Patients with systemic inflammatory and autoimmune diseases are at risk of vaccine-preventable illnesses

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Abstract

Objective. To evaluate vaccine coverage and humoral immunity to tetanus, diphtheria and poliomyelitis in adults followed for systemic inflammatory and/or autoimmune diseases (SIADs).

Methods. A cross-sectional study was conducted between June and August 2006 in a monocentric cohort of adults with SIAD. A standardized questionnaire was administered to collect medical, therapeutic and vaccine coverage data. Blood samples were collected in order to measure antibody titres against diphtheria, tetanus and poliomyelitis (DTP).

Results. One hundred and eighty-six patients, 32% males, mean (s.d.) age 51 (16) years, 79% receiving CSs and/or immunosuppressants, were included. The vaccine coverage was 29% for diphtheria, 48% for tetanus and 33% for poliomyelitis. The percentages of patients with no humoral immunity against DTP were 44, 21 and 12%, respectively, decreasing to 37.5, 10 and 0%, respectively, for those who had received a vaccine booster in the last 10 years. In a multivariate analysis, age and CS treatment were associated with the absence of humoral immunity against diphtheria and female sex, CD4+ T cell <200/mm3 and an absence of tetanus vaccine booster in the last 10 years with the absence of humoral immunity to tetanus.

Conclusion. Vaccine coverage against tetanus, diphtheria and poliomyelitis is low in patients with SIAD despite the risk in this population of severe infection, especially when receiving immunosuppressants. A significant proportion of them had no humoral immunity against diphtheria or tetanus. Specific immunization schedules need to be optimized in these patients.

Key words: Autoimmune disease, Vaccination, Diphtheria, Tetanus, Poliomyelitis.

Introduction

Diphtheria (D), tetanus (T) and poliomyelitis (P) are among the oldest vaccine-preventable diseases. In France, vaccination against diphtheria, tetanus and poliomyelitis (DTP) has been generalized since 1938, 1940 and 1964, respectively. Primary vaccination against DTP is mandatory during childhood (three injections between the age of 2 and 4 months, and a booster at 18 months). DTP boosters are then recommended at 6, 11–13 and 16–18 years, followed by a decennial booster with tetanus and poliomyelitis vaccines. The vaccine booster including a reduced dose (d) of diphtheria toxoid (DT) was added for adult travellers in 1994 and for all adults in 2005 [1]. Most of the European countries provide the same recommendations towards DTP, as the USA recommend polio vaccine boosters only...
for children and at-risk adults (travellers and health-care workers) because adults have a minimal risk of exposure to polioviruses and most are protected as a result of vaccination during childhood [2].

Tetanus is a ubiquitous non-transmissible disease, which was still responsible for 41 declared infections and 13 deaths in France between 2005 and 2007, especially among the elderly [3]. Although diphtheria and poliomyelitis circulation in Western countries is limited due to high rates of immunization, they remain potentially serious diseases with high mortality levels. They may be contracted when travelling in developing countries where they cause outbreaks [4].

In France, vaccination coverage for DTP is very high (>98%) among children due to the legal obligation, although it decreases in the adult population: 29% for diphtheria, 62% for tetanus and 36% for poliomyelitis for people aged >16 years [5], especially among the elderly (10.5% for diphtheria, 60.5% for tetanus and 13% for poliomyelitis for people aged >65 years). A study performed by the European Sero-Epidemiology Network (ESEN) showed that an important proportion (e.g. 35% in the 50- to 60-year-old group in Finland) of the adult European population was not protected against diphtheria [6].

Patients with immunosuppression, either due to an illness- or treatment-related immunosuppression, such as those suffering from systemic inflammatory and/or autoimmune diseases (SIADs), are at higher risk of severe infections than healthy adults and should benefit from the routine vaccination recommendations [7]. Only few data are available regarding vaccination coverage of patients with SIADs. Published studies show that, despite recommendations and risks of severe infections and because of a theoretical risk of vaccine-induced modification of the course of inflammatory diseases [8], immunization rates among immunocompromised patients are lower than in healthy adults [9–12]. There is no published serological data concerning DTP protection in these patients.

Thus, we decided to evaluate the uptake of DTP vaccination in patients with SIAD and the percentage of them with humoral immunity to these three vaccine-preventable diseases.

**Patients and methods**

**Study design and patients**

We conducted a monocentric, cross-sectional, sero-epidemiological study in patients with SIAD followed at our Internal Medicine Department, a national French reference centre for necrotizing vasculitis and SSCs at Paris Descartes University. Every adult patient seen for routine outpatient consultation or hospitalization during a 3-month period was proposed to participate in the study. Patients were contacted by telephone the week before the consultation or the hospitalization to inform them of the study and were asked to bring any document proving their immunizations or vaccination leaflet, if available. A standardized questionnaire was filled during an appointment with an infectious diseases specialist and the data concerning vaccine coverage were checked in the vaccination leaflet when available. Blood samples were taken afterwards. Patients with a history of acute infection in the past 3 weeks and those who had received IVIG during the last 6 months were excluded. The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research, and was approved by the Committee for Protection of Persons (Comité de Protection des Personnes Île de France 3, Paris). All participants gave written informed consent.

**Data collection**

A standardized questionnaire was used to collect information concerning sex, age, type of SIAD, type and dose of immunosuppressive treatment, risk factors for tetanus and specific data about personal immunizations. The SIADs were categorized into three groups, which were chosen for the similarity in pathogenesis to increase the power of the analysis: (i) vasculitis including ANCA-associated vasculitis (Churg–Strauss syndrome, WG and microscopic polyangiitis), lymphocytic vasculitis, polyarteritis nodosa, cryoglobulinaemia vasculitis, Behçet’s disease and GCA; (ii) CTDs: SLE, SSC, idiopathic inflammatory myopathies and SS; and (iii) systemic inflammatory diseases: sarcoidosis, RA, IBD, Carrington’s disease and polychondritis. Blood samples were used for the dosage of antibodies to DT, tetanus toxoid (TT) and poliovirus, and for the determination of total lymphocyte count, CD4⁺ T-cell count and gammaglobulin levels.

**Laboratory procedures**

Dosage of antibodies to DT (anti-DT) and TT (anti-TT) were determined by using commercially available ELISA tests: Tetanus ELISA IgG Test Kit and Diphtheria ELISA IgG Test kit Genzyme Virotech (Ruesselsheim, Germany) distributed in France by Ingen (Chilly-Mazarin, France). The ELISA tests were performed using an ELISA processor ETI-Max 3000 (DiaSorin, Saluggia, Italy). By using standard sera (0.001–0.051 IU/ml) a standard curve is plotted to determine the anti-DT and anti-TT IgG levels in the serum. The anti-DT and anti-TT concentrations are expressed in International Units (IU)s per ml following the WHO Standards. The interpretation was performed according to the manufacturer’s instructions.

Poliomyelitis antibodies were measured with a cytopathic effect neutralization test that was performed in standard conditions against each poliovirus vaccine strain, as previously described [13]; titres of neutralizing antibodies were expressed as the reciprocal of the ultimate serum dilution that neutralizes 50% of the virus cytopathic effect.

**Humoral immunity**

Patients with anti-DT concentrations ≥0.1 IU/ml were considered to have effective humoral immunity to diphtheria, with a low level of humoral immunity for those with anti-DT concentrations between 0.1 and 1 IU/ml and a
high-level humoral immunity for those with anti-DT concentrations \(>1\) IU/ml [14–16].

Patients with anti-TT concentrations \(\geq 0.1\) IU/ml were considered to have effective humoral immunity against tetanus, with a low level of antibodies for those with anti-TT titres between 0.1 and 0.49 IU/ml and a high level of antibodies for those with anti-TT titres \(\geq 0.5\) IU/ml. Humoral immunity against poliomyelitis (1, 2 or 3) was considered effective for patients with an antibody rate \(\geq 8\) (1/dil).

**Definition of vaccine coverage**

Patients were considered up to date for each vaccination if they had received the last vaccine booster dose \(<10\) years before. For the total study population, vaccine coverage was estimated taking into account both the declarative data for patients who had no vaccination booklet and the available data for those with proof of vaccination.

**Statistical analysis**

Categorical variables were expressed as percentages and continuous variables were expressed as means (s.d.). Antibody titres were expressed as geometric mean titres (GMTs). Comparisons of categorical variables used chi-square or, when appropriate, Fisher’s exact test. For each of the three vaccines, separate uni- and multivariate logistic regression analyses were fitted to determine factors associated with a status of seroprotection; these analyses used no humoral immunity (based on serological data) as dependent variable and the following 15 predefined parameters as potential predictors: sex, age, country of birth, type of SIAD, duration of the disease, current use of CSs, immunosuppressive treatment, infectious risk factors, lymphocyte count, CD4+ T-cell count, serum gammaglobulin level, serum IgG level and vaccine booster received in the last 10 years. All the parameters for which a \(P \leq 0.2\) was obtained in univariate analyses were entered in the multivariate regression model and we then applied a backward stepwise selection algorithm.

For all statistical analyses, two-tailed \(P \leq 0.05\) was considered to be significant and CIs were calculated at the 95% level. All statistical analyses were performed using Stata version 8.2 (Stata Corporation, College Station, TX, USA).

**Results**

**Characteristics of the study population**

Between 6 June and 31 August 2006, a total of 210 patients were contacted by phone before their consultation or hospitalization. Among them, 186 were included in the study. Reasons for non-inclusion were: age \(<18\) years \((n = 2)\); missing the appointment \((n = 5)\); and refusal to participate \((n = 17)\). The characteristics of the study population are reported in Table 1. Their mean age was 51 (16) years, 59 (32%) were men and 32 (17%) were born in developing countries. The mean SIAD duration was 10 (9) years and 147 (79%) patients were receiving CSs and/or immunosuppressant. Among the 33 (18%) patients who received only CSs, 16 (9%) received \(>10\) mg/day. Of note, no patient had received IVIGs in the last 2 months before inclusion. Mean total lymphocytes and CD4+ T-cell counts were 1281 (620) and 610 (398)/mm³, respectively.

**Table 1 Characteristics of the study population**

<table>
<thead>
<tr>
<th>All patients ((n = 186))</th>
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<tbody>
<tr>
<td>Sex, men (59) (32)</td>
</tr>
<tr>
<td>Age, mean (s.d.), years (51) (16)</td>
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<tr>
<td>SIADs Group 1 (63) (33.9)</td>
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<tr>
<td>Behçet’s disease (11) (6)</td>
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<tr>
<td>GCA (7) (3.7)</td>
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<tr>
<td>Other vasculitis (45) (24.2)</td>
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<td>Group 2 (84) (45.1)</td>
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<tr>
<td>SLE (32) (17.2)</td>
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<tr>
<td>SSc (26) (14)</td>
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<td>Idiopathic inflammatory myopathy (9) (4.8)</td>
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<td>SS (17) (9.1)</td>
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<tr>
<td>Group 3 (39) (21)</td>
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<tr>
<td>RA (22) (11.8)</td>
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<tr>
<td>Sarcoidosis (10) (5.4)</td>
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<tr>
<td>Others (7) (3.8)</td>
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<tr>
<td>Duration of the disease, years</td>
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<tr>
<td>(0–5) 65 (35)</td>
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<tr>
<td>(5–10) 44 (24)</td>
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<tr>
<td>(10–20) 56 (30)</td>
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<tr>
<td>(&gt;20) 21 (11)</td>
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<tr>
<td>Immunosuppressive agents 114 (61)</td>
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<tr>
<td>One (97) (52)</td>
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<td>Association of two (13) (7)</td>
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<tr>
<td>Association of third (4) (2)</td>
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<tr>
<td>Group 1 MTX (25) (13)</td>
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<tr>
<td>MMF (23) (12)</td>
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<tr>
<td>AZA (25) (13)</td>
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<td>LEF (3) (2)</td>
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<tr>
<td>Group 2 CYC (10) (5)</td>
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<tr>
<td>Ciclosporin (1) (0.5)</td>
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<tr>
<td>Group 3 TNF-(\alpha) inhibitors (19) (10)</td>
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<tr>
<td>Anti-CD20 (6) (3)</td>
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<tr>
<td>Group 4 HCQ (21) (11)</td>
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<tr>
<td>Salazopyrine (2) (1)</td>
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<tr>
<td>CSs (122) (66)</td>
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<tr>
<td>CSs without other immunosuppressive agent (33) (18)</td>
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<tr>
<td>CD4+ cell count/mm³</td>
</tr>
<tr>
<td>(&lt;200) 15 (8)</td>
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<tr>
<td>200–500 (59) (32)</td>
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<tr>
<td>(&gt;500) 106 (57)</td>
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<tr>
<td>Hypogammaglobulinaemia (&lt;6) g/l (18) (10)</td>
</tr>
</tbody>
</table>

Values are represented as \(n\) (%). Others: IBD, Carrington’s disease, polychondritis.
The mean serum gammaglobulin concentration was 10.5 (4) g/l.

Ninety-seven (52%) patients had available proof of vaccination. This proof concerned one or more valence: 71 (73%) patients had proof for diphtheria, 92 (95%) for tetanus and 79 (81%) for poliomyelitis. We found no difference in age, sex, type of SIAD, disease duration and type of immunosuppressive treatment between patients with available proof of vaccination and those for whom no proof of vaccination could be obtained (data not shown).

**Vaccination coverage against DTP**

In our cohort of 186 patients, the vaccine coverage for DTP was 29, 48 and 33%, respectively. Among patients with available proof of vaccination, the vaccine coverage against DTP was 49, 72, and 57%, respectively. The mean time since the last booster dose on proof was 8 (10) years both for diphtheria and poliomyelitis; it was 9 (10) years for tetanus. Among patients without vaccination proof, 6, 21 and 7% declared having received a booster for DTP, respectively, in the past 10 years.

**Humoral immunity to DTP**

Of the 186 patients included in the study, 82 (44%) had an anti-DT antibody level <0.1 IU/ml, 80 (43%) between 0.1 and 1 IU/ml and 24 (13%) >1 IU/ml (Fig. 1). The GMT of anti-DT antibodies was 0.2 IU/ml. Among the 48 patients with available proof of diphtheria vaccine booster administered during the last 10 years, 18 (37%) had an anti-DT antibody level <0.1 IU/ml, 22 (46%) between 0.1 and 1 IU/ml and 8 (17%) >1 IU/ml (Table 2). The GMT of anti-DT antibodies for those patients was 0.79 IU/ml.

Thirty-nine (21%) of the 186 patients had an anti-TT antibody level <0.1 IU/ml, 45 (24%) between 0.1 and 0.49 IU/ml and 102 (55%) >0.5 IU/ml. The GMT of anti-TT antibodies was 0.51 IU/ml. Among the 70 patients with proof of tetanus vaccine booster received during the last 10 years, 10% had an anti-TT antibody level <0.1 IU/ml, 23% between 0.1 and 0.49 IU/ml and 67% >0.5 IU/ml. The GMT of anti-TT antibodies for those patients was 0.82 IU/ml (Table 2).

Finally, 22 (12%) patients had a level of antibodies against poliomyelitis <1/8. All the 55 patients who received a poliomyelitis booster in the last 10 years had a level of antibodies against poliomyelitis >1/8. The GMT
of anti-polio antibodies was 78.35/dil for serotype 1, 86.33/dil for serotype 2 and 67.01/dil for serotype 3.

Factors associated with lack of humoral immunity to DTP

Diphtheria

The univariate analysis identified age >50 years ($P=0.0001$), past or present CS therapy ($P=0.003$) and lymphopenia ($P=0.04$) as being significantly associated with no humoral immunity to diphtheria. In the multivariate analysis, factors associated with no humoral immunity to diphtheria were age >50 years [odds ratio (OR) 5.9; 95% CI 3.09, 11.12; $P<0.001$] and CS therapy (OR 5.04; 95% CI 1.72, 14.76; $P=0.003$) (see supplementary table 1, available as supplementary data at Rheumatology Online).

Tetanus

In the univariate analysis, female sex, age, CD4+ T-cell count and not having received tetanus vaccine booster in the last 10 years, were significantly associated with no humoral immunity to tetanus. In the multivariate analysis, factors associated with no tetanus humoral immunity were female sex (OR 37.9; 95% CI 2.3, 631.7; $P=0.01$) and CD4+ T-cell count <200/mm$^3$ (OR 52.5; 95% CI 3.8, 716.2). Having received a vaccine booster in the last 10 years yielded an OR <1 indicating that this variable was associated with humoral immunity to tetanus (OR 0.09; 95% CI 0.02, 0.38) (see supplementary table 2, available as supplementary data at Rheumatology Online).

Polio

No factor was found to be correlated with a better level of humoral immunity to poliomyelitis.

Discussion

In this cohort of 186 patients with SIAD, we evidenced low vaccine coverage against diphtheria (29%), tetanus (48%) and poliomyelitis (33%) and found that a high proportion of patients had no humoral immunity to diphtheria (44%), but also tetanus (21%) and poliomyelitis (12%). Among patients who have received vaccine booster in the last 10 years, the percentages of patients with no humoral immunity were lower but remained significant: 37 and 10% of them had no humoral immunity to diphtheria and tetanus, respectively.

The literature about vaccine coverage in adults with chronic diseases is very poor. To our knowledge, there are no data on DTP vaccine coverage in patients with SIAD. The vaccine coverage assessed in the French general adult population on declared data is similar (29% for diphtheria, 62% for tetanus and 36% for poliomyelitis) to the vaccine coverage estimated in our cohort of patients with SIAD [5].

Among patients who have received a vaccine booster in the last 10 years, as recommended, only 63% had humoral immunity to diphtheria, 90% to tetanus and 100% to poliomyelitis. These findings mean that 37 and 10% of the patients remained unprotected against diphtheria and tetanus, respectively, despite appropriate vaccination.

The ESEN study, conducted in general population in several European countries, including France, found higher immunity rates to diphtheria, ranging between 95 and 100% [17].

No serological data concerning immunity against tetanus and poliomyelitis are available in the general population. The situation is particular for inactivated poliomyelitis vaccine as it is a very immunogenic vaccine; therefore, almost all patients were protected, even 10 years after the last booster dose [18]. Those findings should lead physicians to be particularly aware when taking care of patients who could be in situations at risk of those diseases, such as travelling in high prevalence countries for diphtheria or gardening for tetanus.

Factors associated with insufficient protection against tetanus and diphtheria include age, sex, CS therapy and CD4+ T-cell count. We know that senescence is responsible of an impairment of the immune response after immunization [6], especially for cell-mediated immunity [19, 20]. Cases of tetanus predominantly affect older women, as men received a booster during military service [3]. The level of CD4+ T cell is linked to the efficacy of the vaccination, as reported before in HIV-infected patients [21], because systemic immune activation is impaired after depletion of CD4 memory cells [22] and vaccine failure is due to a decline in vaccine-induced antibodies [23].

We found no significant statistical difference in univariate analysis between the type of SIAD, the type of immunosuppressive treatment and the immune response. Gluck and Muller-Ladner [24] reported that immunosuppressive treatments in patients with systemic diseases had a variable impact on post-vaccination titres: strong for rituximab and abatacept; moderate for conventional DMARDs such as MTX or AZA; and slight for TNF antagonists.

Physicians taking care of patients with SIAD should be aware that standard immunization recommendations [25, 26] may be insufficient to protect efficiently immunocompromised patients. Nevertheless, immunocompromised patients like those who underwent kidney transplantation [27] or allogeneic bone marrow graft [28, 29] show identical immune responses after a booster dose, although their antibody titres decrease more rapidly with time. The standard recommendations on immunization are those applied to immunocompetent individuals, but immunocompromised people exposed to such pathogens may be proposed scheduled antibody testings and more frequent booster doses.

The major limitation of our study is the heterogeneity of the population, in terms of SIAD and treatment regimens. Further data in more homogeneous populations for both diseases and immunosuppressive treatments will be gathered. It also seems important to evaluate immunogenicity after a booster dose in patients inadequately protected.

In conclusion, treatments for SIAD are becoming more efficient, and offer a better prognosis and quality of life to the patients. However, they are associated with a higher risk of severe infection than in the general population.
In this context, vaccination could be a major measure to avoid infection and studies are needed to better determine specific immunization schedules in those patients.

**Rheumatology key messages**

- Coverage of vaccination against DTP is low in patients with SIAD.
- Seroprotection may not be achieved by a standard immunization programme.

**Disclosure statement:** O.L. is an investigator on vaccine studies sponsored by Sanofi Pasteur-Merck Sharp & Dohme-Chibret, GlaxoSmithKline Biologicals and Merck. The other authors have declared no conflicts of interest.

**Supplementary data**

Supplementary data are available at *Rheumatology* Online.

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