both groups, however, still remained significantly higher compared to baseline. Compared with postvaccination levels at 4 and 8 weeks between two groups, the mean protective antibody levels were higher in control group. In RA, increases of antibody levels at week 8 compared to baseline exerted a negative correlation with age, (p=0.045). There were no clinically significant side effects or reaction after administration of vaccine observed in any of these patients after the 2-month follow-up period, all patients medical conditions were stable.	In RA patients treated with etanercept, vaccination with PCV13 is effective and safe, resulting in protective antibody response one and two months after vaccination. Higher age at vaccination was identified as predictors of impaired protective antibody response. The efficacy of vaccination may be more pronounced in younger RA patients. The vaccine is safe in RA patients on etanercept.

Vaccine (reference)	Type of RA treatment (number of patients)	Methods and endpoints	Results	Comments
Pneumococcus, PCV13 (45)	MTX (10) No DMARDs (10)	Circulating plasmablasts producing total IgG and IgA as well as specific IgG and IgA against two pneumococcal capsular serotypes (6B and 23F) were enumerated using ELISPOT 6 days after vaccination. IgG levels against both these serotypes were determined with ELISA before and 4–6 weeks after vaccination.	After vaccination, RA patients on MTX showed significant increase in pre- to postvaccination antibody levels for 6B ($p<0.05$), while patients without DMARD had significant increases for both 6B and 23F ($p<0.05$ and $p<0.01$, respectively). Only 10% of RA on MTX and 40% of RA patients without DMARD showed positive post-vaccination antibody responses for both serotypes.	MTX treatment in RA leads to reduced vaccine-specific antibody responses and their functionality compared to untreated RA following pneumococcal vaccination using polysaccharide-protein conjugate vaccine.

anti-TNF: anti-tumour necrosis factor; DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate; RA: rheumatoid arthritis; RTX: rituximab, TCZ: tocilizumab.

sociated to a trend towards a reduction of the risk of putative pneumococcal SI by about 45%.

The results of polysaccharide and conjugated pneumococcal vaccines immunogenicity in RA patients receiving different treatments are summarised in Table IV (24, 30-32, 39-45). Several studies have evaluated the immune responses to PPSV23, PCV-7 and PVC-13 in RA patients treated with or without MTX. However, most of experiences regarded the vaccination with PPSV23 and few data are available with PCV7 and PCV13. Humoral response to PPSV23 was not significantly reduced by certulizumab pegol and by tocilizumab (30, 39), was slightly reduced with tofacitinib (when not associated to methotrexate) (31) and was seriously impaired with rituximab (24). In general, any treatment which included methotrexate was associated with a severely impaired immune response to PPSV23. The few studies on conjugated pneumococcal vaccine (PCV7 and PCV13) showed a good immune response patients treated with anti-TNF molecules and confirmed the negative effect on the response in patients treated with methotrexate (43-45).

Adverse events following pneumococcal vaccination are different for conjugated or non-conjugated vaccines. Following non-conjugated vaccines, local reactions range from 9% to 24% (46), while such percentage, following conjugated vaccines, increases to 50% (47). Systemic reactions such as decreased appetite, sleep disturbances, fever and irritability have been reported in 80-85% of recipients of both types of vaccine, while there is a higher frequency of fatigue, myalgia, arthritis, arthralgia and paresthesia following PPSV-23. Such differences may also be the result of having administered the two vaccines to separate age groups. Studies specifically aimed at assessing the safety of vaccines in subjects with autoimmune diseases showed that immunisation was safe (6, 25).

According to the data in the literature, pneumococcal vaccination can be administered to RA patients, possibly before initiating RA therapy, as recommended by the American College of Rheumatology (ACR) guidelines (7). Most of RA treatments do not affect the humoral response to the PPSV-23 vaccine, while few data are currently available on the response to PCV-13 vaccine. Data on the efficacy of using PCV-13 to prime responses to PPSV-23, as recommended by the Advisory Committee on Immunization Practices (ACIP) (48), are also lacking.

Herpes Zoster vaccination

HZ infection, or shingles, is more common in patients with a compromised immune system (49), that is in any condition causing a decreased cell-mediated immunity, such as aging or immunosuppression, and the risk for RA patients is nearly twice the risk for the general population (50). A recent study (51) observed similar risk for all bDMARDs, and a dose-dependent risk with corticosteroids. Medicare (2006-2013) and Marketscan (2010-2014) American databases were analysed to evaluate, in RA patients, the risks of HZ and herpes simplex virus (HSV) infection associated with tofacitinib compared with biologic agents (51). Crude incidence rates were calculated by drug exposure. Overall 2526 patients initiating tofacitinib were compared with patients treated with anti-tumour necrosis factor (TNF) (n=42 850), abatacept (n=12 305), rituximab (n=5078) and tocilizumab (n=6967). The incidence rate of HZ infections ranged from 4.79 cases per 100 patient-years with etanercept to 7.61 cases per 100 patient-year with tofacitinib. Older age, female sex, prednisone treatment at doses >7.5 mg/day, previous outpatient infection and greater number of hospitalisations were associated with increased risk for HZ. These data clearly show an increased risk of HZ infections in patients under RA treatment, particularly tofacitinib, however, the clinical relevance of this phenomenon should be re-evaluated considering the variable severity of such complications as discussed in the following paragraph.

A retrospective evaluation of HZ cases treated with tofacitinib was performed in order to describe the outcomes and identify the risk factors for HZ among tofacitinib-treated patients, and to assess the relative incidence of HZ in tofacitinib treated patients *versus* those receiving placebo (52). Among 4,789 patients treated with tofacitinib 239 cases of HZ were reported (5% of patients; crude IR 4.4 per 100 patient-years, 95% CI 3.8-4.9). Of these, only 16 (7%) were cases of serious HZ requiring hospitalisation or intravenous antiviral therapy, only one HZ case (0.4%) was multidermatomal and none of the cases involved visceral dissemination or death. It should be also considered that the risk of HZ infections in tofacitinib-treated patients, whose global incidence rate was 4.4 cases per 100 patient-year, significantly varied according to the various geographic ar-

eas ranging from 7.7 cases per 100 patient-year in Asia to 2.7 cases per 100 patient-year in western Europe. For other molecules with differential JAK activity, information on infectious side effects is still preliminary and more data are needed.

In order to prevent HZ, a live attenuated vaccine is available and approved for use in subjects aged ≥50 years, regardless of varicella history or previous HZ infection (52-53). The CDC, however, recommends the vaccine only after the age of 60, for cost-effectiveness reasons, and also for concerns about a decrease in vaccine efficacy over time (55). In RA patients, the 2015 ACR guidelines recommend shingles vaccinations from 50 years of age, given the higher risk of shingles (7).

There are no prospective clinical studies evaluating the clinical efficacy and safety of HZ vaccination specifically in RA patients. In a recent retrospective study based on 2006-2013 data from Medicare, adjusted risk ratios over time and incidence rates were estimated and HZ vaccinated and unvaccinated patients with autoimmune diseases were matched 1:2 (54). Overall 53% of the patients in the two groups were affected by RA. Of 59,627 vaccinated patients, crude incidence rate of HZ between the first and the seventh year post vaccination, increased from 0.75 to 1.25/100 person-years. In contrast, the HZ incidence rate among the unvaccinated remained relatively constant (1.3 to 1.7/100 person-years) through 7 years of follow up. Risk of HZ was significantly lower in vaccinated patients compared with the unvaccinated through 5 years but this protective effect was no more significant during the sixth and seventh years after vaccination. This finding raises the possibility that patients might benefit from a booster vaccine at some point after initial vaccination.

The CDC states that the vaccine can be used safely with MTX, low to intermediate dose corticosteroids, intraarticular, bursal, or tendon corticosteroid injections, and azathioprine, but suggests – as well as the ACIP – to avoid it in patients taking bDMARDs or high-dose corticosteroids, due to theoretical concerns regarding the safety of live vaccines (6, 7, 55-57). Ideally, HZ vaccination should be administered prior to begin a biologic therapy, with at least 1-month gap between vaccine and drug start (6). A new herpes zoster subunit vaccine (HZ/su) containing VZV glycoprotein E and the AS01B adjuvant system was found to reduce the risks of herpes zoster and post-herpetic neuralgia among adults including those 70 years of age or older (58). This subunit vaccine may be the best alternative to live attenuated HZ vaccine in RA patients already under bDMARD and tsDMARD treatment.

The German register RABBIT first allowed to identify the risk of HZ with bDMARDs (59). For three bDMARDs combined – infliximab, adalimumab and etanercept – the risk compared with csDMARDs was not statistically significant, but when comparing the single drugs, an increased risk emerged with monoclonal antibodies (infliximab and adalimumab), while not with etanercept. Similar results were reported from a large Veterans Administrative (VA) database in the US (60). In patients treated with medications for moderate (including MTX and leflunomide) or severe (anti-TNF) RA, a higher risk was observed than in patients receiving drugs for milder disease (including sulphasalazine or hydroxychloroquine). The British Society for Rheumatology Biologics Register (BSRBR), which was more adequately powered, showed a significant increase in the risk of early HZ infections during anti-TNF therapy with infliximab associated with the highest rates (61). An observational study (62) using US Medicare data identified 633 patients who were inadvertently vaccinated while using biologics, finding no cases of shingles or varicella in the 6 weeks after vaccination, while in long-term follow up the vaccinated patients had approximately a 40% reduction in shingles risk. Another analysis of claims data from a nationwide US health plan looked at 47 patients with rheumatic conditions who were exposed to biologics (primarily anti-TNF) at the time of vaccination, and again found no cases of shingles within 30 days of vaccination (63).

Taken altogether, these data confirm the opportunity to use HZ vaccine in RA patients. The vaccine can be administered to individuals aged 50 and older. Early observational data suggest that vaccination under bDMARD may not significantly increase the incidence of shingles, however more robust prospective data are needed to establish whether this is true. Once again, vaccination seems to be much safer 1 month prior to starting a bDMARDs or tsDMARD, or 1 month after discontinuing such therapy (6). However, in our opinion, considering the variable incidence of HZ infections according to geographic areas and the very low rate of cases with serious clinical presentation the indication to HZ vaccination in the global RA populations should be carefully evaluated.

Other vaccinations for selected RA patients

• *Human papilloma virus*

The burden of human papilloma virus (HPV) associated diseases in RA patients is not well established. A single population-based cohort study (64) showed an increase in the risk of high-grade cervical dysplasia and cervical cancer among RA female patients compared with healthy controls, which was significant even after adjustment for immunosuppressant use. No data are available on HPV vaccine immunogenicity in RA. A recent systematic review of the existing data in systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), and inflammatory bowel disease (IBD) concluded that the vaccine is well tolerated and effective in most of these patients, though larger studies specifically evaluating the effect of medications on immunogenicity are needed (65, 66). In the light of the current knowledge, ACR and EULAR both recommend HPV vaccine in selected patients where the vaccine is indicated, regardless of concurrent immunosuppression (6, 7).

• *Hepatitis B virus*

The hepatitis B virus (HBV) vaccine is available in Italy for adults as either a single antigen vaccine, or as a combination vaccine with hepatitis A virus. In RA patients, the issue is that those

who carry HBV may reactivate in the setting of RA therapy and also during a prolonged period after eventual treatment discontinuation. Reactivation is well established during treatment with anti-TNF drugs and rituximab. More recently it has also been reported with abatacept and tocilizumab (67-72). Reactivation has been demonstrated mostly in HBsAg-positive patients (73, 74). Data about the impact of biologics on HBV vaccine are scarce, but seem to indicate that TNF-inhibitors may reduce humoral response (75, 76). Screening for HBV is recommended prior to initiation of immunosuppressive therapy, and patients with no natural or vaccine-induced immunity who are at risk for acquiring HBV should be vaccinated (6, 77-79).

Conclusions

Vaccinations in RA patients are of crucial importance due to the increased risk of infections associated with the disease itself and to the immunomodulatory drugs used to treat it, therefore the vaccination status should be assessed in the initial patients' work-up and vaccination strategies should ideally be implemented during stable disease, as recommended by international guidelines (6). To date, several studies have investigated the immune response to various vaccines in RA patients, in particular against influenza and *S. pneumoniae*, but there is few evidence on the clinical effectiveness of vaccinations in the setting of this immunocompromised population. It is still not fully clear how RA treatments may affect vaccine immunisation. However, early data in RA patients using bDMARDs or tsDMARDs indicate that vaccines might be safer in the setting of immunosuppression than previously thought, even live attenuated ones, like the HZ vaccine. We have reviewed the safety and immunogenicity data about influenza, pneumococcal, HZ, HPV, and HBV vaccines and, though such data derived from small case series or expert opinion, we tried to summarise updated, practical suggestions for rheumatologists. Despite the evidence, though uncomplete, is rather reassuring, and despite the recommendations of both ACR and EULAR, vaccinations rates in RA are still low.

To make an informed decision in medicine, there is always a need to weigh the pros and cons. It is recognised that immunological and pathological reactions can occur following vaccination, especially in genetically susceptible hosts. Future studies should help to better understand the association between vaccinations and adjuvants on one side and autoimmune inflammatory diseases and immunomodulatory treatments on the other even though the evidence in the literature is reassuring on the safety of vaccinations up to now. In addition, there is a need for clarification on the optimal re-vaccination intervals for pneumococcal and zoster vaccination. More long-term data are needed, including large-scale epidemiological studies of vaccinations in autoimmune diseases. Any effort should be made to improve the culture of the vaccination practice not only in patients but especially in their physicians.

References

1. WOLFE F, MITCHELL DM, SIBLEY JT *et al*.: The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 481-94.
2. GLUECK T, MUELLER-LADNER U: Vaccination in patients with chronic rheumatic or autoimmune diseases. *Clin Infect Dis* 2008; 46: 1459-65.
3. STRAND V, AHADIEH S, FRENCH J *et al*.: Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis Res Ther* 2015; 17: 362.
4. DORAN MF, CROWSON CS, POND GR *et al*.: Predictors of infection in rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 2294-300.
5. CROWSON CS, HOGANSON DD, FITZ-GIBBON PD, MATTESON EL: Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2012; 64: 2847-55.
6. VAN ASSEN S, AGMON-LEVIN N, ELKAYAM O *et al*.: EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2011; 70: 414-22.
7. SINGH JA, SAAG KG, BRIDGES SL JR *et al*.: 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2016; 68: 1-26.
8. FILLATREAU S: Regulatory roles of B cells in infectious diseases. *Clin Exp Rheumatol* 2016; 34 (Suppl. 98): S1-5.
9. HMAMOUCHI I, WINTHROP K, LAUNAY O, DOUGADOS M: Low rate of influenza and pneumococcal vaccine coverage in rheumatoid arthitis: data from the international COMORA cohort. *Vaccine* 2015; 33: 1446-52.
10. FEUCHTENBERGER M, KLEINERT S, SCHWAB S *et al*.: Vaccination survey in patients with rheumatoid arthritis: a cross-sectional study. *Rheumatol Int* 2012; 32: 1533-9.
11. CALABRO' A, CATERINO A, ELEFANTE E *et al*.: One year in review 2016: novelties in the treatment of rheumatoid arthritis *Clin Exp Rheumatol* 2016; 34: 357-72.
12. SUBESINGHE S, RUTHERFORD AI, IBRAHIM F, HARRIS H, GALLOWAY J: A large two-centre study in to rates of influenza and pneumococcal vaccination and infection burden in rheumatoid arthritis in the UK. *BMC Musculoskelet Disord* 2016; 17: 322.
13. HUA C, MOREL J, ARDOUIN E *et al*.: Reasons for non-vaccination in French rheumatoid arthritis and spondyloarthritis patients. *Rheumatology* (Oxford) 2015; 54: 748-50.
14. COSTELLO R, WINTHROP KL, PYE SR, BROWN B, DIXON WG: Influenza and pneumococcal vaccination uptake in patients with rheumatoid arthritis treated with immunosuppressive therapy in the UK: A retrospective cohort study using data from the Clinical Practice Research Datalink. *PLoS One* 2016; 11: e0153848.
15. LAMPROPOULOS C, ORFANOS P, BOURNIA V *et al*.: Adverce event and infections in patients with rheumatoid arthritis treated with conventional drug or biologic agents. A real-world study. *Clin Exp Rheumatol* 2015; 33: 216-24.
16. FRIEDMAN MA, WINTHROP K: Vaccinations for rheumatoid arthritis. *Curr Opin Rheumatol* 2016; 28: 330-6.
17. HAWKES D, BENHAMU J, SIDWELL T, MILES R, DUNLOP RA: Revisiting adverse reactions to vaccines: A critical appraisal of Autoimmune Syndrome Induced by Adjuvants (ASIA). *J Autoimmun* 2015; 59: 77-84.
18. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2013-2014. 2013. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6207a1.htm. Accessed May 2017.
19. GROHSKOPF LA, SOKOLOW LZ, OLSEN SJ *et al*.: Prevention and control of influenza with vaccines: recommendations of the advisory committee on immunization practices, United States, 2015-16 influenza season. *MMWR Morb Mortal Wkly Re*p 2015; 64: 818-25.
20. DIAZGRANADOS CA, DUNNING AJ, KIMMEL M *et al*.: Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med* 2014; 371: 635-45.
21. IZURIETA HS, THADANI N, SHAY DK *et al*.: Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet Infect Dis* 2015; 15: 293-300.
22. VAN ASSEN S, HOLVAST A, BENNE CA *et al*.: Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum* 2010; 62: 75-81.

23. ELKAYAM O, BASHKIN A, MANDELBOIM M *et al*.: The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. *Semin Arthritis Rheum* 2010; 39: 442-7.
24. REHNBERG M, BRISSLERT M, AMU S *et al*.: Vaccination response to protein and carbohydrate antigens in patients with rheumatoid arthritis after rituximab treatment. *Arthritis Res Ther* 2010; 12: R111.
25. ARAD U, TZADOK S, AMIR S *et al*.: The cellular immune response to influenza vaccination is preserved in rheumatoid arthritis patients treated with rituximab. *Vaccine* 2011; 29: 1643-8.
26. RIBEIRO AC, GUEDES LK, MORAES JC *et al*.: Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. *Ann Rheum Dis* 2011; 70: 2144-7.
27. IWAMOTO M, HOMMA S, ONISHI S *et al*.: Low level of seroconversion after a novel influenza A/H1N1/2009 vaccination in Japanese patients with rheumatoid arthritis in the 2009 season. *Rheumatol Int* 2012; 32: 3691-4.
28. MORI S, UEKI Y, HIRAKATA N *et al*.: Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. *Ann Rheum Dis* 2012; 71: 2006-10.
29. WESTRA J, VAN ASSEN S, WILTING KR *et al*.: Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clin Exp Immunol* 2014; 178: 40-7.
30. KIVITZ AJ, SCHECHTMAN J, TEXTER M *et al*.: Vaccine responses in patients with rheumatoid arthritis treated with certolizumab pegol: results from a single-blind randomized phase IV trial. *J Rheumatol* 2014; 41: 648-57.
31. WINTHROP KL, SILVERFIELD J, RACEWICZ A *et al*.: The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis* 2016; 75: 687-95.
32. ALTEN R, BINGHAM CO 3rd, COHEN SB *et al*.: Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept. *BMC Musculoskelet Disord* 2016; 17: 231.
33. AGMON-LEVIN N, KIVITY S, SHOENFELD Y: Influenza vaccine and autoimmunity. *Isr Med Assoc J* 2015; 11: 183-5.
34. JIT M: The risk of sequelae due to pneumococcal meningitis in high-income countries: a systematic review and meta-analysis. *J Infect* 2010; 61; 114-24.
35. O'BRIEN KL, WOLFSON LJ, WATT JP *et al*.: Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *Lancet* 2009; 374: 893-902.
36. SHEA KM, EDELSBERG J, WEYCKER D, FARKOUH RA, STRUTTON DR, PELTON SI: Rates of pneumococcal disease in adults with chronic medical conditions. *Open Forum Infect Dis* 2014; 1: ofu024
37. IZUMI Y, AKAZAWA M, AKEDA Y *et al*.: The 23-valent pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis: a double-blinded, randomized, placebo-controlled trial. *Arthritis Res Ther* 2017; 19: 15.
38. NAGEL J, GEBOREK P, SAXNE T *et al*.: The risk of pneumococcal infections after immunization with pneumococcal conjugate vaccine compared to non-vaccinated inflammatory arthritis patients. *Scand J Rheumatol* 2015; 44: 271-9.
39. MORI S, UEKI Y, AKEDA Y *et al*.: Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. *Ann Rheum Di*s 2013; 72: 1362-6.
40. MIGITA K, AKEDA Y, AKAZAWA M *et al*.: Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tacrolimus. *Arthritis Res Ther* 2015; 17: 149.
41. MIGITA K, AKEDA Y, AKAZAWA M *et al*.: Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients. *Arthritis Res Ther* 2015; 17: 357.
42. MIGITA K, AKEDA Y, AKAZAWA M *et al*.: Opsonic and antibody responses to pneumococcal polysaccharide in rheumatoid arthritis patients receiving golimumab plus methotrexate. *Medicine* (Baltimore) 2015; 94: e2184.
43. NAGEL J, GEBOREK P, SAXNE T *et al*.: The association between antibody levels before and after 7-valent pneumococcal conjugate vaccine immunization and subsequent pneumococcal infection in chronic arthritis patients. *Arthritis Res Ther* 2015; 17: 124.
44. RÁKÓCZI É, PERGE B, VÉGH E *et al*.: Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept. *Joint Bone Spin*e 2016; 83: 675-9.
45. KAPETANOVIC MC, NAGEL J, NORDSTRÖM I, SAXNE T, GEBOREK P, RUDIN A: Methotrexate reduces vaccine-specific immunoglobulin levels but not numbers of circulating antibody-producing B cells in rheumatoid arthritis after vaccination with a conjugate pneumococcal vaccine. *Vaccine* 2017; 35: 903-8.
46. COOK IF, POND D, HARTEL G: Comparative reactogenicity and immunogenicity of 23-valent pneumococcal vaccine administered by intramuscular or subcutaneous injection in elderly adults. *Vaccine* 2007; 25: 4767-74.
47. BRYANT KA, BLOCK SL, BAKER SA *et al*.: Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. *Pediatrics* 2010; 125: 866-75.
48. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). 2012. Available at: https://www.cdc.gov/mmwr/pdf/wk/mm6140.pdf. Accessed May 2017.
49. INSINGA RP, ITZLER RF, PELLISSIER JM *et al*.: The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med* 2005; 20: 748-53.
50. SMITTEN AL, CHOI HK, HOCHBERG MC *et al*.: The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. *Arthritis Rheum* 2007; 57: 1431e8.
51. WINTHROP KL, YAMANAKA H, VALDEZ H *et al*.: Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2014; 66: 2675e84.
52. COHEN S, KOENING A, WANG L *et al*.: Efficacy and safety of Tofacitinib in US and non-US rheumatoid arthritis patients: pooled analyses of phase II and III. *Clin Exp Rheumatol* 2016; 34: 32-6.
53. MORRISON VA, OXMAN MN, LEVIN MJ *et al*.: Safety of zoster vaccine in elderly adults following documented herpes zoster. *J Infect Dis* 2013; 208: 559-63.
54. YUN H, XIE F, BADDLEY JW, WINTHROP K, SAAG KG, CURTIS JR: Longterm effectiveness of herpes zoster vaccine among patients with autoimmune and inflammatory diseases. *J Rheumatol* 2017. [Epub ahead of print]
55. HALES CM, HARPAZ R, ORTEGA-SANCHEZ I, BIALEK SR: Centers for Disease Control and Prevention CDC. Update on recommendations for use of herpes zoster vaccine. *MMWR Morb Mortal Wkly Rep* 2014; 63: 729-31.
56. HARPAZ R, ORTEGA-SANCHEZ IR, SEWARD JF: Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention CDC. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008; 57: 1-30.
57. RUBIN LG, LEVIN MJ, LJUNGMAN P *et al*.: 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014; 58: 309-18.
58. CUNNINGHAM AL, LAL H, KOVAC M *et al*.: Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med* 2016; 375: 1019-32.
59. STRANGFELD A, LISTING J, HERZER P *et al*.: Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNFalpha agents. *JAMA* 2009; 301: 737e44.
60. MCDONALD JR, ZERINGUE AL, CAPLAN L *et al*.: Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. *Clin Infect Dis* 2009; 48: 1364e71.
61. GALLOWAY JB, MERCER LK, MOSELEY A *et al*.: Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2013; 72: 229e34.
62. ZHANG J, XIE F, DELZELL E *et al*.: Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA* 2012; 308: 43-9.
63. ZHANG J, DELZELL E, XIE F *et al*.: The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study. *Arthritis Res Ther* 2011; 13: R174.
64. KIM SC, GLYNN RJ, GIOVANNUCCI E *et al*.: Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. *Ann Rheum Dis* 2015; 74: 1360-7.
65. PELLEGRINO P, RADICE S, CLEMENTI E: Immunogenicity and safety of the human papillomavirus vaccine in patients with

autoimmune diseases: a systematic review. *Vaccine* 2015; 33: 3444-9.
66. GÖTESTAM SKORPEN C, HOELTZENBEIN M, TINCANI A *et al*.: The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016; 75: 795-810.
67. NARD FD, TODOERTI M, GROSSO V *et al*.: Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologic treatment: extending perspective from old to newer drugs. *World J Hepatol* 2015; 7: 344-61.
68. RYU HH, LEE EY, SHIN K *et al*.: Hepatitis B virus reactivation in rheumatoid arthritis and ankylosing spondylitis patients treated with anti-TNFa agents: a retrospective analysis of 49 cases. *Clin Rheumatol* 2012; 31: 931-6.
69. MORI S, FUJIYAMA S: Hepatitis B virus reactivation associated with antirheumatic therapy: risk and prophylaxis recommendations. *World J Gastroenterol* 2015; 21: 10274-89.
70. PEREZ-ALVAREZ R, DIAZ-LAGARES C, GARCIA-HERNANDEZ F *et al*.: Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicin*e (Baltimore) 2011; 90: 359-71.
71. CARROLL MB, FORGIONE MA: Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol* 2010; 29: 1021-9.
72. TAN J, ZHOU J, ZHAO P, WEI J: Prospective study of HBV reactivation risk in rheumatoid arthritis patients who received conventional disease-modifying antirheumatic drugs. *Clin Rheumatol* 2012; 31: 1169-75.
73. YEO W, CHAN TC, LEUNG NW *et al*.: Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009; 27: 605-11.
74. PEI SN, CHEN CH, LEE CM *et al*.: Reactivation of hepatitis B virus following rituximab-based regimens: a serious complication in both HBsAg-positive and HBsAg-negative patients. *Ann Hematol* 2010; 89: 255-62.
75. SALINAS GF, DE RYCKE L, BARENDREGT B *et al*.: Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. *Ann Rheum Dis* 2013; 72: 1037-43.
76. GISBERT JP, VILLAGRASA JR, RODRIGUEZ-NOGUEIRAS A, CHAPARRO M: Efficacy of hepatitis B vaccination and revaccination and factors impacting on response in patients with inflammatory bowel disease. A*m J Gastroenterol* 2012; 107: 1460-6.
77. LOK AS, MCMAHON BJ: Chronic hepatitis B: update 2009. *Hepatology* 2009; 50: 661-2.
78. SORRELL MF, BELONGIA EA, COSTA J *et al*.: National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. *Ann Intern Med* 2009; 150: 104-10.
79. WEINBAUM CM, WILLIAMS I, MAST EE *et al*.: Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 2008; 57: 1-20.