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ORIGINAL ARTICLE

Vaccination survey in patients with rheumatoid arthritis: a cross-sectional study

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Abstract The objective of this study is to evaluate the vaccination status in rheumatoid arthritis (RA) patients during routine clinical practice, data from a German non-interventional cross-sectional study. In this prospective study, patients with rheumatoid arthritis were interviewed using a standardized questionnaire focusing on vaccination. Available vaccination documents were evaluated, and titers for common vaccination antigens (hepatitis B, rubella, mumps, measles, diphtheria, tetanus) were analyzed with special regard to the underlying treatment and age of patients. A total of 301 RA patients treated with conventional DMARDs alone (cohort I, $n = 125$), TNF-blocking agents (cohort II, $n = 117$), or B-cell depletion with rituximab (cohort III, $n = 59$) have been studied. Significantly more patients in the biologic cohorts II and III were aware of an increased risk of infections (I: 67.7%, II: 83.8%*, III: 89.9%*, $P < 0.05$). Pneumococcal vaccination rate was significantly higher (I: 20.2%, II 36.8%* and III: 39.0%*, $P < 0.05$) compared with cohort I. Differences were less evident for influenza. Significantly more patients ≥60 years of age have been vaccinated against *Streptococcus pneumoniae* and influenza. An obvious discrepancy existed between vaccination awareness and actual vaccination rates for all cohorts. No significant differences in vaccination titers could be seen between the three cohorts. Awareness of infectious complications was more present in patients treated with biologicals, and also, the rate of patients vaccinated against *Streptococcus pneumoniae* increased significantly depending on the underlying treatment. Nevertheless, there was a discrepancy between vaccination awareness and actual vaccination rates for all cohorts.

Keywords Rheumatoid arthritis · Vaccination · Influenza · *Streptococcus pneumoniae* · DMARD · Rituximab · TNF

Abbreviations

DMARD	Disease-modifying antirheumatic drug
RF	Rheumatoid factor
ACPA	Anti-citrullinated-peptide Antibodies
DAS28	Disease activity score 28
WHO	World health organization
STIKO	German standing vaccination committee (Ständige Impfkommission)
MTX	Methotrexate

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that manifests in pain, swelling, and loss of functionality of joints accompanied by decreasing quality of life and increased mortality. Therapeutic options have improved continuously over the past decade, especially by introducing biologic agents.

For both conventional DMARDs and biologic agents, an increase in infection rates is a common adverse side effect [1–3]. Furthermore, the underlying disease itself may lead to an increased infection risk [4]. In prospective studies, an

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increased risk neither of disease flares nor of initiation of autoimmune disorders has been found so far [5]. Vaccination with not live vaccines regularly can be regarded to be safe and relatively effective even in patients treated with immunosuppressant drugs [6]. Titer responses vary in dependence of medication, and therefore, control of titers has been recommended in these patients [7–10]. The surveillance of patients' vaccination schedule should be the integral part of rheumatologic care in our days.

The WHO regularly delivers general vaccination recommendations that are adapted by national vaccination committees all over the world. The German Standing Vaccination Committee (STIKO) is the major federal commission for Germany dealing with vaccination issues and delivering recommendations regarding vaccination practices. Despite the increasing number of patients receiving immunosuppressive drugs due to immune-mediated diseases, no specific recommendations for vaccination procedures for these patients have been published by the federal commission so far. The German Society of Rheumatology (DGRh) has published some vaccination recommendations for the rheumatologic setting (http://www.dgrh.de).

Vaccination is beyond controversy the most effective strategy to prevent infectious complications [11, 12]. As a consequence of the obviously increased risk of infectious diseases in the rheumatologic setting, vaccination strategies with special regard to the underlying immunosuppressive regimen are needed. Conventional DMARDs such as methotrexate and leflunomide are widely used in the treatment of RA and still reflect the corner stone of DMARD therapy in RA. Regularly, these DMARDs are combined with glucocorticoids or biologic agents. Both are associated with a further increase in infection rates. Rituximab is of special interest with regard to vaccination titers because of its specific mode of action by targeting the precursors of antibody-producing cells [13–17]. Despite all the available data, there is still some concern of flares [18] or fear of lacking efficacy when vaccinating patients with autoimmune diseases like rheumatoid arthritis. Consequently, both patients and physicians often refrain from vaccinations. So far, there are no clear data available that describe the vaccination status under clinical routine conditions. Therefore, we performed this cross-sectional study at our rheumatologic outpatient clinic.

Patients and methods

Study design

This report utilizes data from a single-center, prospective, non-interventional cross-sectional study that included patients with RA treated with conventional DMARDs (cohort I), TNF-blocking agents (cohort II) or the B-cell depleting antibody rituximab (cohort III). DMARD treatment was carried out according to published guidelines. Basic variables assessed included positivity for rheumatoid factor (RF) and ACPA, erosions, disease activity (DAS28), and acute phase reactants.

Recruitment was conducted consecutively from March till December 2009 and was stopped when a total of more than 300 patients ($n = 301$) were evaluable. Due to the fact that in cohort III only patients with rituximab were documented, the size of cohort III was expectedly lower. In addition to routine blood parameters, antibody titers of hepatitis B, rubella, mumps, measles, diphtheria, and tetanus were assessed. Patients were interviewed using a standardized questionnaire and were required to be at least 18 years of age, have an established diagnosis of RA according to the 1987 ACR criteria, and provide written consent for participation. No other selection criteria were applied. All patients were informed about the objectives of the study and gave written consent to their voluntary participation and the anonymous use of their personal data in statistical analyses. The study protocol was approved by the ethic committee of the University of Wuerzburg (AZ 49/09).

The primary objectives of this study were to evaluate the awareness of increased risk of infections under immunosuppressive therapy, the knowledge about the possibility of preventing infectious complications by vaccination with special regard to influenza and *Streptococcus pneumoniae*, and the actual performed vaccinations. In addition, vaccination titers against major vaccination antigens were analyzed. For age-specific subgroup analyses, patients were divided according to the STIKO recommendations into the groups <60 and ≥60 years of age.

Data analyses

Statistical analyses were performed for all data as appropriate using Excel or SPSS software (SPSS inc., Chicago, USA). All performed tests were usually two tailed and considered to be statistically significant at $P < 0.05$. Chi-square tests were used to compare frequencies of categorical variables between patient subgroups. Moreover, analysis of variance (one-way ANOVA) was used to test for differences in continuous variables between patient groups based on treatment cohort and age.

Results

Patient disposition and characteristics

A total of 301 RA patients treated with conventional DMARDs (cohort I, $n = 125$, 41.5%), TNF-blocking agents

(cohort II, $n = 117$, 38.9%), or rituximab (cohort III, $n = 59$, 19.6%) have been studied. Overall, 52.8% of the patients were <60 years of age. Mean disease duration was 13.3 years, mean age 58.4 years, mean CRP 0.79 mg/dl, and mean DAS28 3.39; 53.8% suffered from erosive disease; 70.1% of the patients were RF, and 58.8% were ACPA positive. More than half of the patients (63.5%) had a concomitant use of glucocorticoids. Mean disease duration, age, DAS28, CRP, and the number of patients with erosions were comparable in all the three cohorts, while the frequency of ACPA-positive patients showed a trend toward a higher frequency in the biological cohorts II und III. Significantly more patients were positive for RF in cohort III compared with cohort I (83.1 vs. 63.2%, $P = 0.02$). Mean DAS28 did not differ significantly between the three cohorts. Overall, the number of patients with DAS28 remission (defined by DAS28 $\leq$ 2.6), low- (2.6 < DAS28 $\leq$ 3.2), moderate- (3.2 < DAS28 $\leq$ 5.1), and high disease activity (DAS28 > 5.1) was 30.0, 14.3, 44.7 and 11.0%, respectively. Furthermore, there was no significant difference in mean DAS28 by age. Table 1 summarizes demographic characteristics of the study population by cohorts.

Table 1 Patient disposition and characteristics ($n = 301$, * $P < 0.05$)

Cohort	I	II	III
n (%)	125 (41.5%)	117 (38.9%)	59 (19.6%)
RF positive (%)	63.2	70.9	83.1*
ACPA positive (%)	52.8	62.4	64.4
Erosive disease (%)	50.4	59.8	49.2
Disease duration (years), mean	13.94	13.26	12.07
DAS28	3.26	3.39	3.69
DAS28 $\leq$ 2.6	30.4%	33.3%	22.4%
2.6 < DAS28 $\leq$ 3.2	19.2%	11.1%	10.3%
3.2 < DAS28 $\leq$ 5.1	40.8%	44.4%	53.4%
DAS28 > 5.1	9.6%	11.1%	13.8%
Age (years), mean	59.42	58.44	56.36
$\geq$60 years (%)	49.65%	45.3%	45.8%
CRP [mg/dl], mean	0.76	0.81	0.80
<60 years, *n* (%)	63 (50.4%)	64 (54.7%)	32 (54.2%)
>60 years, *n* (%)	62 (49.6%)	53 (45.3%)	27 (45.8%)

Infections of the lower respiratory tract within the last 12 months

Forty-six patients (15.3%) reported an infection of the lower respiratory tract within the last 12 months leading to the consultation of a physician. The frequency was significantly higher in cohort III (I: 16.1%, II: 9.4%, III: 25.4%*, $P = 0.02$) and in the group of patients <60 years (20.3%* vs. 9.9% age $\geq$ 60 years, $P = 0.013$). Only 6 of 46 patients have been admitted to hospital for inpatient treatment with a calculated frequency of inpatient treatment within the last 12 months due to a lower respiratory tract infection of 2% in the whole cohort. Four of these six patients were younger than 60 years of age.

Vaccination in general

Overall, 83.3% of the studied patients owned a vaccination card at the time of evaluation (Table 2). Only 6.7% stated that they had never owned such a document. The rest lost vaccination card at some time. There were no significant differences by cohort or age.

Significantly more patients in the biological cohorts II and III were aware of an increased risk of infectious

Table 2 Answers to questionnaire by cohort and age ($P < 0.05$, * significance compared with cohort I or age < 60 years, respectively)

	I (%)	II (%)	III (%)	<60 years (%)	≥60 years (%)
General aspects					
Vaccination card available	86.3	81.2	81.4	84.2	82.4
Awareness of increased risk of infectious complications	67.7	83.8*	89.8*	82.3	73.9
Discussion vaccination in general by rheumatologist/general practitioner	36.3	47.9	54.2*	46.8	41.5
Vaccination against Streptococcus pneumoniae					
(A) Awareness of the possibility to vaccine against *Streptococcus pneumoniae*	50.8	56.4	71.2*	53.2	61.3
(B) Vaccination against *Streptococcus pneumoniae* actively recommended by rheumatologist/general practitioner (out of A)	55.6	74.2	64.3	51.2	78.2*
(C) Vaccination against *Streptococcus pneumoniae* actually performed	20.2	36.8*	39.0*	16.5	45.8*
Vaccination against influenza					
(D) Awareness of the possibility to vaccine against influenza	94.4	97.4	91.5	94.3	95.8
(E) Vaccination against influenza actively recommended by rheumatologist/general practitioner (out of D)	90.6	86.8	90.7	85.9	92.6
(F) Vaccination against influenza actually performed	64.5	69.2	59.3	55.7	76.1*

Table 3 Subgroup analysis by age within cohorts (* $P < 0.05$)

	I		II		III	
	<60 years ($n = 63$) (%)	≥60 years ($n = 62$) (%)	<60 years ($n = 64$) (%)	≥60 years ($n = 53$) (%)	<60 years ($n = 32$) (%)	≥60 years ($n = 27$) (%)
Vaccination against Streptococcus pneumoniae						
(A) Awareness of the possibility to vaccine against *Streptococcus pneumoniae*	45.2	56.5	54.7	58.5	65.6	77.8
(B) Vaccination against *Streptococcus pneumoniae* actively recommended by rheumatologist/general practitioner (out of A)	42.9	65.7	62.9	87.1*	42.9	85.7*
(C) Vaccination against *Streptococcus pneumoniae* actually performed	9.7	30.6*	23.4	52.8*	15.6	66.7*
Vaccination against influenza						
(D) Awareness of the possibility to vaccine against influenza	93.5	95.2	95.3	100.0	93.8	85.2
(E) Vaccination against influenza actively recommended by rheumatologist/general practitioner (out of D)	87.9	93.2	82.0	92.5	90.0	91.7
(F) Vaccination against influenza actually performed	56.5	72.6	57.8	83.0*	50.0	70.4

complications compared with cohort I (I: 67.7%, II: 83.8%*, III: 89.8%*, $P = 0.001$). Furthermore, there was a trend toward a higher degree of awareness in the younger patients <60 years. In addition, significantly more patients in cohort III have been informed by their rheumatologist/general practitioner about vaccination in general compared with cohort I within the last 12 months. The frequency continuously increased from cohort I to cohort III reaching statistical significance for cohort III (Table 2). There were no significant differences by age. Almost all of these patients reported having been actively recommended by their rheumatologist/general practitioner to complete their vaccination status. There were no significant differences by cohort (data not shown).

Vaccination against *Streptococcus pneumoniae*

There were 57.0% of the interviewed patients knew about the possibility of pneumococcal vaccination with significantly more patients in cohort III compared with cohort I (I: 50.8%, II: 56.4%, III: 71.2%*, $P = 0.033$) (Table 2A). There was also a trend toward a higher degree of knowledge in older patients. The source of information in the biological cohorts II and III and also in the patients ≥60 years was mainly the rheumatologist/general practitioner. Surprisingly, almost half of the patients younger than 60 years had their knowledge from other sources than from rheumatologists or general practitioners (data not shown).

Significantly more patients ≥ 60 years of age had been recommended to get vaccinated against *Streptococcus pneumoniae* compared with the younger ones in cohorts II and III (Table 3A–C). Nevertheless, only 30.3% of all patients were actually vaccinated against *Streptococcus pneumoniae* with a significantly higher frequency in the biological cohorts (I: 20.2%, II: 36.8%*, III: 39.0%*, $P = 0.005$) and the group of older patients (45.8%* vs. 16.5%, $P < 0.001$) (Table 2C). This was independent of the actual cohort (Table 3C).

Also in a subgroup analysis of patients being aware of pneumococcal vaccination and who were actively recommended to get vaccinated, not all got vaccinated. Again, significantly more patients in cohorts II and III (I: 57.1%, II: 77.6%*, III: 85.2%*, $P = 0.03$) and in the group of ≥60 years (≥60 years: 85.3%*, <60 years: 53.5%, $P < 0.001$) were vaccinated (data not shown).

Vaccination against influenza

In contrast to pneumococcal vaccination, 95.0% of all patients were aware of the possibility of vaccination against influenza. There were no significant differences by age or cohort (Table 2D–F). Overall, 65.3% had actually been vaccinated against influenza (I: 64.5%, II: 69.2%, III: 59.3%). The vaccination rate was significantly higher in patients ≥60 years (76.1%* vs. 55.7%, $P < 0.001$). Subgroup analyses of the cohorts by age revealed a trend toward a higher degree of information about influenza and also a higher vaccination rate in the elderly (Table 3D–F). Again, not all patients being aware of the possibility to vaccinate against influenza and who have been recommended to get vaccinated actually got vaccinated (I: 75.5%, II: 78.8%, III: 69.4%, <60 years: 68.0%, ≥60 years: 83.3%) (data not shown).

Vaccination titers

Supposedly, protective titers against mumps, measles, and rubella were found in 73.3, 96.0, and 91.7% of patients,

Table 4 Vaccination titers (* $P < 0.05$)

		I (%)	II (%)	III (%)	<60 years (%)	≥60 years (%)
Mumps	Protective	75.0	71.8	72.9	75.3	71.1
Measles	Protective	97.6	94.9	94.9	96.2	95.8
Rubella	Protective	91.1	92.3	91.5	94.9	88.0
Diphtheria	Protective	54.8	56.4	59.3	49.4	64.1*
Tetanus	Protective	84.7	79.5	89.8	92.4*	73.9
Hepatitis B anti-HBs (anti-HBc neg.)	≥10 IU/ml	23.2	12.8	3.4	22.0	7.7
Hepatitis B anti-HBs (anti-HBc neg.)	≥100 IU/ml	8.8	3.4	0	6.9	2.8

Due to differing cutoff levels in United States and Europe titers for hepatitis B have been evaluated separately

respectively. There were no significant differences by cohorts or age. Positive titers could be found in 83.7% for tetanus and 56.3% for diphtheria. The rate of positive titers was significantly higher for tetanus ($P < 0.001$) and significantly lower for diphtheria ($P = 0.005$) in the cohort <60 years compared with ≥60 years.

Hepatitis B surface antibodies could be found in 17.7% of patients. Thirty-two patients (10.6%) were positive for antibodies against hepatitis B surface antigen but negative for hepatitis B core antibodies representing a vaccinated status. There were no significant differences by cohort or age for hepatitis B vaccination status (Table 4). Hepatitis B core antibodies were found in 7.0%. There were no significant differences between cohorts and age. None of them was positive for hepatitis B surface antigen. Only two patients were positive for antibodies against Hepatitis B core antigen but negative for hepatitis B surface antibodies representing a high risk collective for reactivation.

Discussion

Patients with rheumatic diseases represent an "at risk" group for infections. Both immunosuppressive, anti-rheumatic therapy and underlying disease contribute to the increased risk. Data from international studies during approval and also registry data diligently document and support the increased risk of infectious diseases under biologic therapy. Genovese reported a rate of serious infections of 5.2 per 100 patient-years for rituximab and 3.7 per 100 patient-years in the placebo group in RA patients refractory to TNF-blocking agents [19]. Listing reported a rate of 2.7% for inpatient treatment due to infections within the German RABBIT registry [3]. In our own cohort, the overall frequency for hospitalization requiring systemic antibiotics due to a lower respiratory tract infection was 2% comparing well with the published data.

Given the obviously increased risk of infections, vaccination seems to be particularly important for patients with rheumatic diseases. Vaccination in general has been proven to be one of the most effective preventive strategies for infection. Influenza vaccination can prevent up to 70% of influenza infections in adults and decrease overall mortality in the elderly by up to 48% [12, 20]. Similarly, pneumococcal vaccination cost-effectively reduces the risk of pneumococcal bacteremia and invasive disease [11, 21]. Several national guidelines support vaccination in RA. The German Society of Rheumatology (http://www.dgrh.de) has published some recommendations for vaccination against influenza, *Neisseria meningitidis*, and *Streptococcus pneumoniae* in rheumatic patients emphasizing for rituximab to complete vaccination schedule at least 4 weeks before the initiation of therapy. The recommendations from the American College of Rheumatology (ACR) advise influenza vaccination for all patients prior to starting hydroxychloroquine, leflunomide, MTX, sulfasalazine, and all biologic agents and pneumococcal vaccination prior to starting leflunomide, MTX, sulfasalazine, and all biologic agents.

In our study, the degree of awareness of infectious complications was significantly higher in the biological cohorts II and III. This is probably due to an intensified discussion concerning vaccination promoted by the availability of cytokine inhibitors and other biologics particularly rituximab with its long-lasting and B-cell-specific mode of action. As a consequence, significantly more patients in cohort III have talked with their rheumatologist about vaccination in general compared with cohort I in our study (Table 2).

There are 83.3% of our patients actually owned a vaccination record that could be presented during their visit. Particularly, the knowledge of vaccination against influenza is very prominent in the population. Here, we find a very high awareness and the frequency of influenza-vaccinated people is much higher compared with *Streptococcus pneumoniae*.

There are different national vaccination recommendations. In the United Kingdom, the Department of Health recommends vaccination against influenza and *Streptococcus pneumoniae* in those aged 65 and in "at risk" groups

<65 years of age (http://www.dh.gov.uk/en/index.htm). The German STIKO similarly developed differential vaccination recommendations setting the recommendation age to older than 60 years independent of medication or morbidity. Our data from 301 patients with RA in 2009 for the first time documented vaccination behavior according to use of biologics. We found a very high degree of awareness of the possibility to vaccinate against influenza. Nevertheless, only 55.7% (<60 years) and 76.1% (≥60 years) actually received a vaccination. For *Streptococcus pneumoniae*, the situation in our cohort was very similar; 53.2% of patients younger than 60 years of age, and 61.3% ≥60 years were aware of the possibility of a specific vaccine, but only 16.5 and 36.8%, respectively, were actually vaccinated. The highest rates of pneumococcal-vaccinated patients were found in the biologic cohorts II and III and the group ≥60 years both reaching statistical significance. Our results extend a study performed by Fahy in the United Kingdom 2005 that assessed the level of influenza vaccine awareness and performance in 100 patients with rheumatic conditions treated with conventional DMARDs [22]. Rheumatoid arthritis represented 85% of the patients studied. Awareness of the influenza vaccine was high across all age groups. Influenza vaccination was relatively poor in the <65 years of age group with 46%, although 96% were aware of the possibility to vaccine. In the group ≥65 years, vaccination rate was 81%; 65% (<65 years) and 96% (≥65 years) knew about the possibility of vaccination against *Streptococcus pneumoniae*, the actual vaccination rates were 12 and 54%, respectively. These results are quite comparable with our study.

It seems likely that the knowledge of influenza vaccination is efficiently transported via the media, and therefore, many people are very much aware of. Therefore, we did not find a difference between our cohorts. This is different to pneumococcal vaccination. Here, obviously, the rheumatologists seem to be more operative by recommending vaccination particularly to patients under biologic therapy. In our study, the use of biological agents led to an increase in vaccination frequency by about 1.9 when compared with cohort I. Therefore, the choice of medication is an important factor for vaccinating against *Streptococcus pneumoniae*.

Additional subgroup analyses in our study revealed a significant increase in pneumococcal vaccination rates in patients ≥60 years of age for all cohorts. This is in accordance with the German STIKO recommendations. As a consequence, the highest rate of vaccinated patients was found with 66.7% in the cohort III (B-cell depletive therapy with rituximab) and ≥60 years of age, and the lowest rate with 9.7% could be found in cohort I (conventional DMARD) and <60 years of age. Regarding influenza, these differences become less pronounced. A significant difference was only found by age for influenza but not for treatment cohorts.

In summary, patients treated with biologic agents are better informed about pneumococcal vaccine. Both age and choice of immunosuppressive treatment were relevant factors for vaccination against *Streptococcus pneumoniae* while for influenza age rather than rheumatic therapy was the main driver. Nevertheless, there is an unexplained discrepancy between vaccination awareness and actual vaccination rates for both pneumococcal and influenza vaccination. In Germany, the attending rheumatologist usually delegates the process of vaccination to a general practitioner. This may confound vaccination results. Improved comanagement between primary care and rheumatologists probably might improve this situation and lead to higher vaccination rates. In the United States, the use of an electronic health record with best practice alert significantly increased influenza and pneumococcal vaccination in rheumatologic patients taking immunosuppressive drugs [23]. Therefore, specific national surveillance strategies seem to be required.

Regarding vaccination titers, no significant differences could be found between the cohorts including patients undergoing temporal B-cell depletion with rituximab. This is in accordance with published studies where vaccination titers seemed to be stable [14, 24, 25]. Furthermore, no significant differences could be found for mumps, measles, and rubella by age. The rate of positive titers for tetanus was significantly higher ($P < 0.001$) in the cohort <60 years. The reason for this may be the fact that vaccination against tetanus is regularly repeated in the context with injuries that may be more prevalent in younger patients.

Since the early 1990s, the German STIKO recommends vaccination against hepatitis B for all children and for populations at special risk. There were no significant differences by cohort or age for hepatitis B vaccination status. The prevalence of anti-hepatitis B core-positive patients in our cohort was 7%, which is consistent with data from a national survey by the Robert-Koch-Institute in 2009 (http://www.rki.de, Robert Koch-Institute, Berlin, 2010).

The prevention of infections by vaccination is well documented. However, the implementation of a comprehensive vaccination program for patients suffering from rheumatoid arthritis under immunosuppressive therapy is not yet completed. Our data implicate that the introduction of biologics spurred the awareness of vaccination and led to a significant higher vaccination rate particularly for *Streptococcus pneumoniae* in patients under biologic therapy. Whereas the information for influenza vaccination is widely transported, vaccination against *Streptococcus pneumoniae* seems to be significantly influenced by the efforts of the rheumatologists. Nevertheless, there is an obvious discrepancy between vaccination awareness and actual vaccination

rates. There is still an unmet need to implement better vaccination strategies for rheumatoid patients. The surveillance of patients' vaccination schedule needs to be an integral part of rheumatologic care.

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Conflict of interest The authors have nothing to disclose.

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