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Concise report

Influenza vaccination in chronic inflammatory arthritis undergoing immunosuppressive treatments: temporal trend and factors of adherence

Luca Quartuccio [1], Alen Zabotti [1], Tolinda Gallo[2], Salvatore De Vita[1] and Francesca Valent[3]

Abstract

Objectives. To verify the level of adherence to the influenza vaccination program in a population of patients suffering from RA, PsA or AS undergoing immunosuppressive treatment.
Methods. Administrative databases from the Regional Health Information System of Friuli Venezia Giulia (FVG), Italy, were used. Subjects were residents in FVG, suffered from chronic inflammatory arthritis and had at least one prescription for a DMARD in the 9 months before the start of the vaccination season (from 1 October to 31 December). The observation ranged from 2006 to 2018. Logistic regression was used to assess the association between vaccination and the patient's characteristics in the 2018–2019 influenza season.
Results. Overall, vaccination adherence decreased from the highest value of 35.7% (662/1853) in 2006 to the lowest value of 25.3% (926/3663) in 2014; in people $\geq$65 years of age it also decreased over time from 61.6% (577/936) in 2008 to 43.9% (701/1595) in the 2014. By logistic analysis on the 2018–2019 season, which included 4460 patients, older subjects were more likely to be vaccinated [people 65–74 years, odds ratio (OR) 4.58 (95% CI 3.72, 5.64); people 75–84 years, OR 6.47 (95% CI 5.04, 8.32); both *vs* <65] as were those with diabetes [OR 1.66 (95% CI 1.05, 2.64)]. Treatment with a biologic agent alone [OR 0.64 (95% CI 0.52, 0.80)] and RA diagnosis [OR 0.69 (95% CI 0.51, 0.93)] were associated with lower adherence.
Conclusion. Influenza vaccination adherence is alarmingly low in a population at higher risk of infectious complications, in particular in elderly patients.

Key words: arthritis, influenza, vaccine, biologic agent, small molecules

Introduction

Vaccination is one of the most important medical interventions to prevent infectious complications in populations at higher risk, including patients suffering from autoimmune inflammatory rheumatic diseases (AIIRDs), and research is ongoing to improve influenza virus vaccine efficacy [1, 2]. Nakafero *et al.* [3] demonstrated the efficacy of inactivated influenza vaccine in lowering the risk of respiratory morbidity and mortality in subjects with AIIRDs, thus calling for the active promotion of seasonal influenza vaccination in immunosuppressed subjects with AIIRDs by healthcare professionals. Patients with inflammatory chronic arthritides were likely the most representative group of patients in AIIRDs. The aim of this study was to verify the level of adherence to the influenza vaccination program in a regional population of patients suffering from RA, PsA or AS undergoing treatment with conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). Among them, the coverage should be high independent of age, due to the underlying chronic disease and the immunosuppressive treatment employed.

[1]Clinic of Rheumatology, Department of Medicine, Academic Hospital "Santa Maria della Misericordia", Azienda sanitaria universitaria Friuli Centrale, University of Udine, [2]Department of Prevention, Azienda sanitaria universitaria Friuli Centrale and [3]Institute of Epidemiology, Academic Hospital "Santa Maria della Misericordia", Azienda sanitaria universitaria Friuli Centrale, Udine, Italy

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Correspondence to: Luca Quartuccio, Clinic of Rheumatology, Department of Medicine, Academic Hospital "Santa Maria della Misericordia", Azienda sanitaria universitaria Friuli Centrale, University of Udine, Via Colugna 50, 33100 Udine, Italy. E-mail: luca.quartuccio@asufc.sanita.fvg.it

CLINICAL SCIENCE

Rheumatology key messages

- Influenza vaccine adherence is lower than expected in a highly vulnerable population.
- Immunosuppressive treatments and socio-economic status may affect adherence.
- Vaccination policies urgently need to be improved in this setting.

Methods

This is a retrospective cohort study that used the Regional Health Information System of Friuli Venezia Giulia (FVG) as the source of information (supplementary material, section Organization of the Regional Health Information System of Friuli Venezia Giulia, available at *Rheumatology* online). This method has been previously applied for other research purposes [4]. The target population of this study was selected based on the following inclusion criteria: patients must be residents in FVG and they had to carry the exemption code for RA, PsA or AS and have at least one prescription of MTX, LEF, a bDMARD or a tsDMARD in the 9 months before the start of the vaccination season (from 1 October to 31 December). The observation period comprises the years from 2006 to 2018.

We calculated the frequency of influenza vaccination per year in the whole population and in the subgroup of patients ≥65 years. Subanalyses were performed for each disease. The influenza vaccination coverage in the whole population of patients suffering from chronic arthritis on the basis of the exemption codes (as reported in the supplementary material, section Organization of the Regional Health Information System of Friuli Venezia Giulia, available at *Rheumatology* online) was also reported in the supplementary materials for descriptive comparison (Supplementary Table S1 and Supplementary Fig. S1, available at *Rheumatology* online).

Multivariate logistic regression was used to assess the association between the probability of vaccination and demographic and clinical patient characteristics in the influenza season 2018–2019. In particular the following features were considered other than treatment: age category, gender, comorbidity (i.e. cardiovascular, respiratory, endocrinological, diabetes, neurologic, cancer, chronic renal insufficiency, rare disease) and socio-economic status. For each patient we abstracted information of all medications prescribed from the exemption date to 2019. In particular we identified prescriptions of glucocorticoids, MTX, LEF, bDMARDs and tsDMARDs according to the Anatomical Therapeutic Chemical Classification System codes.

All the analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA). *P*-values <0.05 were considered significant.

All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Since this analysis was based on anonymous administrative data, patient informed consent and ethical committee approval were not required in Italy.

Results

Thirteen influenza vaccination seasons were analysed, accounting for 3254 patients/year. The number of patients selected for each year, with the relative percentage of vaccination coverage, are summarized in Supplementary Table S2, available at *Rheumatology* online, and Fig. 1; also, the same analyses performed in the subgroups of each chronic inflammatory arthritis are presented. The female:male ratio of vaccinated patients remained stable over time, reflecting the epidemiologic gender distribution of the disease (Supplementary Fig. S2, available at *Rheumatology* online). Overall, influenza vaccine coverage decreased over time from 35.7% (662/1853) in 2006 to 25.3% (926/3663) in 2014; in people ≥65 years of age it also decreased over time, from 61.6% (577/936) in 2008 to 43.9% (701/1595) in 2014.

For RA, influenza vaccine adherence decreased from 38.5% (551/1432) in 2006 to 28.3% (708/2501) in 2014; in people ≥65 years of age it ranged from 61.9% (385/622) in 2006 to 44.3% (563/1272) in the 2014.

In contrast, in PsA, influenza vaccine adherence increased from 21% (189/900) in 2014 to 32.6% (399/1223) in 2018; however, in people ≥65 years of age it decreased from 67.5% (81/120) in 2009 to 44.9% (130/289) in 2014.

For AS, influenza vaccine adherence increased from 10.1% (22/218) in 2012 to 25.1% (91/362) in 2018; however, in people ≥65 years of age it decreased from 66.7% (10/15) in 2010 to 23.5% (8/34) in 2014.

In the logistic model applied on the population of the 2018–2019 seasonal vaccination (Table 1), older subjects were more likely to be vaccinated [65–74 years, OR 4.58 (95% CI 3.72, 5.64); 75–84 years, OR 6.47 (95% CI 5.04, 8.32)], as were those with diabetes [OR 1.66 (95% CI 1.05, 2.64)], while patients with an RA diagnosis [OR 0.69 (95% CI 0.51, 0.93)] and those who were treated with biologic agents alone had a lower probability of being vaccinated [OR 0.65 (95% CI 0.52, 0.80)]. Finally, a lower borderline-significant probability of being vaccinated was also observed among patients with low socio-economic status [OR 0.83 (95% CI 0.68, 1.00)].

By excluding the disease diagnosis from the model, the role of comorbidity in general emerged as the major

Fig. 1 Temporal trend of influenza vaccination in chronic inflammatory arthritis, by disease and age ≥65 years

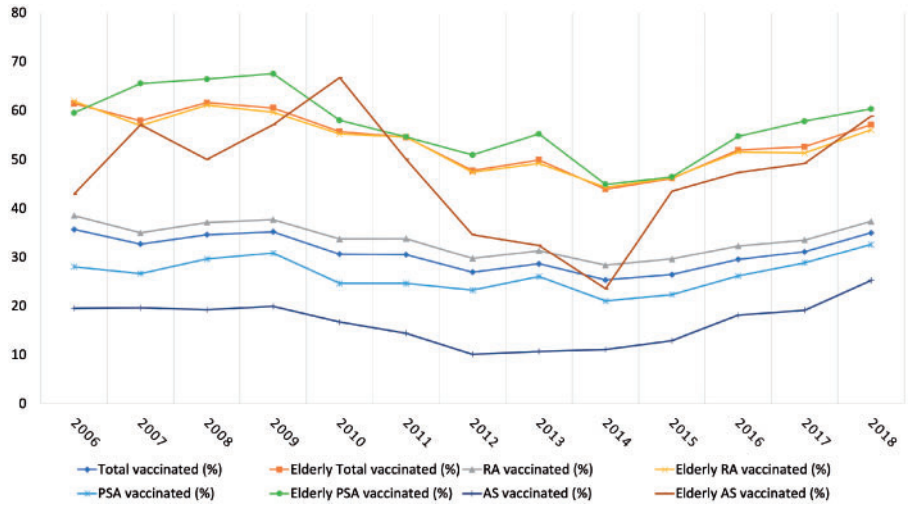

Table 1 Characteristics of patients studied during the 2018–19 seasonal vaccination ($N = 4460$)

Feature	Frequency	Percent	OR	95% CI	*P*-value
RA	2862	64.2	0.69	0.51, 0.93	0.02
PSA	1237	27.7	0.90	0.57, 1.43	0.70
AS	361	8.1	Reference	Reference	Reference
Age category 0–44 years	551	12.3	0.69	0.51, 0.94	**0.02**
Age category 45–64 years	1947	43.7	Reference	Reference	Reference
Age category 65–74 years	1163	26.1	4.58	3.72, 5.64	**<0.0001**
Age category 75–84 years	701	15.7	6.47	5.04, 8.32	**<0.0001**
Age category ≥85 years	98	2.2	8.07	4.97, 13.10	**<0.0001**
Male	1467	32.9	0.92	0.78, 1.08	0.31
Cardiovascular	2314	51.9	1.45	0.94, 2.22	0.09
Respiratory	152	3.4	1.40	0.81, 2.42	0.23
Diabetes	417	9.3	1.66	1.05, 2.64	**0.03**
Endocrinological	632	14.2	1.20	0.76, 1.91	0.43
Gastrointestinal	1720	38.6	1.28	0.84, 1.97	0.25
Neurological	234	5.2	1.12	0.68, 1.86	0.64
Cancer	1046	23.4	0.96	0.62, 1.47	0.83
Chronic renal insufficiency	41	0.9	0.92	0.41, 2.02	0.83
Rare disease	63	1.4	0.74	0.35, 1.60	0.45
Lower socio-economic status	1444	32.4	0.83	0.68, 1.00	0.05
Glucocorticoids	772	16.2	1.02	0.85, 1.24	0.80
MTX or LEF alone	2887	64.7	Reference	Reference	Reference
b/tsDMARD alone	836	18.7	0.65	0.52, 0.80	**<0.0001**
b/tsDMARD combined with MTX or LEF	737	16.5	1.1	0.91, 1.33	0.33

The boldface numbers highlight the variables with significant *P*-values.

driver of influenza vaccination in chronic inflammatory arthritides (Supplementary Table S3, available at *Rheumatology* online).

Discussion

International recommendations definitely pointed out the need for vaccination for those patients suffering from chronic inflammatory arthritides, which require prolonged immunosuppressive treatments, particularly bDMARDs or tsDMARDs, independent of age [2].

Our study of >10 years of observation demonstrated a lower adherence to influenza vaccine than expected in people suffering from chronic inflammatory arthritides. During the whole period of observation, the coverage was always under the minimum desirable threshold of 75% and far from the optimum target of 95% according to the National Italian Plan for Vaccination in the

population at risk. Notably, even in the subgroup of older patients (age ≥65 years), adherence has remained far below the threshold of 75% during all the years of observation. This level of adherence to international guidelines for the management of AIIRDs is lower than that reported in other countries [5–7]. A recent study from our region reported, as of 1 October 2017, a 53% overall rate of vaccination against influenza virus in patients suffering from diabetes (65.5% in patients of ≥65 years of age) [8]. Even if lower than expected in chronic diseases, it was much higher than in AIIRD subjects who were included in the present study.

In addition, the influenza vaccine coverage from 2006 to 2018 in the population >65 years of age in our region, as reported by the Italian Ministry of Health, was usually higher than that reported herein in rheumatic patients [9].

The EULAR recommendations discourage the use of live-attenuated influenza vaccine in immunocompromised patients [2], thus generating a possible indication bias. However, live attenuated influenza vaccine is not commercially available in Italy. During the 2018–2019 target season the large majority of patients underwent the inactivated quadrivalent vaccine (Supplementary Table S4, available at *Rheumatology* online).

The overall lower coverage seen in PsA or AS compared with RA is related to the older age of RA patients. Nevertheless, RA diagnosis appeared to be a factor that discouraged influenza vaccination in the 2018–2019 season. Thus, even in the older people, doubts about the performance of the vaccination in patients chronically under immunosuppressive treatments and the fear of immunogenic reactions or relapse of the autoimmune disease may explain our results. In fact, there are concerns that MTX and rituximab impair the serological response to influenza vaccine [10]. However, it seems that biologic agents themselves as monotherapy rather than csDMARDs or even the association between csDMARDs and bDMARDs discouraged influenza vaccination in our study. It can be argued that biologic treatment, when employed alone rather than with other immunosuppressors, reduces the patient's perception of being at risk. In previous studies, treatment type was not identified as a variable associated with vaccination [11, 12]. Moreover, this observation supports the existence of a gap of knowledge dissemination at several levels, i.e. specialists, general practitioners and the general population [13], and it emphasizes the role of the physician's recommendation as the strongest predictor of vaccination [12].

Nevertheless, the effectiveness of influenza vaccine in preventing patient-centred outcomes such as influenza, pneumonia and death has only been recently addressed [3, 12]. Overall, the lack of knowledge about the need for vaccination and vaccine effectiveness are the most important barriers to vaccination [13], and socioeconomic status may have a role. In Italy, since the 2009–2010 season, the Italian National Institute of Health has promoted case–control studies to verify the efficacy of the influenza vaccine. In 2010–2011 and 2011–2012, it was 48.1% and 65.7%, respectively [14]. In the 2015–2016 season the efficacy of the influenza vaccine in Italy was moderate for H1N1 strain (47.5%) but absent for the other strains [15]. This issue, which deserves well-designed case–control studies, can contribute to the rate of influenza vaccination.

In addition, our study found that when the need for vaccination has been clearly stated and defined in certain age categories or chronic diseases such as diabetes, this indication overcomes all the doubts and unjustified fears of side effects in an autoimmune background [16]. On the other hand, the diagnosis of a chronic inflammatory arthritis that requires an immunosuppressive treatment has not yet been recognized as an indication for influenza vaccination.

This study has several limitations. Enrolling patients who were taking immunosuppressors could have excluded patients with milder diseases who were treated with NSAIDs, antimalarials or sulphasalazine, which are not categorized in the class of immunosuppressors. However, it is unlikely that patients with an AIIRD requiring stronger immunosuppression and, of consequence, closer clinical and laboratory follow-up, did not request the exemption code in our country. Probably the former is a group with milder disease and at lower risk, even if not vaccinated. Also, since the study covered a wide period, it is unlikely that this proportion of patients could have significantly affected the rate of influenza vaccine coverage. Nevertheless, the descriptive analysis of the whole cohort of patients carrying an exemption code for chronic arthritis as reported in Supplementary Table S2 and Supplementary Fig. S1, available at *Rheumatology* online, showed similar rates and trends over time. In addition, our results may have underestimated the impact of low income or serious disability, which are considered more powerful for medical charges than exemptions due to diseases.

The lack of clinical evaluation is a limitation of our study, since disease activity may affect the probability of vaccination [17]. However, this feature can be more properly captured by multinational clinical studies with a shorter time frame [17, 18]. Nevertheless, even if the evidence is not strong, it seems that disease activity does not affect the seroprotection by influenza vaccination in patients with RA [19]. On the other hand, many works have reported that influenza vaccination does not influence the activity of the underlying autoimmune disease and the adverse events seem comparable to those in healthy controls [2].

Finally, as in all studies using data on medicine prescription, there remains some degree of uncertainty regarding the actual drug intake. Despite these limitations, the use of administrative data allowed us to study a large number of patients, with full coverage of the regional population, for a long time span and with no recall bias.

To conclude, influenza vaccine adherence is alarmingly low in a highly vulnerable population [20]. Correct information and risk management by physicians should

overcome the barriers to vaccine program adherence and improve protection for patients with chronic rheumatic inflammatory diseases.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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