



Physicians' Agreement on and Implementation of the 2019 European Alliance of Associations for Rheumatology Vaccination Guideline: An International Survey

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Objective: To evaluate the perspective of healthcare professionals towards the 2019 European Alliance of Associations for Rheumatology (EULAR) vaccination guideline in patients with autoimmune inflammatory rheumatic diseases (AIIRD).

Methods: Healthcare professionals who care for patients with AIIRD were invited to participate in an online survey regarding their perspective on the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD. Level of agreement and implementation of the 6 overarching principles and 9 recommendations were rated on a 5-point Likert scale (1~5).

Results: Survey responses of 371 healthcare professionals from Asia (42.2%) and North America (41.6%), Europe (13.8%), and other countries were analyzed. Only 16.3% of participants rated their familiarity with the 2019 EULAR guideline as 5/5 ("very well"). There was a high agreement ($\geq 4/5$ rating) with the overarching principles, except for the principles applying to live-attenuated vaccines. There was a high level of agreement with the recommendations regarding influenza and pneumococcal vaccinations; implementation of these recommendations was also high. Participants also reported a high level of agreement with the remaining recommendations but did not routinely implement these recommendations.

Conclusion: The 2019 update of EULAR recommendations for the vaccination of adult patients with AIIRD is generally thought to be important by healthcare professionals, although implementation of adequate vaccination is often lacking. Better education of healthcare providers may be important to optimize the vaccination coverage for patients with AIIRD.

Keywords: Vaccination, Surveys and questionnaires, Guideline, Autoimmune diseases

INTRODUCTION

Patients with autoimmune inflammatory rheumatic diseases (AIIRD) are at increased risk of infection. This increased risk

may be due, in part, to underlying immune dysfunction and treatment-induced immunosuppression [1-3]. Vaccinations against preventable diseases are vital for AIIRD patients [4-6]. However, vaccination coverage (i.e., the proportion of patients

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who receive the recommended vaccines) of patients with AIIRD is low [7-9]. One possible explanation is that rheumatologists believe that vaccination of the patients with AIIRD should be managed by their primary care physicians. That said, primary

care providers may not be familiar with the impact of autoimmune disease and treatment-associated immunosuppression on vaccine efficacy and safety. Consequently, they may feel uncomfortable managing vaccinations for patients with AIIRD. This is

Table 1. Baseline characteristics of 371 survey participants

	Variables	Number (%)
Continent of practice*	Asia (East, Southeast, Central, South Asia)	156 (42.2)
	North America (e.g., Canada, Mexico, USA)	154 (41.6)
	Europe	51 (13.8)
	South America	7 (1.9)
	Other	2 (0.5)
Age group	20~30 years	13 (3.5)
	31~40 years	95 (25.6)
	41~50 years	115 (31.0)
	51~60 years	78 (21.0)
	61~70 years	54 (14.6)
	>70 years	16 (4.3)
Sex	Female	147 (39.6)
	Male	224 (60.4)
Work experience	1~5 years	28 (7.5)
	6~10 years	49 (13.2)
	11~15 years	53 (14.3)
	16~20 years	64 (17.3)
	21~25 years	50 (13.5)
	26~30 years	40 (10.8)
	>30 years	87 (23.5)
Level of training	Resident-in-training	11 (3)
	Fellow-in-training	34 (9.2)
	Board-certified/eligible	312 (84.1)
	Others	14 (3.8)
Medical specialty	Rheumatology	330 (88.9)
	Internal medicine	13 (3.5)
	Orthopedic surgery	8 (2.2)
	Family medicine	4 (1.1)
	Infectious disease	1 (0.3)
	Others	15 (4.0)
Practice setting	Primary care/Private practice	79 (21.3)
	Secondary care/General hospital (not university-affiliated)	47 (12.7)
	Tertiary care/Academic medical center (University-based or university-affiliated)	245 (66)
Number of patients [†]	<10 patients	141 (38)
	11~20 patients	127 (34.2)
	21~30 patients	50 (13.5)
	31~40 patients	28 (7.5)
	41~50 patients	12 (3.2)
	>50 patients	13 (3.5)

*One answer is missing. [†]Number of patients per half-day clinic.

a particularly important issue for live-attenuated vaccines such as yellow fever, which may induce infection in an immunocompromised patient, and the new COVID-19 vaccines [10,11]. Scarcity of data regarding the safety of these vaccinations in patients with AIIRD may further contribute to the low vaccination coverage of these patients [9,12,13].

The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) formulated several vaccination guidelines for patients with rheumatoid arthritis and/or AIIRD [4,6,14]. However, even the recent EULAR 2019 guideline for vaccination of adult patients with AIIRD is based more on expert opinion than on clinical evidence derived from clinical trials [6]. Whether healthcare professionals agree with and implement these guidelines in their routine clinical practice is unknown.

In light of emerging novel infections such as SARS-CoV-2, it is more important than ever that rheumatologists be prepared to take a direct role in managing vaccinations for patients with AIIRD [10,11,15,16]. To this end, we conducted an international survey to evaluate the perspective of the healthcare professionals who care for patients with AIIRD, to determine their agreement with and implementation of the 2019 EULAR vaccination guideline for patients with AIIRD.

MATERIALS AND METHODS

Survey

Healthcare professionals who care for patients with AIIRD were invited to participate in an approximately 15-minute-long anonymous online survey regarding their general vaccination practices and their perspective on the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD.

Participants were asked to rate their level of agreement using a 5-point Likert scale with the following anchors: 1=strongly disagree and 5=strongly agree. In addition, the participants were asked whether they implement these guideline/recommendations in their routine practice (1=not at all and 5=always).

The original recommendations 3, 4, and 9 from the 2019 EULAR guideline were modified slightly. Recommendations 3 and 4 portrayed more than one situation, so each was rewritten as two scenarios. For recommendation 9, Bacillus Calmette-Guérin (BCG) was added as recommendation 9a in order to provide a concrete example (Supplementary Table 1).

Survey distribution and data collection

An official invitation email was sent to 8,535 healthcare providers using the email lists provided by rheumatology societies. Japan College of Rheumatology and Korean College of Rheumatology actively disseminated the survey to their members. In addition, the link to the survey was posted on EULAR Newsletter (published in April 2020).

The Google Forms survey platform was used for data collection. The survey was conducted between April and June 2020. This study was conducted in compliance with the Declaration of Helsinki and it was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2004-023-1115).

The survey is available from the corresponding author on the reasonable request.

Statistical analysis

Descriptive statistical analyses were performed using SPSS version 22.0 (IBM Co., Armonk, NY, USA).

RESULTS

Participants

Of 381 respondents, 371 (96.2%) were healthcare providers who actively cared for patients with autoimmune inflammatory rheumatic diseases. Analysis was limited to responses from these 371 participants. Information on their demographics and medical practice are summarized in Table 1. The majority of responses came from Asia (42.2%) and North America (41.6%), followed by Europe (13.8%) and South America (1.9%). Among the participants, 88.9% were rheumatologists and 84.1% were board-certified/eligible (i.e., had completed their training in rheumatology subspecialty). With regard to practice setting,

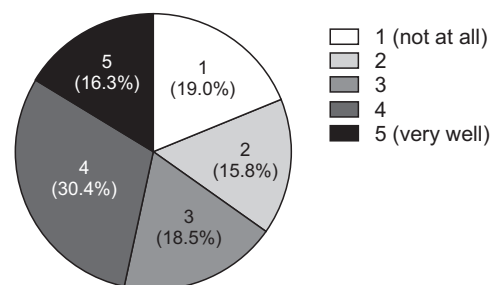


Figure 1. Familiarity with the principles and recommendations of 2019 EULAR guideline. Familiarity was rated on 1~5 scale (1=not at all, 5=very well). EULAR: European Alliance of Associations for Rheumatology.

66.0% worked in a tertiary medical center while 21.3% worked in a primary care setting, and 12.7% worked in a secondary care setting. A majority of the participants (72.2%) treated up to 20 patients per half-day clinic session.

Familiarity with the 2019 EULAR guideline

Only 16.3% of participants rated their familiarity with the 2019 EULAR guideline as 5/5 (“very well”) on a 5-point Likert scale (Figure 1). An additional 30.4% of participants rated their familiarity as 4/5.

Agreement with and implementation of the principles and recommendations of 2019 EULAR guideline

There was a high level of agreement ($\geq 4/5$ rating) with the overarching principles 1 to 5 of the 2019 EULAR guideline, but a lower rate of agreement with principle 6 (i.e., use of live-attenuated vaccines). However, participants did not routinely implement all of these principles. The difference between agreement and practice was high for principles 1 (4.2/5 vs. 3.5/5), 2 (4.2/5 vs. 3.5/5), and 4 (4.5/5 vs. 3.9/5), while the difference for principles 3 (4.0/5 vs. 3.6/5), 5 (4.4/5 vs. 4.3/5) and 6 (4.4/5 vs. 4.3/5) was more modest (Table 2).

Among the 9 recommendations, agreement and implementation were high for recommendations regarding influenza vaccination (recommendation 1) and pneumococcal vaccination (recommendation 2). Participants also reported a high level of agreement (i.e., $\geq 4/5$ on the rating scale) with recommendation 3 (toxoid tetanus vaccination), 4 (hepatitis vaccination), 6 (yellow fever vaccination) and 9b (“avoid BCG during the first 6 months of life”). There was a high level of agreement ($\geq 4/5$) with zoster vaccination (recommendation 5), but this was not routinely implemented in routine practice ($< 4/5$). Overall, recommendations 3 through 9 were less practiced in routine clinical care. In addition, agreement and implementation differed among Asia, North America and Europe (Supplementary Table 2).

Understanding of safe immunosuppressive therapy for live-attenuated vaccination

We surveyed physician understanding of Centers for Disease Control and Prevention (CDC) recommendations for the use of live-attenuated vaccines in patients using disease modifying antirheumatic drugs (DMARDs). Only 37.6% of participants correctly identified prednisone 20 mg/day or less as safe for live-

attenuated vaccine use. Furthermore, only 21.3% and 22.3% could identify methotrexate (MTX) at 0.4 mg/kg/week and azathioprine at 3.0 mg/kg/day, respectively, as the safe dosing limit for live-attenuated vaccines (Figure 2A~2C). Most participants knew that a combination of conventional DMARDs did not decrease the safety of live-attenuated vaccines when compared to MTX alone (Figure 2D).

DISCUSSION

This international survey is the first to evaluate healthcare providers’ perspective on the 2019 EULAR vaccination guideline. In general, participants agreed with most of the guideline’s principles and recommendations. However, there was a discrepancy between the level of agreement with and implementation of the guideline in routine clinical practice.

Participants in this international online survey were mainly located in Asia, North America and Europe, and two-thirds of them worked at a tertiary academic medical center (Table 1). The high percentage of academic rheumatologists in the survey is, in part, explained by that the survey was mainly disseminated with help of rheumatology societies such as EULAR, the Japanese College of Rheumatology, the Korean College of Rheumatology, and American state rheumatology societies. Only 46.7% were very familiar ($\geq 4/5$) with the new 2019 EULAR vaccination guideline. Academic rheumatologists’ low level of familiarity with vaccination guideline was unexpected, since we expected that healthcare providers at academic centers were the most likely to be familiar with the recent clinical practice guideline. This may indicate that academic rheumatologists do not prioritize vaccinations in their routine clinical care. Educating rheumatologists on the important role they play in the appropriate vaccination of AIIRD patients may dramatically improve the care they receive.

The first and second overarching principles of the 2019 EULAR guideline, which recommend that vaccinations be managed by rheumatologists, in collaboration with the patient’s primary care physician, were met with a high level of agreement but were, again, less often implemented (Table 2). This could result from a systemic failure in communication among health care professionals. A centralized (e.g., web-based) sharing of the vaccination record, which could be accessed by all treating physicians, might improve this outcome substantially.

While the participants, in general, agreed with the overarch-

Table 2. Agreement with and implementation of the principles and recommendations of 2019 EULAR guideline

	Agreement	Implementation	Difference*
Overarching principles			
1. The vaccination status and indications for further vaccination in patients with AIIRD should be assessed yearly by the rheumatology team	4.2±0.9	3.5±1.2	0.7±0.9
2. The individualised vaccination programme should be explained to the patient by the rheumatology team, providing a basis for shared decision-making, and be jointly implemented by the primary care physician, the rheumatology team and the patient	4.2±0.9	3.5±1.2	0.7±0.9
3. Vaccination in patients with AIIRD should preferably be administered during quiescent disease	4.0±1.0	3.6±1.1	0.3±0.7
4. Vaccines should preferably be administered prior to planned immunosuppression, in particular B cell depleting therapy	4.5±0.7	3.9±1.0	0.6±0.9
5. Non-live vaccines can be administered to patients with AIIRD also while treated with systemic glucocorticoids and DMARDs	4.4±0.8	4.3±0.9	0.1±0.5
6. Live-attenuated vaccines may be considered with caution in patients with AIIRD	3.6±1.2	3.3±1.4	0.3±0.7
Recommendations			
1. Influenza vaccination should be strongly considered for the majority of patients with AIIRD	4.7±0.6	4.6±0.8	0.2±0.5
2. Pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD	4.6±0.7	4.2±1.0	0.4±0.7
3a. Patients with AIIRD should receive toxoid tetanus vaccination in accordance with recommendations for the general population	4.2±1.0	3.4±1.4	0.8±1.1
3b. Passive immunisation should be considered for patients treated with B cell depleting therapy	3.3±1.1	2.8±1.2	0.6±0.9
4a. Hepatitis A and hepatitis B vaccination should be administered to patients with AIIRD at risk	3.9±1.0	3.2±1.4	0.8±1.1
4b. In specific situations booster or passive immunisation of hepatitis A or hepatitis B is indicated	3.6±1.0	2.8±1.3	0.8±1.1
5. Herpes zoster vaccination may be considered in high-risk patients with AIIRD	4.3±0.9	3.5±1.4	0.8±1.1
6. Vaccination against yellow fever should be generally avoided in patients with AIIRD	3.6±1.3	3.2±1.5	0.4±0.9
7. Patients with AIIRD, in particular patients with SLE, should receive vaccinations against HPV in accordance with recommendations for the general population	4.1±1.0	3.1±1.4	1.0±1.2
8. Immunocompetent household members of patients with AIIRD should be encouraged to receive vaccines according to national guidelines with the exception of the oral polio vaccines	4.2±0.9	3.2±1.4	1.0±1.2
9. Live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy	4.0±1.1	3.5±1.4	0.5±1.0
9a. Bacillus Calmette–Guérin should be avoided during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy	3.9±1.1	3.4±1.4	0.5±1.0

Values are presented as mean±standard deviation. Agreement: 1=strongly disagree; 5=strongly agree. Practice: 1=not at all; 5=all the time. EULAR: European Alliance of Associations for Rheumatology, AIIRD: autoimmune inflammatory rheumatic diseases, DMARDs: disease modifying antirheumatic drugs, SLE: systemic lupus erythematosus. *Difference between agreement and implementation.

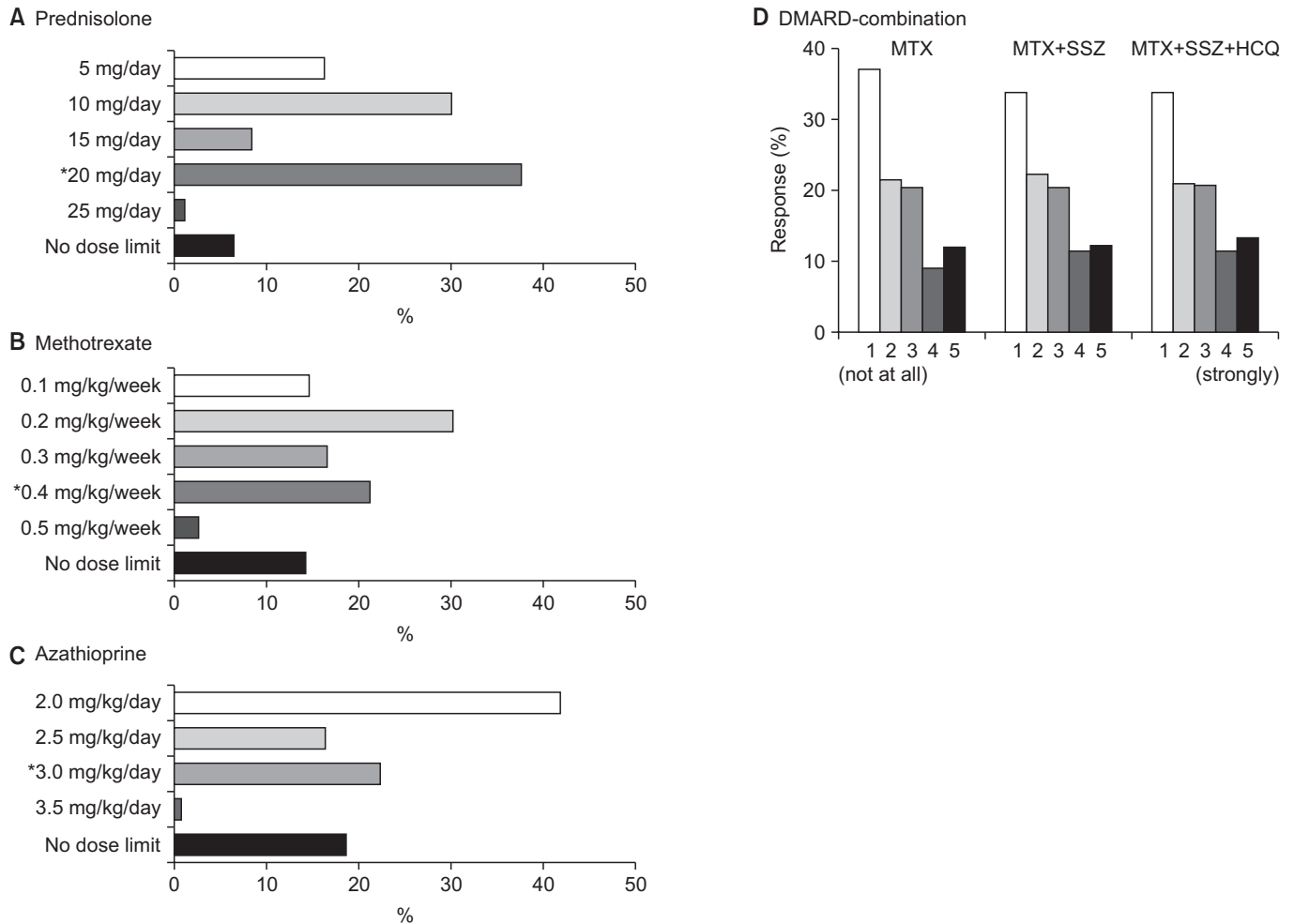


Figure 2. Immunosuppressive dosing limit for live-attenuated vaccines. Safe dose of prednisolone (A) methotrexate (B), and azathioprine (C) for live-attenuated vaccines (*the dose under which administration of the live-attenuated vaccines were considered safe per Centers for Disease Control and Prevention recommendations). (D) Safety of conventional DMARDs for live-attenuated vaccines: 1=completely safe; 5=strongly contraindicated. DMARDs: disease modifying antirheumatic drugs, MTX: methotrexate, SSZ: sulfasalazine, HCQ: hydroxychloroquine.

ing principles strongly (Table 2), participants did not agree with principle 6 (i.e., live-attenuated vaccines in AIIRD patients). Interestingly, the EULAR expert panel that constructed the vaccination guideline also demonstrated a low level of agreement (53%) with this principle 6. This reflects conflicting opinions regarding the safety of live-attenuated vaccines in AIIRD patients. By contrast, the pneumococcal and influenza vaccines, which have been ingrained into routine clinical practice, were widely administered. The fear of live-attenuated vaccines might come in part from a misunderstanding regarding the degree of immunosuppression associated with increased risk; only 20%~25% of the participants knew that standard doses of DMARDs were not a contraindication for the use of live vaccinations, according to the CDC. The complex effects of autoimmune disease and

immunosuppressive treatment on vaccine safety and efficacy in patients with AIIRD could make non-rheumatologists uncomfortable with making clinical decisions about the administration of live-attenuated vaccines in such patients.

Participants agreed that immunizations should be administered before immunosuppression is instituted (principle 4) and when the rheumatic disease is quiescent (principle 3), but these principles are not implemented routinely. Since patients often present with active disease and need “semi-urgent” treatment, it is not always easy to vaccinate before starting immunosuppression. In addition, annual influenza vaccination and routine vaccinations such as pneumococcal vaccines are administered when patients are already on DMARDs. Therefore, these recommendations are difficult to implement in real-world practice.

Recommendations regarding immunosuppressant management in the peri-vaccination period, such as temporarily stopping DMARDs, could be addressed by the next iteration of the EULAR guidelines [17-19].

Vaccines such as toxoid tetanus (recommendation 3), hepatitis (recommendation 4), yellow fever (recommendation 6) and HPV (recommendation 7) were used less commonly than the 2019 EULAR guideline recommend. Low rates of use are likely due to the different patient populations represented by the surveyed physicians, since the majority of patients with AIIRD in most of the practices surveyed are not at risk of these diseases.

Understanding the hurdles faced by rheumatologists when it comes to implementing the 2019 EULAR guideline may help improve vaccination coverage. Initiatives designed to teach rheumatologists about the new guidelines may be especially effective. Such an intervention would make rheumatologists aware of their pivotal role in vaccination coverage for patients with AIIRD (principle 1 and 2). Understanding that they need to take a lead role in patient vaccinations may motivate them to learn more about the vaccination guideline and to think about implementation when they see patients. Especially, different healthcare system, social structure and socioeconomic status as well as the cultural preference in practicing regions might affect the participant's attitude towards vaccination and need to be considered (Supplementary Table 2).

This study has several limitations. First, the response rate was not high (i.e., 381 responses out of 8,535 official invitations), and participants may have been more likely to have an interest in the vaccination than the average rheumatologist. Therefore, the level of adherence to the guideline may be even lower in real world practice. In addition, responses to a survey might be inaccurate due to recall bias. A prospective study would be better able to assess actual physician behavior.

CONCLUSION

In conclusion, the 2019 update of EULAR recommendations for the vaccination of adult patients with AIIRD is generally thought to be important by rheumatologists, although implementation of adequate vaccination is often lacking. Further studies should be undertaken to understand the reasons underlying poor compliance with vaccination recommendations and to improve vaccination rates among this high-risk patient population.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at <https://doi.org/10.4078/jrd.22.0012>.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

JKP conceived of the study. PS, KW, EBL, and JKP participated in its design and coordination. PS, KW, AHS, SC, WH, HAP, EBL, and JKP contributed to the collection, analysis and interpretation of the data. All authors participated in preparation of the manuscript. All authors read and approved the final manuscript.

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