Do vaccinations affect the clinical course of systemic necrotising vasculitis? A prospective observational web-based study

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ABSTRACT

Objective. *To estimate the impact of vaccinations, infections and traumatic life events on the disease activity of a web-based cohort of systemic necrotising vasculitis (SNV) patients.*

Methods. *Adults diagnosed with SNV self-reported vaccinations, infectious episodes and traumatic life events every 3 months during follow-up on a secure dedicated website. Participants reported information on disease activity assessed with 3 scores: the French version of the Medical Outcome Study Short Form-36 (SF-36), the visual numerical scale for Patient Global Assessment (PGA) and the modified Disease Extent Index (mDEI).*

Results. *Between December 2005 and October 2008, 145 participants (mean ± SD age 53±13 years; 57% males) were included. Mean follow-up was 445±325 days. SNVs were distributed as follows: 46% granulomatosis with polyangiitis (Wegener's), 22% eosinophilic granulomatosis with polyangiitis (Churg-Strauss), 18% polyarteritis nodosa and 8% microscopic polyangiitis. During follow-up, 94 vaccinations, 57 acute infectious episodes and 274 traumatic life events were reported. In univariate and multivariate analyses, only traumatic life events were significantly associated with decreased SF-36 mental and physical component scores. No significant SF-36, PGA and mDEI scores variations were reported during the 3 months following acute infectious episode or vaccine administration.*

Conclusion. *No significant clinical impact of vaccinations on SNV activity was found in this prospective observational study.*

Introduction

Systemic necrotising vasculitides (SNVs) are multisystem diseases characterised by inflammation and necrosis of small- and medium-sized blood vessels. Infections are more frequent and severe in SNV patients, mainly because of widespread use of immunosuppressive therapies (1). Vaccination against vaccine-preventable diseases is therefore crucial, but immunisation rates remain low (2, 3). The reticence of physicians and patients partly reflects the difficulty of balancing the perceived risk of disease aggravation versus the vaccine-conferred protection. SNV are a very heterogeneous group of diseases, and their pathogeneses are poorly understood (4, 5). The triggering events initiating and driving SNVs are unknown and may vary among the different entities. An association between SNV and environmental risk factors, including vaccines, has been advanced previously (6-9).

To determine more clearly the impact of vaccines, infections and traumatic life events on disease activity, we established via the Internet a cohort of SNV patients who prospectively self-reported information on their disease activity and exposures of interest. During follow-up, some patients received routine vaccinations according to local practices and national recommendations, had acute infections or experienced stressful life events. This innovative patient-centered approach and the heterogeneity of patients' experiences enabled us to assess the impact of such events on the course of SNVs.

Patients and methods

Study procedure and data collected

Participants were recruited in December 2005 from the French Vasculitis Study Group (FVSG) database. To be eligible, a patient had to be ≥18 years old, have a SNV fulfilling the Chapel Hill Consensus Conference definitions or American College of Rheumatology classification criteria for SNV (10, 11) and have access to Internet throughout the study period. First, 125 pa-

tients followed by 2 of the authors in a tertiary referral centre were asked to participate. Among them, 55 did not respond, 3 declined participation and 24 did not meet the inclusion criteria; finally, 43 SNV patients were enrolled. To increase recruitment, an email was subsequently sent to the 548 physicians registered in the FVSG mailing list, inviting their patients to participate. This procedure recruited an additional 102 patients, leading to a total of 145 participants, who were asked to log on to a secure website to complete a standardised auto-questionnaire at inclusion, then every 3 months during follow-up. At inclusion, participants provided information on their demographic and socioeconomic status, date of SNV diagnosis and treatments received. Thereafter, every trimester, they were asked to complete a questionnaire on selected remarkable events - vaccinations, episodes of infection or traumatic life events - that had occurred since the last connection.

Definitions

Vaccinations. Vaccine administration was self-reported. The following list of commercialised vaccines (given with vaccine antigens and commercial names) was suggested to the participants: diphtheria-tetanus-poliomyelitis, seasonal influenza, pneumococcal and meningococcal diseases, hepatitis A and B, rubella, typhoid, Japanese encephalitis, tick-borne encephalitis, yellow fever and rabies.

Infections. Participants were asked to report any clinical episode of infection with a brief description of symptoms, consequences (consultation or hospitalisation) and treatments administered for the event. Information entered by the patients was reviewed by an internist, blinded to the other sections of the questionnaire. Clinical infectious episodes were defined as the sudden onset of compatible clinical manifestations *e.g.*, cough, runny nose, polyuria or fever.

Stressful or traumatic life events. Examples of stressful events were given in the questionnaire, *e.g.*, death of a relative, any disease or serious problem affecting a relative, or financial or legal problems (12). The participant scored each of traumatic life event from 0 ("the event did not affect me at all") to 10 ("the worst possible emotional impact"). Only events of intensity ≥5 were considered stressful or traumatic.

Quality-of-life and disease activity

During follow-up, SNV activity was evaluated every trimester with 3 scores.

Medical Outcome Study Short-Form-36 (SF-36). In the analysis, the SF-36 was divided into mental (MCS) and physical component scores (PCS), both ranging from 0 (most impaired quality of life) to 100 (best quality of life).

Patient Global Assessment (PGA). Participants were asked to self-evaluate their disease activity on a scale ranging from 0 (totally inactive) to 10 (highly active).

Disease Extent Index® (DEI). The DEI was initially designed and validated for physicians to assess disease staging and grading in patients with anti-neutrophil cytoplasm antibody-associated vasculitides (13). For the purpose of this study, a modified version of the DEI (mDEI) was developed to allow patient self-reporting. DEI items were rewritten with syntactical modifications to improve patients' comprehension: *e.g.* the item *"nasal obstruction, crusty, bloody discharge"* was rephrased to *"stuffy nose, bloody or crusty discharge from the nostrils"*. The mDEI was calculated like the DEI, and ranged from 0 (SNV in complete remission) to 21 (highly active SNV).

Statistical methods

Our analysis evaluated the relationship between 'exposure variables' (*i.e.*, vaccines, infections and traumatic life events) and 'outcome measures' (SF-36, PGA and mDEI). A generalised estimating-equation approach was used to account for repeated measurements. The score change over a trimester was estimated by taking into consideration the occurrence of exposure events during that time period and adjusting to the score value at the previous connection, as previously described (12). Briefly, the effect of vaccination was tested by comparing SF-36, PGA and mDEI changes over the 3-month periods during which the patient had been vaccinated ('exposed periods') to changes over periods without any vaccination ('non-exposed periods'). For each exposure, the analysis yielded the expected score variation after exposure during the previous trimester. All exposure variables, age and sex were included in univariate and multivariate analyses. In the latter, backward selection of variables was done until all remaining variables achieved $p<0.05$. Robust variances were used for tests and confidence intervals. Statistical analyses were computed with the R software version 2.13.2 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the Ambroise-Paré Hospital Institutional Review Board and informed consent was obtained from every participant.

Results

Between December 2005 and October 2008, the 145 study participants (mean ± standard deviation (SD) age 53±13 years; 83 males (57%)) connected 1,213 times to the website, for a mean of 9±2.7 connections per participant, with a mean of 115±51 days between 2 connections and mean follow-up of 445±325 days. Almost half of the patients (n = 66, 46%) had granulomatosis with polyangiitis (Wegener's), 31 (22%) eosinophilic granulomatosis with polyangiitis (Churg-Strauss), 26 (18%) polyarteritis nodosa and 12 (8%) microscopic polyangiitis (Table I). The SNV had been diagnosed a mean of 6.9±5.3 years earlier. At study enrollment, 91 (63%) participants were taking corticosteroids, 82 (57%) an immunosuppressant. Corticosteroids and an immunosuppressive agent were associated in 62 patients (56%). Fifty-nine (41%) participants had a university degree and 52 (36%) worked full-time at inclusion. Among the 78 (54%) participants with no professional activity, 43 (55%) were retired and 26 (33%) were on long-term disability. At study enrolment, the mean MCS was 62.1±19.9, PCS 57.7±21.9, PGA 3.2±2.2 and mDEI 4.2±3.6). Sixty six different participants received 103 vaccinations during the study period: 70 against seasonal influenza, 16 against diphtheria-tetanus-poliomyeli-

Table I. Baseline characteristics of study participants. Results are presented as n (%) or median (range).

Study participants	n=145
Females	62 (43)
Age, years	53 (22; 84)
Educational level	
Middle School or less	11 (8)
High School	74 (51)
College or more	59 (41)
Comorbidities	
Hypertension	37 (26)
Asthma	36 (25)
Current smoker	21 (15)
Diabetes mellitus	8 (6)
Stroke	7 (5)
Vasculitis	
Granulomatosis with polyangiitis	66 (46)
Eosinophilic granulomatosis with polyangiitis	31 (22)
Polyarteritis nodosa	26 (18)
Microscopic polyangiitis	12 (8)
Time since diagnosis of vasculitis, years	6 (<1; 24)
Treatments	
Corticosteroids	91 (63)
Daily dose of equivalent-prednisone, mg	7 (1 ; 70)
Immunosuppressive agents	82 (57)
Mycophenolate mofetil	22 (15)
Azathioprine	48 (33)
Methotrexate	12 (27)
Cyclophosphamide	3 (2)
Ciclosporine	1 (0.5)
Infliximab	1 (0.5)
Rituximab	1 (0.5)

tis, 7 against hepatitis B, 5 against invasive pneumococcal disease, 2 against hepatitis A and typhoid, and 1 against rubella. During follow-up, 93 and 47 participants respectively self-reported 274 traumatic life events or 57 acute infectious episodes. All patients (n=145) were included in the statistical analysis, including those without any event.

According to our univariate and multivariate analysis (Table II), only traumatic life events – not vaccinations or infections – were significantly associated with decreased SF-36 scores: -10.3 for MCS (95% confidence Interval [CI] -14.8; -5.7, $p=10^{-5}$) and -5.4 for PCS (95% CI –10.0; –0.7, $p=0.02$), with no significant impact on PGA, or mDEI. The multivariate analysis retained only traumatic life events as being significantly associated with SF-36 MCS and PCS variations.

Discussion

The role of infections and vaccinations in triggering or worsening SNV has long been debated. Disease flares post-vaccination have been reported, particularly in patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (6-8). In a prospective study on 199 patients with autoimmune diseases, 6 mild disease flares were reported during the 30 days following the administration of seasonal or pandemic influenza vaccines (9). However, distinguishing between true vaccine-caused adverse reactions and events only temporally associated by chance is difficult. To address this issue, we compared, for each participant, SNV activity during periods with or without exposure to vaccines, infections or traumatic life events. With this approach, no significant SF-36, PGA or mDEI changes were observed during the 3 months following vaccinations or infections, while traumatic life events had a negative impact on PCS and MCS. According to our computations, if exposure always triggered a score change, the number of patients included would have made it possible to demonstrate with 80% probability (*i.e.* statistical power was 80% for these differences) a 5-point difference for SF-36, 0.5 for PGA and 0.9 for mDEI. Smaller changes would have been more difficult to discern. However, in light of the observed small effect-sizes, it is unlikely that vaccination has a clinically meaningful impact on any of the analysed outcome measures.

Our study relied on patients' self-assessment of SNV activity through 3 clinical scores. Initially, those scores were not designed to be self-administered. However, the agreements be-

Table II. Multivariate analysis of the variation of each score according to age, sex and each exposure variable*.

	SF-36 MCS		SF-36 PCS		Patient Global Assessment		Modified Disease Extent Index#	
Exposure variable†	Estimate [95% CI]	p‡	Estimate [95% CI]	p‡	Estimate [95% CI]	p‡	Estimate [95% CI]	p‡
Age	–0.1 [-0.2 ; +0.1]	0.23	–0.1 [-0.2 ; 0.0]	0.10	0.0 [0.0 ; 0.0]	0.5	0.0 [0.0 ; 0.0]	0.20
Sex	-0.2 [-4.0 ; +3.5]	0.90	+1.1 [-2.4 ; +4.6]	0.55	-0.1 [-0.5 ; +0.4]	0.73	+0.2 [-0.3 ; +0.7]	0.37
Vaccination	+0.4 [-5.1 ; +5.9]	0.88	+2.7 [-3.2 ; +8.7]	0.37	+0.1 [-0.5 ; +0.7]	0.84	-0.4 [-1.2 ; +0.3]	0.21
Traumatic event	-10.3 [-14.8 ; -5.7]	10^{-5}	-5.4 [-10.0 ; -0.7]	0.02	+0.3 [-0.1 ; +0.8]	0.12	+0.4 [-0.2 ; +0.9]	0.16
Infection	+3.4 [-4.1 ; +10.9]	0.37	+0.9 [-6.1 ; +7.9]	0.79	-0.4 [-1.0 ; +0.2]	0.18	-0.2 [-0.8 ; +0.4]	0.60

*SF-36: short-form 36; MCS: mental component score; PCS: physical component score; CI: confidence interval.
†For a given vaccination, traumatic event and infectious episode exposure, the estimated regression coefficient (designated "Estimate") reflects the observed score variation when exposure to the variable occurred during the previous 3 months.
‡Wald's test. #Modified to allow patient self-reporting.

tween patients' and physicians' assessments are excellent and confirm the ability of the SF-36 to estimate disease progression over time (14-17). PGA scores were strongly associated with the subsequent occurrence of a disease relapse in granulomatosis with polyangiitis (Wegener's) patients (14). The results of other studies demonstrated the feasibility of PGA to predict systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis or cancer activity (15-17). We developed mDEI that could be used for online self-reporting with language suitable for patients. In other settings, such transformations of health-assessment tools designed for clinicians into patient-reported versions have proved appropriate (14). The strength of self-administered scores is to enable patients to independently report information on their disease and health status. In addition, each patient served as his/her own control, thereby limiting biases and confounding factors. Moreover, patient-driven risk assessment is an interesting approach, since patients might prefer being given information based on the impressions of other patients rather than on physicians' evaluations alone (16).

This study has several limitations. First, although the small sample size limited the power of the statistical analysis, the study was sufficiently powered to detect an impact of traumatic life events on SF-36 MPS and PCS (p<10–5 and 0.04, respectively). Second, the study is mainly based on patient reported outcomes and few data were available on patients' clinical status (disease manifestations, damage, treatments). Patients rated their disease activity with self-administered scores, rather than expert-recommended physician-evaluated clinical activity scores. These scores were not designed for use by the patients but the results of several studies indicated excellent agreement between patients' and physicians' assessments, and also confirmed the ability of SF-36 to estimate disease progression over time (14-17). Like all observational studies, several biases, e.g., recall bias on the date of vaccine administration, might have influenced the results. However, the prospective study design was intended to temper the impact of such inaccuracies. Participants to this internet-based study may also not be representative of the whole population of SNV patients, as recognised previously for patients included in randomised controlled trials (18).

This innovative, patient-centered approach used new tools to measure SNV activity and evaluate potential epidemiological links between vaccines and disease flares. Such approaches are complementary to more fundamental or physician-driven studies on vaccinations. The results are reassuring regarding the risk of SNV worsening after vaccination.

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