Italian recommendations for influenza and pneumococcal vaccination in adult patients with autoimmune rheumatic diseases

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Abstract

Objective
To provide evidence-based recommendations for vaccination against influenza virus and S. pneumoniae in patients with autoimmune rheumatic diseases (ARDs).

Methods
A Consensus Committee including physicians with expertise in rheumatic and infectious diseases was established by two Italian scientific societies, Società Italiana di Reumatologia (SIR) and Società Italiana di Malattie Infettive e Tropicali (SIMIT). The experts were invited to develop evidence-based recommendations concerning vaccinations in ARDs patients, based on their clinical status before and after undergoing immunosuppressive treatments. Key clinical questions were formulated for the systematic literature reviews, based on the clinical pathway. A search was made in Medline (via PubMed) according to the original MeSH strategy from October 2009 and a keyword strategy from January 2016 up to December 2017, updating existing EULAR recommendations. Specific recommendations were separately voted and scored from 0 (no agreement with) to 100 (maximal agreement) and supporting evidence graded. The mean and standard deviation of the scores were calculated to determine the level of agreement among the experts' panel for each recommendation. Total cumulative agreement ≥70 defined consensus for each statement.

Results
Nine recommendations, based on 6 key clinical questions addressed by the expert committee, were proposed. The aim of this work is to integrate the 2011 EULAR recommendations on vaccination against influenza and S. pneumoniae in ARDs patients. An implementation plan was proposed to improve the vaccination status of these patients and their safety during immunosuppressive treatments.

Conclusion
Influenza and pneumococcus vaccinations are effective and safe in patients with ARDs. More efforts should be made to translate the accumulated evidence into practice.

Key words
disease-modifying anti-rheumatic drugs, autoimmune rheumatic diseases, influenza vaccine, pneumococcal vaccine

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Introduction

Patients with autoimmune rheumatic diseases (ARDs) are at increased risk of infections. Vaccination is both an individual right and a societal responsibility. Vaccines provides personal benefits and, at the same time, indirectly protect the wider population including those who cannot be vaccinated. Over the years, scientific societies have developed clinical practice recommendations aiming to provide guidance on optimal use of vaccines and improve vaccination adherence among patients with ARDs in whom there is an increased morbidity and mortality attributable to infection.

In rheumatoid arthritis (RA), an exemplar ARDs, patients have double the rate of infections of matched non-RA controls, due to a combination of disease and drug-related immune system disturbances (1–3).

On this basis, preventative strategies such as vaccination, are especially relevant in ARDs patients. Many infections are either preventable using vaccination or, alternatively, vaccinations might make the clinical course less severe. To date, there is a general agreement that inactivated vaccines can be safely given to patients treated with immunosuppressive drugs, while concerns still exist on the safety of live attenuated vaccines in these patients, despite the absence of conclusive data.

Vaccination rates of RA patients are lower than in the general population, probably in part due to physician miscounselling about vaccinations and the prejudices of vaccine-related side effects (4).

The objective of this study group was to reassess, through a systematic literature review (SLR), the efficacy and safety of influenza and pneumococcal vaccination in ARDs patients. The SLR has been restricted to these two vaccinations because they are directed against widespread diseases with a high rate of morbidity and mortality (5, 6).

A steering committee, including Italian experts in rheumatic and infectious diseases, convened to develop the recommendations, combining evidence from clinical studies with expert opinion, when adequate evidence was lacking, according to the treatment status of the patients. These recommendations, although produced by the Italian scientific community, derive from available international literature and cover an important topic of general interest, providing an evidence-based medical behaviour in the setting of immunosuppression.

Methods

Expert committee and key clinical questions

A consensus committee including 35 physicians with expertise in rheumatic and infectious diseases was established by two Italian scientific societies (Società Italiana di Reumatologia: SIR, and Società Italiana di Malattie Infettive e Tropicali: SIMIT). The experts were invited to develop evidence-based recommendations concerning vaccinations against influenza and *S. pneumoniae* in ARDs patients, on the basis of their clinical status before and after immunosuppressive treatments.

Six key clinical questions (KCQ) were formulated for the SLR (Table I).

Definitions

Definition of ARDs and immunosuppressive drugs followed those reported in the "EULAR recommendations for vaccination in adult patients with systemic autoimmune rheumatic diseases" (7). In addition, targeted synthetic modifying anti-rheumatic drugs (tsDMARDs) were considered.

Vaccinations included any schedule and vaccination type for influenza and *S. pneumoniae*.

Systematic literature review

Based on the KCQ and disease and treatment definitions, a general review question was formulated. According to the previously published SLR informing the 2011 EULAR recommendations (8), an updated literature search was performed. A total of 56 studies met the inclusion criteria and were included. The search was extended to include any paper referenced in previous reviews as well as papers identified from experts on the panel; in this way 45 articles were added (Fig. 1).

A search was made in Medline (via PubMed) according to the original

MeSH strategy from October 2009 and a keyword strategy from January 2016 up to December 2017 (See Supplementary online file).

Inclusion criteria include: patients with ARDs (inflammatory arthritis, connective tissue diseases, vasculitides); influenza or *S. pneumoniae* vaccine; data on safety or efficacy (seroconversion, infection rate); study design (randomised control trial: RCT, observational); publication in English.

The data were screened independently by two reviewers (CS and GG), recorded on a prespecified extraction form and summarised qualitatively. The results were sent to the committee before the second meeting, together with proposals for recommendations.

Development of recommendations

The recommendations summarised represent a consensus of published evidence and expert opinions (Table II). For each recommendation, we used a currently accepted hierarchy for categorising the available evidence and the strength of the recommendations (evidence categories A-D) (Suppl. file). Specific recommendations were separately voted and scored from 0 (no agreement with) to 100 (maximal agreement). The mean and standard deviation (SD) of the scores were calculated for each statement to estimate the strength of the recommendation (SOR) of the experts' panel. An agreement ≥70 defined consensus for each statement. In the case of lack of agreement, the statement was reworded according to the results of the discussion and then re-voted in further rounds.

Results

Recommendations

1. In patients with ARDs, the vaccination status for S. pneumoniae should be assessed in the initial investigation. [mean (SD) SOR: 87.00 (17.42); Grade IV (D)]

The initial assessment of ARDs patients, before starting immunosuppressive therapies, should include the evaluation of the immunisation status, according to the national vaccination programmes of each country. In accordance to the available literature, the

Table I. Key clinical questions.

ID	Key clinical questions
1	In patients with untreated ARDs, is vaccination against influenza virus or *S. Pneumoniae* equally effective and safe compared to the general population?
2	In patients with ARDs receiving csDMARDs, is vaccination against influenza virus or *S. pneumoniae* equally effective and safe compared to the general population?
3	In patients with ARDs receiving GCs, is vaccination against influenza virus or *S. pneumoniae* equally effective and safe compared to the general population?
4	In patients with ARDs receiving bDMARDs or tsDMARDs, is vaccination against influenza virus or *S. pneumoniae* equally effective and safe compared to the general population?
5	In patients with ARDs receiving a combination of cs- and bDMARDs or tsDMARDs, is vaccination against influenza virus or *S. pneumoniae* effective and safe compared to monotherapy?
6	In patients with ARDs receiving csDMARDs and/or tsDMARDs or bDMARDs and/or GCs is vaccination against influenza virus or *S. pneumoniae* effective and safe in active compared to inactive disease?

ARDs: autoimmune rheumatic diseases; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; GCs: glucocorticoids; bDMARDs: biological disease-modifying anti-rheumatic drugs; tsDMARDs: targeted synthetic disease-modifying anti-rheumatic drugs.
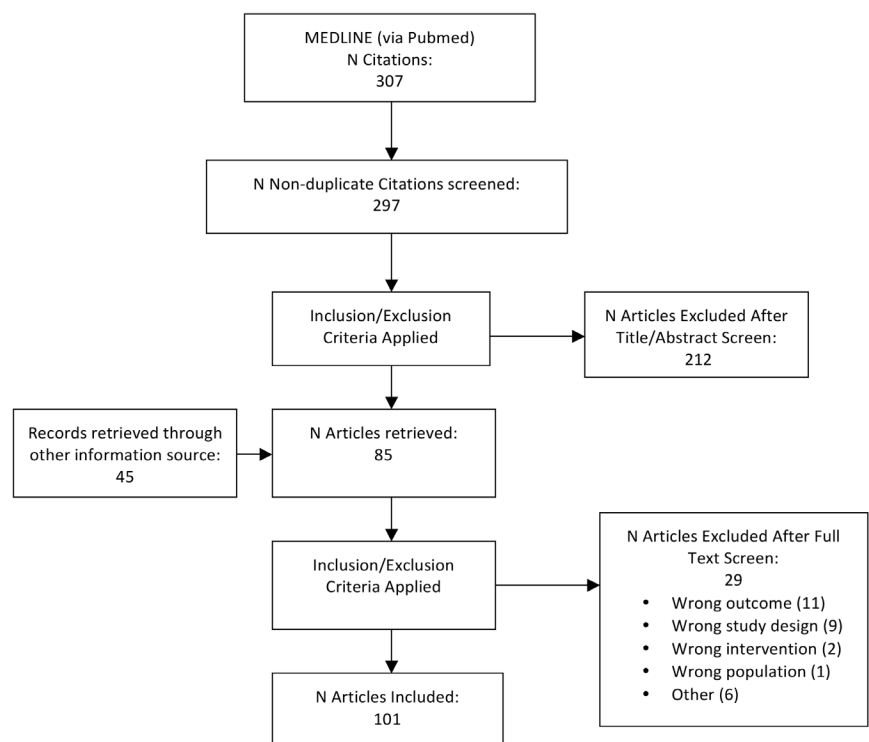

Fig. 1. Flow diagram.

vaccination status against S. pneumoniae should be assessed to select patients to be vaccinated.

Kapetanovic *et al.* have shown a good antibody response in arthritis patients following pneumococcal 7-valent conjugate vaccine (PCV-7), but 1.5 years after PCV-7 vaccination the antibody levels had reverted, in several cases, to pre-vaccination levels (9).

Other authors demonstrated that the efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPSV-23) was preserved for at least 10 years among patients with ARDs treated with methotrexate (MTX) and tumour necrosis factor (TNF) alpha or interleukin (IL)-6 receptor inhibitors (10). Consequently, the authors suggested that antibody levels should be considered to identify patients who may benefit from revaccination.

Recent international guidelines mostly agree on revaccination, suggesting a re-

Table II. Summary of the recommendations.

Record ID	mean	SD
1. In patients with ARDs, the vaccination status for *S. pneumoniae* should be assessed in the initial investigation.	87.00	17.42
2. In patients with ARDs, immunisation against influenza can be safely administered during the use of csDMARDs.	90.38	11.13
3. In patients with ARDs, immunisation against *S. pneumoniae* can be safely administered during the use of csDMARDs, even though a slight impairment of effectiveness is expected, in particular with methotrexate.	90.93	10.48
4. In patients with ARDs, immunisation against influenza and *S. pneumoniae* can be safely administered during the use of GCs, though a better response is expected at low GC dosage.	88.97	13.04
5. In patients with ARDs, immunisation against influenza or *S. pneumoniae* can be safely administered during the use of bDMARDs or tsDMARDs, even in combination with csDMARDs, though a slight impairment of effectiveness of pneumococcal vaccine is expected, in particular with rituximab, abatacept and tofacitinib.	89.83	9.75
6. Patients with ARDs should be actively immunised against influenza (yearly). Adjuvated vaccines may be more efficacious, in particular in patients on bDMARDs.	85.83	17.88
7. Patients with ARDs should be actively immunised against *S. pneumoniae*.	89.86	11.24
8. In patients with ARDs, vaccination should ideally be administered during stable disease.	82.17	20.74
9. In patients with ARDs, vaccination against *S. pneumoniae* should ideally be administered before starting any immunosuppressive treatment, in order to maximise effectiveness and safety. In particular, vaccination should be administered before starting abatacept and at least 4 weeks before starting rituximab.	92.69	8.23

ARDs: autoimmune rheumatic diseases; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; GCs: glucocorticoids; bDMARDs: biological disease-modifying anti-rheumatic drugs; tsDMARDs: targeted synthetic disease-modifying anti-rheumatic drugs.

call dose with PPSV-23 5 years after the first dose of PPSV-23. Only Australian Technical Advisory Group on Immunisation favours a second dose of PPSV-23 5 to 10 years after the previous one, and a third dose at 65 years (11).

In patients treated with rituximab (RTX), abatacept (ABA), golimumab (GOL), and tofacitinib (TOF), which may reduce immunogenicity against pneumococcal vaccines, testing the antibody titres should be considered 4-6 weeks after a completed primary course of vaccination. If serological threshold is not reached, additional doses may be necessary for achieving protection.

2. In patients with ARDs, immunisation against influenza can be safely administered during the use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). [mean (SD) SOR: 90.38 (11.13); Grade II(B)]
In patients with ARDs treated with csDMARDs, adverse events following influenza vaccination seem to be comparable to those occurring in the general population (7).

The disease activity does not seem to be significantly modified by the administration of the vaccine, regardless of the type (adjuvanted *vs.* not adjuvanted). No increased rates of serious adverse events (SAEs) have been reported after

influenza vaccination in patients with RA (12, 13), psoriatic arthritis (PsA) (14), systemic lupus erythematosus (SLE) (15-19), mixed connective tissue disease (20), dermatomyositis and polymyositis (21).

3. In patients with ARDs, immunisation against S. pneumoniae can be safely administered during the use of csDMARDs, even though a slight impairment of effectiveness is expected, in particular with methotrexate. [mean (SD) SOR: 90.93 (10.48); Grade II (B)]
The majority of data do not show the occurrence of severe adverse effects following pneumococcal vaccination in patients undergoing a csDMARDs regimen (22-24). Among csDMARDs, MTX significantly lowers the immunological response to the aforementioned vaccination (10, 23, 25-28).

However, in a small low-quality retrospective study, Coulson *et al.* stated that a single dose of PPSV-23 offers protection in patients with RA on MTX, on the basis of a 9.7 adjusted relative risk for developing pneumonia among non-vaccinated patients (*p*=0.0007) (29).

Rezende *et al.* showed a reduced immunological response to PPSV-23 vaccination in SLE patients treated with mycophenolate mofetil (MMF), azathioprine (AZA) and cyclophosphamide (CYC) (30).

4. In patients with ARDs, immunisation against influenza and S. pneumoniae can be safely administered during the use of glucocorticoids (GCs), though a better response is expected at low GC dosage. [mean (SD) SOR: 88.97 (13.04); Grade II (B)]
Many studies support the safety of influenza vaccination in patients with ARDs treated with GCs (17, 31, 32).

Several reports indicate that GCs do not alter the effectiveness of influenza vaccination in patients with ARDs when administered at low-dose (12, 20, 21, 32-37), while high doses reduce the immunological response to vaccinations (31, 38, 39).

Borba *et al.* showed that, in patients suffering from SLE, a mean prednisone dose of >12 mg/day significantly reduced the seroconversion rate compared to untreated patients (18).

A meta-analysis showed that the seroprotection rate in patients with SLE treated with GCs was significantly reduced in comparison to the healthy control group (15).

Similar results apply to pneumococcal vaccinations. No increase in serious adverse effect rate was reported in patients with ARDs treated with GCs after the aforementioned vaccination. Low doses of GCs do not seem to reduce vaccination efficacy (25, 30).

In the study by Broyde *et al.*, the use

of low doses of GCs did not change the long-term efficacy of PPSV-23 in patients with RA, PsA and spondyloarthritis (SpA) (10).

In patients with ARDs treated with high doses of GCs, a reduction in the immunogenicity of the vaccination has been reported (40).

Paradoxically, in patients suffering from RA the use of GCs in association with anti-TNF-alpha or MTX was associated with a stronger immunological response to influenza and *S. pneumoniae* vaccines (25, 27).

5. In patients with ARDs, immunisation against influenza or S. pneumoniae can be safely administered during the use of biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), even in combination with csDMARDs, though a slight impairment of effectiveness of pneumococcal vaccine is expected, in particular with rituximab, abatacept, and tofacitinib. [mean (SD) SOR: 89.83 (9.75); Grade II (B)]

The administration of influenza vaccination appears safe in patients receiving anti-TNF-alpha , ABA (41), tocilizumab (TCZ) (42) and RTX.

No SAEs have been reported in relation to a combined therapy with anti-TNF-alpha and csDMARDs in patients with RA and SpA (43-46). However, substantial studies to evaluate safety are not available.

The efficacy of influenza vaccination tends to be sustained or slightly reduced in RA (28, 33, 43-46) and SpA (44) patients receiving anti-TNF-alpha. In the study by Franca *et al.*, SpA patients receiving infliximab (IFX) or adalimumab (ADA) had a significantly reduced seroconversion rate after influenza vaccination compared to healthy controls (51.6% *vs.* 74.3%, *p*=0.002), whereas no difference was observed for patients on etanercept (ETA) (86.7% *vs.* 74.3%, *p*=0.09) (46).

Studies show that ABA can reduce the efficacy of influenza vaccination in ARDs patients (44). According to Ribeiro *et al.*, the efficacy of influenza vaccination in RA patients receiving ABA was considerably reduced in comparison to patients receiving MTX (and to normal healthy controls) (41). However, other studies show that ABA cannot significantly change the efficacy of influenza vaccination. Alten *et al.* have evaluated 191 patients receiving ABA, and 82% of them developed clinically relevant antibody titres *versus* 2 or 3 antigens of trivalent influenza vaccine (47).

Limited data are available on the efficacy of TCZ in patients undergoing influenza vaccination. Mori *et al.* showed that the antibody response to influenza vaccine in RA patients was not affected by TCZ (42), and similar results can be found in the study by Tsuru *et al.* (48). RTX significantly minimises the antibody response and the success of influenza vaccine in RA patients (8, 31, 44, 49). Arad *et al.* revealed that humoral response was notably reduced in RA patients receiving RTX, compared to subjects receiving csDMARDs and to controls (26.4% *vs.* 68.4% *vs.* 47.1%). However, cellular response to vaccine was similar in patients treated with RTX and csDMARDs (50). The effect of RTX on influenza vaccine seems related to drug administration timing. Influenza vaccine should be given at least 4 weeks before or at least 6 months after treatment with RTX (51).

In 2012, Chatham *et al.* demonstrated that the antibody titre against the influenza vaccine antigens was preserved after 52 weeks since belimumab (BEL) onset. When vaccination was given during treatment, patients treated with BEL had a lower immunological response than the placebo arm (52).

An RCT evaluated the efficacy of tofacitinib on influenza and pneumococcal vaccines. Similar proportions of patients among those treated with tofacitinib or placebo showed a satisfactory immunological response to influenza vaccination (56.9% *vs.* 62.2%). However, the seroprotection rate was significantly reduced in subjects treated with tofacitinib in association with MTX compared to patients receiving tofacitinib monotherapy (64.9% *vs.* 91.1%). Temporary withdrawal of treatment with tofacitinib did not lead to an improvement in immunological response to vaccination (39).

Pneumococcal vaccination in ARDs patients treated with bDMARDs is generally safe and the rate of severe adverse events is not significantly increased. This can be seen in patients with RA and SpA treated with anti-TNF-alpha (25, 53), ABA (22) and RTX (54).

Efficacy of pneumococcal vaccines has been evaluated on the basis of clinical protection and of antibody response.

Protection against invasive pneumococcal disease (IPD) in patients with cs- and bDMARDs is controversial and data about clinical efficacy rely on few studies that show several limitations (Table III).

PPSV-23 has been evaluated in a multi-centre RCT in Japanese patients treated with immunosuppressive agents, including biologic drugs. Seventeen (3.7%) of 464 patients in the vaccine group and 15 (3.4%) of 436 patients in the placebo group developed pneumonia. The authors concluded that the vaccine did not prevent against pneumonia overall in RA patients (55).

The only study investigating the occurrence of pneumococcal infections in RA and SpA patients after use of PCV-7 concluded that vaccination tend to reduce the risk of putative serious pneumococcal infections by about 45%, although the difference lacked statistical significance. The study had a retrospective design and the diagnosis of pneumococcal infection was presumed, because identification of bacteria in the site of infection was lacking. (56)

In conclusion, although a favourable trend was observed in vaccinated patients (PPSV-23 and conjugate vaccines), a more recent and better-designed study (on PPSV-23) did not confirm this suggestion.

The immunogenicity of pneumococcal vaccines varies depending on treatment. On this topic, only two RCTs are available, one demonstrating that the percentages of RA patients achieving a response to PPSV-23 were similar in the ADA and placebo groups (57), and a second one observing that IgG responses to GOL were lower than those in the MTX alone or control groups, whereas the opsonisation index (OI) responses were similar. (24)

The quality of the other non-ran-

Table III. Immunogenicity of pneumococcal vaccine.

		high dose GCs	MTX	DMARDs–ISS	TNFi	MTX + TNFi	RTX	ABA	TCZ	BEL	TOF
PPSV-23	RA		Reduced (27,93)	Reduced (95)	Good (27,55,56,82,96)	Reduced (27)[ns],(93)[A/E/I] Reduced but good OI (24)[G]	Reduced (59,86)	Reduced but good OI (24) Good (47)	Good (48,58)		Reduced (39)
	ARDs	Reduced (10)	Reduced (10)	Good (10)[E/I] Reduced (91,97)[E/I]					Good (10)		
	SLE			Reduced (30)					Good (60)		
	PsA		Reduced (98)		Good (98)[E]						
PCV-7	RA		Reduced (27,29)		Good (27,29)[ns]	Reduced (27,29)[ns]	Reduced (54)	Reduced (54)	Good (54)		
	SpA		Reduced (25)		Good (25)[ns]	Reduced (25)[ns]					
PCV-13	RA		Reduced (26)		Good (53)[E]						
	SLE/sV		Reduced (99)	Reduced (61,99)					Good (61)		

ARDs: autoimmune rheumatic diseases; GCs: glucocorticoids; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs; ISS: immunosuppressive therapy; ABA: abatacept; BEL: belimumab; OI: opsonisation Index; PsA: psoriatic arthritis; SpA: spondyloarthritis; sV: systemic vasculitis; TNFi: TNF inhibitors [[A] adalimumab (RCT); [G] certolizumab pegol; [E] etanercept; [E/I] infliximab/etanercept; [G] golimumab (RCT); [I] infliximab; [ns] not specified]; TCZ: tocilizumab; TOF: tofacitinib.

domised studies was low or very low. The results of these studies generally show that anti-TNF-alpha drugs do not reduce the efficacy of pneumococcal vaccine in patients with RA and SpA (10, 25, 28, 53).

At present, there are conflicting data on the efficacy of vaccination in patients treated with ABA. In 2013, Kapetanovic *et al*. showed a significantly reduced antibody response to PCV-7 in RA patients treated with ABA (54). Further works showed that the IgG response *versus* 6B serotype of PPSV-23 is reduced in subjects treated with ABA compared to controls, while OI is not impaired (22). These and other data suggest that immunisation with PPSV-23 results in a preserved immune response in RA patients treated with ABA (47).

Few studies evaluated the effect of anti-IL-6 therapy on the pneumococcal vaccine. In 2013, a RCT showed that a smaller percentage of patients treated with TCZ in association with MTX responds to PPSV-23 compared to those treated with MTX monotherapy (60% *vs*. 71%), although the difference was not statistically significant (58). On the contrary, another study evidenced that immunogenicity of PPSV-23 performs better in patients with RA treated with TCZ than in controls treated with TCZ and MTX or MTX alone (42). Moreover, RA patients treated with TCZ had a sufficient antibody response after the administration of the pneumococcal 7-valent conjugate vaccine, in contrast to patients treated with RTX, ABA and MTX (54).

RTX reduces the efficacy of pneumococcal vaccine (28). Kapetanovic *et al*. showed a statistically significant reduction in IgG directed against 23F and 6B serotypes in patients with RA treated with RTX (54). In 2010, a controlled trial showed that patients treated with RTX and MTX had a reduced response to PPSV-23 compared to patients treated with MTX alone: 57% of patients treated with the combination of RTX and MTX achieved a 2-fold titre increase in at least 1 serotype compared to 82% in MTX monotherapy patients (59).

Several studies showed that treatment with BEL does not reduce the immunological response to pneumococcal vaccination in patients with SLE (52, 60, 61).

Tofacitinib has been shown reduce the efficacy of PPSV-23 in RA patients (39).

6. Patients with ARDs should be actively immunised against influenza (yearly). Adjuvated vaccines may be more efficacious, in particular in patients on bDMARDs. [mean (SD) SOR: 85.83 (17.88); Grade II (B)]

Influenza vaccination rate is below the level set by the WHO, both among healthy individuals and patients living with chronic diseases. Most authors largely attribute the poor uptake of influenza vaccination in patients with ARDs to the lack of its prescription by the rheumatologist or the general practitioner (62). The uptake is higher among those RA patients considered at highest risk for complicated influenza, such as the elderly and patients with severe co-morbidities (63). Whatever condition might hamper the increase of vaccination rate, a more practical goal may be to optimise the time of vaccine administration early before the onset of flu season to obtain maximal protection (64). Influenza vaccination significantly reduces mortality and infection-related complications in patients with

chronic obstructive pulmonary disease (COPD) (65), whereas among other categories of patients with chronic diseases, such as diabetes and cancer (66, 67), the actual benefits of flu vaccination are less clear.

The strength of recommendation for patients with ARDs is limited by small number of studies and low grade of evidence (68-70). Although more controlled trials would be desirable to better estimate the real clinical outcome of the influenza vaccination, the available data on safety and immunogenicity, as measured by surrogate markers of protection such as the geometric mean titre of haemagglutinin inhibition antibodies, justify routine recommendation.

Each patient with ARDs should be vaccinated annually, before the onset of the influenza season, regardless the DMARDs regimen used.

Some authors suggest a temporary withdrawn of DMARDs in the time frame immediately preceding and following the administration of influenza vaccine to improve humoral responses, though such a strategy may promote flare of the rheumatologic disease (13, 39).

Patients with ARDs treated with DMARDs should receive the non-live inactivated formulation of influenza vaccine. There are no controlled studies performed with the live attenuated intranasally administered vaccines (71). In a recent meta-analysis, Huang *et al.* describe an overall better humoral response in RA patients comparable to healthy controls with the use of adjuvanted vaccine than with the non-adjuvanted formulation. Concerns exist with the use of adjuvanted form in patients with abnormal immunity, given the potential risk of autoimmune syndrome induced by adjuvants (ASIA). However, in the review by Huang *et al.*, the study attributing RA flare-up to adjuvant date back to 1979, and no studies have reported comparable adverse event since (72). To comment in detail on the immunogenicity of specific influenza strains in patients with ARDs is beyond the remit of this work. There are studies describing RA patients with a lower antibodies response either for H1N1 strain (72) or for H3N2 and B strains (39) compared to healthy controls. Expo-

sure to immunosuppression throughout a lifetime as well as environmental exposure to influenza conceivably condition vaccine specific immune responses. Virus strains encountered earliest in life have longer lasting effects and influence responses to subsequent infection or vaccination. In addition, humoral responses to inactivated influenza vaccine are largely due to the boosting of pre-existing antibodies rather than new priming (73, 74) (Table IV).

7. Patients with ARDs should be actively immunised against S. pneumoniae. [mean (SD) SOR: 89.86 (11.24); Grade II (B)]

The available data show that immunogenicity of pneumococcal vaccines in ARDs patients is frequently decreased, but the majority of patients are able to mount immunogenic responses that achieve protective antibody titres (Table III).

Conjugate vaccines induce higher affinity antibody responses, longer lasting immune responses and memory responses than polysaccharide vaccines. Responses to PCV-7 are better than those observed for PPSV-23 in elderly (75,76) and HIV-infected patients (77–79)**,** an additional benefit of the conjugated vaccine over the non-conjugated vaccine has not clearly documented in other immunosuppressed individuals. (80) The only study comparing the two vaccines in patients with RA receiving immunosuppressive treatment (primarily MTX and/or anti-TNF-alpha) showed that PCV-7 elicits similar antibody response as PPSV-23 (27).

Therefore, the standard of care supported by several guidelines in immunocompromised patients (11) as in general population is represented by pneumococcal 13-valent conjugate vaccine (PCV-13). However, no data are still available about the effectiveness of PCV-13 in ARDs patients.

Since PCV-13 and PPSV-23 cover different serotypes broader protection should be expected through use of both PCV-13 and PPSV-23 in series because conjugated vaccine might hypothetically prime the immune system for an enhanced secondary response to PPSV-23 (11). Despite recommended PPSV-

23 does not prevent pneumonia overall in RA patients at risk for infections (7). Consequently, sequential administration of PCV-13 and PPSV-23 has been advocated, even though no evidence supports this hypothesis in ARD population.

Based on the expert opinion, extrapolating data form other immunocompromised populations (78, 81-83) considering the high frequency of the invasive pneumococcal disease (IPD) cases in Italy covered by PPSV-23 (and not by PCV-13), the panel suggests a combined administration of the two pneumococcal vaccinations, in which conjugated vaccine should precede PPSV-23. In vaccination-naïve patients, the recommended schedule is a sequence of PCV-7 or PCV-13 followed by PPSV-23, with an interval of at least 8 weeks. This interval may be extended up to 12 months, depending on the patient's conditions.

In patients already vaccinated with PPSV-23, PCV-13 should be given at least 12 months later.

8. In patients with ARDs, vaccination should ideally be administered during stable disease. [mean (SD) SOR: 82.17 (20.74); Grade IV (D)]

There are few studies evaluating the efficacy of vaccination in patients with active ARDs. Likewise, studies comparing the efficacy of vaccination in patients with stable and unstable disease are rare. Ribeiro *et al.* pointed out that increased disease activity in RA patients does not preclude immune response to influenza vaccine and it is not linked to a higher rate of adverse events. (33)

Other studies record that the efficacy of influenza vaccination in SLE patients with increased disease activity seems to be reduced (18, 84).

Considering that the level of immunosuppression is high in patients with unstable disease and therefore the effectiveness of vaccination could be reduced, vaccination should be performed, preferentially, during stable phases of the disease.

9. In patients with ARDs, vaccination against S. pneumoniae should ideally be administered before starting any immunosuppressive treatments, in order to maximise effectiveness and safety.

Table IV. Immunogenicity of Influenza vaccine.

		GCs	HCQ	MTX	DMARDs - ISS	TNFi	MTX + TNFi	RTX	ABA	TCZ	BEL	TOF
Seasonal influenza (no adjuvanted)	RA	*Good immuno-genicity*		*Does not significantly attenuate humoral response* (12,39,42) *Reduced immuno-genicity* (13,33,41,46)	*Good immuno-genicity* (50)	*Good immuno-genicity* (33,46) *Good to moderate immuno-genicity.* (43)		*Reduced* (49–51)	*Reduced immuno-genicity* (41)	*Good immuno-genicity* (42,48)		*Does not significantly attenuate humoral response* (39)
Seasonal influenza (adjuvanted)	RA	*Good immuno-genicity* (31)(45)		*Reduced immuno-genicity* (44)	*Reduced immuno-genicity* (31)	*Partially reduced immuno-genicity** (44) *Good immuno-genicity* (45)	*Reduced immuno-genicity* (44)	*Reduced immuno-genicity* (31,44)	*Reduced immuno-genicity* (44)	*Good immuno-genicity* (44)		
Seasonal influenza (adjuvanted)	ARDs	*Good immuno-genicity* [106]		*Reduced immuno-genicity* (100)	*Good immuno-genicity* (100)	*Good immuno-genicity* (100)	*Reduced immuno-genicity* (100)	*Reduced immuno-genicity* (100)	*Reduced immuno-genicity* (100)			
Seasonal influenza (adjuvanted)	SpA	*Good immuno-genicity* (31)		*Reduced immuno-genicity* (44)	*Reduced immuno-genicity* (31)	*Good immuno-genicity* (44)	*Reduced immuno-genicity* (44)	*Reduced immuno-genicity* (31)				
Seasonal influenza (not adjuvanted)	SpA			*Reduced immuno-genicity* (46)		*Reduced immuno-genicity* (only for INF/ADA) (46)						
Seasonal influenza (not adjuvanted)	SLE/ CTD/sV	*Reduced immuno-genicity* (18,19,38) *Good immuno-genicity* (20,21,32)	*Good immuno-genicity* (18–20,32,38)	*Reduced immuno-genicity* (18) *Good immuno-genicity* (20)	*Reduced immuno-genicity* (18,19,38,84) *Does not significantly attenuate humoral response* (20,21,32,101)					*Reduced immuno-genicity* (52)		
Seasonal influenza (adjuvanted)	SLE/ CTD/sV	*Good immuno-genicity* (31)			*Reduced immuno-genicity* (31)			*Reduced immuno-genicity* (31)				

ARDs: autoimmune rheumatic diseases; GCs: glucocorticoids; HCQ: hydroxychloroquine; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs; ISS: immunosuppressive therapy; ABA: abatacept; BEL: belimumab; OI: Opsonisation Index; RA: rheumatoid arthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis; sV: systemic vasculitis; SLE: systemic lupus erythematosus; CTD: connective tissue disease; TNFi: TNF inhibitors [[A] adalimumab (RCT); [G] certolizumab pegol; [E] etanercept; [E/I] infliximab/etanercept; [G] golimumab (RCT); [I] infliximab; [ns]not specified]; TCZ: tocilizumab; TOF: tofacitinib.
*boosting with an additional dose improved antibody response.

In particular, vaccination should be administered before starting abatacept and at least 4 weeks before starting rituximab. [mean (SD) SOR: 92.69 (8.23). Grade II(B)]

Many studies show that the immunological response following pneumococcal vaccination in patients with ARDs is similar to that of healthy controls, while other studies show impaired efficacy, especially in patients with SLE (10, 30, 85). Immunosuppressive therapies can reduce the immunogenicity of pneumococcal vaccination, depending on the type, total dose administered and timing (22, 23, 25, 26, 29, 47, 53, 54, 58). However, in some cases, the proportion of patients generating a response to pneumococcal vaccination does not depend on the time of administration of vaccine, as in the case of BEL (60).

On the contrary, immune responses were severely reduced in healthy volunteers when pneumococcal vaccination was given 2 weeks after ABA (76) and patients vaccinated 6 months after RTX had worse outcomes than those vaccinated 6 days before (86). No difference was observed between patients vaccinated <180 days and >180 days after RTX administration (19).

On this basis, in order to maximise the effectiveness of the vaccination, patients on immunosuppressive treatment should be vaccinated when the dosage of the therapy is tapered in stable disease or ideally before the introduction of the immunosuppressive drugs (87). This recommendation may not be feasible in everyday clinical practice under certain circumstances. Patients with ARDs in an active phase need to start

immunosuppressive therapies as soon as possible, often without the chance to vaccinate before the start of treatment. If it is advisable to vaccinate patients when the disease is in a stable clinical phase, it should not be overlooked that such a condition often occurs, in most cases, after the beginning of the immunosuppressive treatment.

It must be noted that this statement cannot be applied to influenza vaccinations, which follow a pre-established vaccination programme.

Implementation plan
The SIR and SIMIT societies plan to perform a baseline national survey on the vaccination status of patients with ARDs, and disseminate the present guidelines to the scientific society members. The same survey will be repeated on an annual basis to assess the implementation of the recommendations into practice.

Discussion

Vaccinations represent one of the most effective measure to prevent certain infections as well as to reduce morbidity and mortality (88).

Vaccines confer protection against infections by eliciting an immune response through the production of specific antibodies, thus their effectiveness requires an adequate immunologic status. Data from literature highlight the increased risk of infections in ARDs patients, which may be more severe when compared with the general population (89). This risk is due to the immunological dysfunction associated with the disease and the increased use of different immunosuppressive drugs. This study group reviewed the scientific evidence about the safety and efficacy of vaccination against influenza and *S. pneumoniae,* thus providing recommendations for clinical practice in ARDs patients.

We systemically reviewed the published data from 2009 to 2017 and, if the data were lacking expert opinions were taken into account. At present, only 1 RCT was published, exploring the role of PPSV-23 in preventing pneumococcal pneumonia in RA patients treated with bDMARDs. Surprisingly, PPSV-23 seems not to be effective to prevent pneumonia in vaccinated pa-

tients respect to non-vaccinated ones. The possible explanations for this paradox might be searched for some specific biases of the design study, including the short follow-up and the small sample size together with the difficulty in obtaining a definitive pathological cause of pneumonia (55).

Furthermore, the authors highlight the possibility that PPSV-23 alone may not be effective in protection against pneumonia, as reported in the guidelines for pneumococcal disease prevention (90). In fact, a sequential administration of PCV-13 (in vaccination-naïve patients can be used PCV-7 or PCV-13) and PPSV-23 could be a more appropriate approach for the prevention for pneumonia in RA patients receiving immunosuppressive treatments.

We pointed out the importance in assessing the patients' vaccination status for *S. pneumoniae*, in order to define the correct approach for each patient as well as the specific vaccination schedule at ARDs diagnosis, although this procedure is still not frequently met in clinical practice.

Data from literature show that PPSV-23 and PCV-7 may be safely administered in ARDs patients treated with csDMARDs. Among csDMARDs, MTX treatment regimen was associated with a decreased total immunoglobulin levels and impairment of vaccine-specific IgG levels following pneumococcal vaccination (26). On the other hand, some papers report the evidence of anti-pneumococcal antibodies in RA patients treated with MTX 10 years after specific vaccination (10, 29). As far as GCs therapy is concerned, low dosages seem unable to reduce the vaccine efficacy and safety (10, 25, 30), although a slightly impairment should be reported at prednisone dosage ≥10 mg/day (40). The introduction of bDMARDs for ARDs posed new questions about the safety and the efficacy of vaccination in general and about the pneumococcal vaccines specifically. Pre- and post-vaccination studies did not show increased adverse events in RA patients, irrespective of the type of bDMARD (22, 25, 53, 54, 57, 59, 91, 92)

In fact, anti-TNF-alpha molecules and TCZ used in monotherapy did not de-

crease the efficacy of pneumococcal vaccination. On the other hand, a combination therapy including MTX may reduce the immune response to the pneumococcal vaccinations, irrespective of the type of vaccine (27, 29, 93, 94). Furthermore, a special attention concerning the vaccination status of the patients should be paid before starting therapy with ABA and RTX.

RTX reduces the efficacy of pneumococcal vaccine (28) and still conflicting data are available about the effects of ABA. Despite the similar target for treatment, BEL, differently from RTX, seems to be unable to decrease the immunological response after pneumococcal vaccinations (52, 60, 61).

As far as the JAK inhibitors are concerned, emerging data highlight the possibility that tofacitinib may reduce the efficacy of PPSV-23 in RA patients, and this needs to be confirmed in larger cohorts.

In daily practice, influenza vaccination should be strongly recommended in ARDs patients before the onset of the immunosuppressive drugs, in order to maximise the effectiveness of the vaccination or, alternatively, when therapies are set at the lowest effective dosages (87). It has been shown that vaccine against influenza is effective and safe in ARDs patients treated with low dosage of GCs, csDMARDs, tsDMARDs and/or bDMARDs (12-21). Furthermore, it has been proposed that treatment with anti-malarial drugs (chloroquine) may improve the protective effect of the influenza vaccination (18). Its effectiveness is slightly reduced in patients treated with RTX (28, 31, 43, 44, 49). Furthermore, the effect of RTX on influenza vaccine seems to be related to RTX administration. In fact, influenza vaccine should be given at least 4 weeks before and at least 6 months after treatment with RTX to maximise the effect. Finally, data from a RCT evaluating the effectiveness of influenza vaccines in patients treated with tofacitinib showed a satisfactory immunological response to influenza vaccination and the sero-protection rate was significantly higher in those patients treated with tofacitinib in monotherapy when compared to subjects treated with tofacitinib and MTX (39).

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