

Vaccination and Rheumatic Diseases: Is There Still a Dilemma?

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Abstract: The development of rheumatic diseases after immunization has been reported in the medical literature but a causal relationship has not been established. Infections remain an important cause of morbidity and mortality in patients with rheumatic diseases who may be immunodepressed for immunological dysfunctions or immunosuppressed due to the pharmacologic therapy. Although vaccines against infectious diseases are considered the standard way in preventive medicine, it is still a controversial issue among rheumatologists whether or not patients with rheumatic disorders should undergo vaccination.

In recent decades increased numbers of studies on influenza and pneumococcal vaccines administered to patients with systemic lupus erythematosus have proven their safety. These vaccinations, generally immunogenic (i.e. able to induce a protective level of specific antibodies), may not induce an adequate response in patients receiving immunosuppressive therapy. The safety and the immunogenicity of Tetanus toxoid, and HBV vaccinations in SLE patients are not completely defined so far.

Considering the few available studies, influenza, pneumococcal, and HBV vaccines seem to be safe and immunogenic in patients with rheumatoid arthritis. The effect of TNF α blocking therapies on human immune responses to vaccination is discussed. We also review existing knowledge on vaccination in patients with Sjogren's syndrome and in children with rheumatic disorders, discussing risks and benefits.

Keywords: Immunization, vaccination, vaccine, rheumatic diseases, systemic lupus erythematosus, rheumatoid arthritis.

INTRODUCTION

Whether or not patients with rheumatic disorders should receive vaccinations is a controversial issue among rheumatologists.

Several case specific considerations have to be done before administering a vaccine: risk of infection, infection morbidity and mortality, immunogenicity of the vaccine and its toxicity.

Infectious diseases are one of the leading causes of morbidity and mortality among rheumatic patients who may be immunocompromised due to immunological dysfunctions of the disease or immunosuppressed due to the pharmacologic therapy [1-4]. Moreover, there is concern about the potential role of infections in exacerbation of the underlying disease.

According to the Advisory Committee on Immunization Practices recommendations, patients with chronic diseases should receive influenza and pneumococcal vaccines [5], however, the safety and the immunogenicity of these vaccines in rheumatic patients is still a matter of debate. There is a great deal of concern about which type of vaccine should be used (attenuated/inactivated) and the number and type of antigens, some are more immunogenic than others. Whether disease activity may influence the immunogenicity of the vaccine is still being under discussion. The role of post-

exposure vaccination is another consideration to be answered. In addition, rheumatic patients are likely not to develop seroconversion or reach protective antibody levels after vaccination [6-8]. A reaction to components of the vaccine as adjuvants, stabilizers, bacteriostatics, remnants of cellular cultures or other processes of preparation has been reported [9]. Actually, in 1999 U. S. Public Health Service and others recommended reducing or eliminating the content of thimerosal, a mercury-containing compound used as bacteriostatic, in vaccines. Now there are either thimerosal-free preparations or with only trace amounts of the preservative, especially in the childhood immunization manufactured products [10].

Most of the data against the use of vaccines come from the reported cases of previously healthy individuals who presented the onset of rheumatic diseases after vaccination, suggesting the vaccine may have triggered a persistent auto-immune response in genetically predisposed subjects (i.e. IgA-deficit, hypocomplementaemia, specific HLA-DR) ("Hit and run theory") [9, 11-13]. However, case-reports are inadequate to support a causal link between immunization and rheumatic diseases; therefore, population-based epidemiologic studies are needed.

The overall purpose of this review is to update the knowledge about the occurrence of rheumatic diseases after immunization and to assess the risk/benefit ratio of vaccination in patients with rheumatic diseases. Moreover, practical advice to rheumatologists and physicians who take care of these patients will be given herewith.

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METHODS

Relevant publications were searched using the Medline (1966-2006) database. The following keywords were used: systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, juvenile rheumatoid arthritis, vasculitis, systemic sclerosis, dermatopolymyositis, rheumatic diseases, vaccine, vaccination, immunization. We extended the search by screening the reference lists of all the relevant articles. As the variation of the methodological quality of prognostic studies may influence the results and conclusions of a systematic review, we scored the quality of the prognostic studies included in this review using a seven criteria set based on those proposed by Altman [14]. Checklist included seven questions (total quality score 0-8): 1) were patients diagnosed in line with ACR criteria? (score 0-1), 2) were clinical and demographic characteristics fully described? (score 0-1), 3) was the sample representative (score 0-1), 4) was the follow-up >1 month? (score 0-1), 5) were the outcomes objective and fully defined? (score 0-1), 6) were appropriate statistical adjustments analysed for all important factors? (score 0-1), 7) was the best study design performed? (score 0-2). With regard to this last question the studies were scored according to the type of study design. To clarify the safety and the immunogenicity of vaccination in rheumatic disease patients, double-blind randomized placebo controlled trials were judged to have the most valid design (score 2). We considered of minor strength randomized controlled trials and controlled studies (score 1) and, descriptive studies (score 0). Case-reports, evidence from expert committee reports or opinions or clinical experience of authorities were not considered for this quality criteria score. Studies were classified as high (score >6), medium (score 4-6), or low quality (score <4).

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

SLE and Infections

During the past decades there has been a marked improvement in the survival rate of SLE patients, but major infections probably remain the largest cause of death among these patients; as a matter of fact from one third to one-half of SLE patients suffer major infections during the course of the disease presenting an increased infection rate in comparison with normal healthy controls [1,3,15-17]. In 1974 Staples and co-workers demonstrated that the risk of infection in SLE patients is significantly higher in comparison to pa-

tients with rheumatoid arthritis (RA) or nephrotic syndrome [18], but this evidence was only partially corroborated by later studies [19].

With regard to vaccine preventable diseases (VPDs), influenza and pneumococcal bacteraemia are well known to induce morbidity and mortality mainly among adults over 65 or with chronic diseases [10, 20], but no epidemiological information exists on their incidence in SLE patients. However, several case-reports have documented septicaemia and death due to pneumococcal infection in these patients [1-3, 21-24].

SLE patients present several conditions that predispose them to infections, such as altered phagocytic cell activity of the neutrophils, impaired membrane metabolism and defects in cell-mediated immunity associated with lymphopenia. Neutropenia, decreased production of cytokines, low levels of immunoglobulins (IgG subclass deficiencies or IgA deficiency), abnormalities of complement receptors, acquired or inherited complement deficiency states may as well impair the efficacy of the immunity system [1-4]. About 4% of SLE patients presents a functional asplenia with decreased clearance of encapsulated organisms [21, 25-26]. Moreover, disruption of anatomic barriers (erosions and/or ulcers of cutaneous and mucous surfaces) may represent the portal of entry for systemic infections [1-2]. Though treatment with steroids and immunosuppressive agents may favour infections, the risk of steroid-related infection is controversial; actually, glucocorticoids, modulating the altered immune system, may improve its function [1,4].

SLE After Vaccination

The occurrence of SLE after immunization has been reported in the medical literature, actually the papers are few, mainly case-reports, related to older vaccines, still they are historically relevant inducing a worldwide fear in vaccinating SLE patients (Table 1).

In 1943, Fox reported the first case of post-vaccination SLE, in a 17-year-old nursemaid shortly after the inoculation of anti-tetanus horse serum [27]. Five years later, Ayvazian and Badger reported the occurrence of fatal SLE in three of 750 student nurses followed over a 15 year period [28]. All the three 18-year-old girls had received multiple different inoculations (diphtheria toxin, streptococcal erythrogenic toxin, scarlet fever *Streptococcus* toxin, and typhoid-paratyphoid vaccine) few weeks before the onset of the dis-

Table 1. Cases of SLE After Vaccination

Authors	Type of Vaccination	Type of Study	No. of Patients
Fox 1943 ^a	Anti-tetanus serum	Case report	1
Ayvazian and Badger 1948 ^b	Streptococcal toxin, diphtheria toxin, typhoid-paratyphoid	Retrospective	3
Tudela <i>et al.</i> 1992 ^c , Mamoux <i>et al.</i> 1994 ^d , Guiserix 1996 ^e , Shapiro and Kopicky 2000 ^f , Finielz <i>et al.</i> 1998 ^g , Fineschi 2001 ^h	Anti-HBV	Case report	7
Older <i>et al.</i> 1999 ⁱ	Multi-vaccine Anthrax Typhoid, HAV	Retrospective	3 1 1

a: [27]; b:[28]; c:[29]; d:[30]; e:[31]; f:[32]; g:[33]; h: [34]; i: [11].

ease which progressively led them to death within one year, 15 months and seven years [28].

In 1992, Tudela *et al.* described the case of a 43-year-old woman presenting the symptoms of SLE 15 days after the first dose of recombinant hepatitis B virus (HBV) vaccine [29]. Additional case-reports described the occurrence of the disease in a 17-year-old girl two weeks after the third dose of the vaccine, in a 26-year-old and a 43-year-old women respectively one week and two weeks after vaccinations, in two members of the same family after HBV vaccine, and in a 27-year old woman with a family history of autoimmune diseases [30-34].

Recently, onset of SLE has been observed in five U.S. soldiers two to three weeks after they received several immunizations [11].

In conclusion, in the medical literature few case-reports of SLE onset after immunization have been reported. Whether these cases represent a coincidental finding or a cause-and-effect relationship has not been established. Considering the temporal relationship between immunization and disease onset it is possible to hypothesize that vaccines could represent an environmental trigger for the development of SLE in genetically predisposed subjects. However, large prospective studies are needed to compare the incidence of SLE in vaccinated and unvaccinated subjects.

Vaccinations in SLE Patients

SLE and Influenza Vaccination

From 1978 to 2006 several studies examined the risk/benefit ratio of influenza vaccination in SLE patients (Table 2).

The observation reported in 1948 by Ayvazian and Badger (see above) about the onset of fatal SLE in three girls after multiple vaccinations, prevented the use of immunization in SLE patients for three decades [28]. In 1976 the threat of a possible swine influenza epidemic (A/New Jersey/76 Hsw1N1) reawakened interest in influenza immunization in patients with rheumatic disorders. Therefore, the 1976 National Influenza Immunization Program encouraged several study groups to evaluate the safety and immunogenicity of influenza immunization in SLE patients.

Five research groups accepted the challenge, and 146 patients with SLE were enrolled in these studies; 125 of them were vaccinated. The results of four of these five studies were published in the same issue of *Annals of Internal Medicine* in 1978 [35-38]. In these studies the clinical efficacy of influenza immunization was not tested as the feared epidemic did not occur. Safety was considered on the subjective reported symptoms and on serological changes in complement proteins and autoantibody levels. However, no vali-

Table 2. Safety and Immunogenicity of Influenza Vaccination in SLE Patients

Authors	Type of Study	Subjects	Follow-Up (Weeks)	Safety	Immunogenicity	Quality Score ^{&}
Williams <i>et al.</i> 1978 ^a	Randomized, placebo controlled, double-blind	19 SLE cases; 21 SLE controls; 36 healthy controls	20	1 disease flare-up in each group	Reduced	7
Brodman <i>et al.</i> 1978 ^b	Controlled	46 patients; 58 healthy controls	8	No major flare-ups	Similar	5
Louie <i>et al.</i> 1978 ^c	Controlled	11 patients; 8 healthy controls	12	1 diffuse proliferative GN	Similar	4
Ristow <i>et al.</i> 1978 ^d	Controlled	29 patients; 29 healthy controls	8	1 focal GN	Quite similar	4
Herron <i>et al.</i> 1979 ^e	Controlled	20 patients; 32 healthy controls	16	1 major flare-up	Similar	5
Turner-Stokes <i>et al.</i> 1988 ^f	Retrospective controlled <i>in vitro</i>	28 patients; 35 healthy controls	-	-	Reduced [§]	3
Abu-Shakra <i>et al.</i> 2000 ^{g,h,i}	Controlled	24 SLE cases; 24 SLE controls	12	Decrease of mean SLE-DAI in cases and controls	Reduced	6
Mercado <i>et al.</i> 2004 ^j	Controlled	18 SLE patients; 18 healthy patients	8	Decrease of mean Mex-SLEDAI	Reduced	3
Holvast <i>et al.</i> 2006 ^k	Controlled	56 SLE patients; 18 healthy controls	4	No increased SLEDAI	Reduced	6
Del Porto <i>et al.</i> 2006 ^l	Controlled	14 SLE cases; 14 SLE controls; 10 healthy controls	24	2 flare-ups in cases, 1 flare-up in controls; no increased SLEDAI	Quite similar	4

GN, glomerulonephritis.

a: [35]; b: [36]; c: [37]; d: [38]; e: [6]; f: [8]; g: [39]; h: [40]; i: [41]; j: [42]; k: [43]; l: [44].

^aSeroconversion (fourfold or greater increase in antibody titres) or geometric mean antibody titres compared with normal control subjects.

[§]*In vitro* anti-influenza antibody response by lymphocytes.

[&]Total quality score 0-8: studies were classified as high (score >6), medium (score 4-6), or low quality (score <4).

^lSeroprotection rate exceeding 70% and/or a seroconversion rate exceeding 40% and/or a seroconversion factor exceeding 2.5.

dated disease activity index was used and the effect of vaccination on the overall SLE activity could not be measured. Furthermore, these studies did not enrol acutely ill patients who may be at greater risk during an influenza epidemic. Williams and co-workers carried out the only study with a randomized, controlled, double-blind design to assess the safety and immunogenicity of a bivalent influenza vaccine: A/New Jersey/8/76 (A/NJ) and A/Victoria/3/75 (A/VIC) (quality score 7). Forty SLE patients received influenza vaccine (No=19) or placebo (saline) injection (No=21) [35]. Fourteen patients in each group had diffuse glomerulonephritis. Thirty-six healthy volunteer subjects were selected as control group for the purpose of antibody measurements. The observation period lasted 20 weeks, the longest follow-up of these studies. Disease flare-up requiring hospitalization occurred in two patients, one in each group, between the 15th and 20th week of follow-up. No vaccinated patient showed renal deterioration. Regarding the immunogenicity, a reduced rate of serological conversion in SLE patients compared with normal control subjects was observed. Actually seroconversion against A/NJ and A/VIC resulted respectively in 94% and 78% of normal volunteers, while it was reported only in 47% and 32% of SLE cases, with a lower immune response in patients receiving more than 20 mg of prednisone daily [35].

Brodman and co-workers enrolled 46 SLE patients and compared their immune response to influenza vaccine with that of 58 healthy control subjects (quality score 5) [36]. Enrolled subjects were vaccinated with a monovalent influenza vaccine (A/New Jersey/8/76). One month later 37 SLE patients and 42 healthy controls received a second dose (booster) of a bivalent vaccine (A/New Jersey/8/76 and A/Victoria/3/75) and were followed-up for an additional month. No major flare-up of disease occurred after vaccination, and the specific immune response was not significantly different between the two groups. After two months, the geometric mean antibody titres (GMTs) \pm 2 SD for A/NJ rose from 7.5 ± 5 to 80 ± 5 in SLE cases and from 9.6 ± 5 to 102 ± 5 in controls. With regard to A/VIC, GMTs changed from 6.9 ± 4 to 18 ± 6 in SLE patients and from 7.6 ± 4 to 17 ± 6 in controls. The authors did not find any significant correlation between antibody response to vaccination and patient's therapy or HLA profile [36].

Louie and colleagues checked the safety and the immunogenicity of a bivalent influenza vaccine in a cohort study (quality score 4) including 11 unselected SLE patients and eight control subjects [37]. Within the 3-month observation period one patient with active disease developed diffuse proliferative glomerulonephritis. The immune responses did not show any detectable differences between patients and controls [37].

Ristow and associates evaluated the immunogenicity of a monovalent influenza vaccine (A/New Jersey/8/76) in 29 SLE patients and 29 control subjects (quality score 4) [38]. One patient with active disease developed renal involvement (focal glomerulonephritis) during the observation period. Regarding the immunogenicity, seroconversion rate in SLE patients was lower compared with control subjects (48% of SLE patients vs. 62% of controls) and also the post-vaccination GMTs tended to be lower (4.5 ± 2.5 in SLE pa-

tients vs. 5.5 ± 2.9 in controls) but these differences were not statistically significant [38].

The last study, from Herron and co-workers, was published one year later. It was a cohort study which evaluated bivalent influenza vaccination (A/New Jersey/76 and A/Victoria/75) in 62 patients with rheumatic diseases (included 20 SLE patients) and 32 healthy volunteers (quality score 5) [6]. These individuals were examined one week, three weeks, and four months later. During the follow-up four SLE patients developed a mild disease flare-up, only one presented a major flare-up, an exacerbation of a previous nephritis occurring 4 months after the vaccination. In this individual patient the seroconversion did not occur. However, seroconversion rate in SLE patients was not different from healthy subjects (anti-A/NJ in 81% of SLE patients vs. 87% of normal subjects; anti-A/VIC in 67% of SLE patients vs. 69% of normal subjects), even though it resulted less frequent in patients treated with glucocorticoids [6].

During two seasons (1985-6, 1986-7), 28 SLE patients were vaccinated with two different trivalent influenza vaccines (quality score 3) [8]. The major aim of this study was to evaluate the response to influenza immunization measuring the *in vitro* production of antibodies by peripheral blood mononuclear cells (PBMC) from patients and 35 age-matched normal healthy subjects. The results demonstrated an impaired antibody response by PBMC from SLE patients, significantly associated with lymphocytopenia and higher serum anti-DNA antibodies. The authors observed that most of the *in vitro* non-responders reached *in vivo* seroconversion, and they hypothesized that the decreased *in vitro* response could be due to influenza activated B cells sequestration in lymphoid tissues [8].

More recently, between October and November 1998, Abu-Shakra and co-workers enrolled 48 consecutive SLE patients, 24 of whom were vaccinated with a trivalent influenza vaccine (A/Sydney/05/97-H3N2-; A/Beijing/262/95-H1N1-; B/Harbin/07/94) (cases) and the other 24 did not receive the vaccine (controls). The authors published the results of this investigation separately in three different articles; considering all together, the major limitation was the absence of a randomized, double-blind, placebo controlled design (quality score 6) [39-41]. On the other hand, this was the first study in which SLE disease activity index (SLE-DAI) has been used to assess the effect of influenza vaccination on the overall disease activity. During the follow-up, the mean SLEDAI scores significantly decreased within each group compared with the pre-vaccination assessment, and influenza vaccine did not cause exacerbation of renal conditions. Seroconversion against A/Syd was observed in 58% of SLE cases, anti-A/Beijing in 37%, anti-B/Harbin in 62% [40]. Unfortunately, an age- and sex-matched normal control group was missing and the percentages of responders were compared with those expected in immunized people from the general adult population (WHO report) (anti-A/Syd in 89%, anti-A/Beijing 66%, anti-B/Harbin in 97%) resulting lower, in particular in older patients (age \geq 50 yrs), and in those treated with azathioprine or prednisone \geq 10 mg/day. Conversely, methotrexate therapy seemed not to influence the immunogenicity of influenza vaccine [40]. Vaccination was associated with a short term increased titre of four autoantibodies reacting with extractable nuclear antigens (ENA: Sm,

Sm/RNP, Ro, La), although it was not related to clinical manifestations [41].

Recently, in Mexico, 18 SLE women have been vaccinated with an inactivated trivalent vaccine (A/Moscow/10/99 H3N2-like, A/New Caledonia 20/99 H1N1-like, B/Sichuan/379/99-like), disease activity (Mex-SLEDAI) and autoantibodies were checked before, 4 and 8 weeks after (quality score 3) [42]. Notably, two patients with glomerulonephritis treated with intravenous cyclophosphamide and two dialysed patients were included in the trial. After vaccination the authors observed a significant decrease of the mean Mex-SLEDAI score ($p=0.02$) and a stable anti-ds DNA mean antibody titre. The percentage of patients who achieved protective antibody titres ($> 1:40$) to the 3 influenza antigens was lower than in 18 healthy controls (67%, 72%, 61% against A/Moscow/10/99 H3N2-like, A/New Caledonia 20/99 H1N1-like, B/Sichuan/379/99-like vs. 77%, 94% and 94%, respectively). Antibody response was not influenced by disease activity, treatment, age or IgG levels [42].

In a further study, carried out by Holvast and co-workers, between October and November 2003 56 SLE patients and 18 healthy controls were immunized with a trivalent vaccine (A/Moscow/10/99-like H3N2, A/New Caledonia/20/99-like H1N1, B/Hong Kong/330/2001-like) (quality score 6) [43]. SLE patients, all with quiescent disease (SLEDAI ≤ 5), were divided into 4 groups according to their therapy. Influenza vaccination did not modify mean SLEDAI score 30 days after vaccination. Regarding the immunogenicity, GMTs increased after vaccination and did not differ significantly between patients and controls. However, SLE patients had less seroconversions or 4-fold titre rises against A/H1N1 ($p < 0.001$) and A/H3N2 ($p = 0.001$) compared to controls, in particular patients using azathioprine [43].

Del Porto and colleagues published a study on 28 SLE, 20 RA patients and 10 healthy controls, half of patients were immunized against influenza with a trivalent split influenza vaccine (A/New Caledonia/20/99 [H1N1], A/Moscow/10/99 [H3N2], B/Shangdong/7/97) (quality score 4) [44]. At the enrolment all SLE patients presented a SLEDAI score < 12 and/or a stable disease. During the follow-up, the authors did not observe a significant increase of mean SLEDAI score in vaccinated patients, 2 flare-ups were reported in the case group versus 1 in the controls and responded to minor therapeutic modifications. Moreover, no significant increase of ANA, anti-ds DNA, ENA, anticardiolipin, and anti- $\beta 2$ -glycoprotein-I antibody titres was registered in both immunized and non-immunized patients. The seroconversion rate in SLE patients was 57%, 93% and 36% for A/Moscow, A/New Caledonia and B/Shangdong/7/97, respectively, versus 70%, 50% and 50% in the healthy controls [44].

In conclusion, the available data, coming from one high quality score study, seven medium quality score studies, and two low quality score studies support influenza vaccination as safe for SLE patients. With regard to the immunogenicity, the seroconversion rate in SLE patients resulted quite similar or slightly reduced when compared to normal subjects in the different studies, mostly in patients receiving glucocorticoids or immunosuppressive agents; nevertheless, a considerable proportion of patients developed protective antibody serum levels. Therefore, routine influenza immunization in SLE patients should be encouraged.

SLE and Pneumococcal Vaccines

Encapsulated bacteria such as pneumococci, *Haemophilus influenzae*, and meningococci are the leading infective agents in patients with abnormal humoral immune-response, such as SLE patients [1-3]. Patients with SLE complicated by nephrotic syndrome, functional asplenia, and hypocomplementaemia run the risk of developing fulminant pneumococcal infection [1-3, 21-24].

In the late 1970s, the general view of a preventive medicine and the recognition that influenza vaccine was safe for SLE patients encouraged investigators to assess the safety and immunogenicity of pneumococcal vaccination in SLE patients (Table 3) [6, 35-38].

The first study was carried out by Klippel and colleagues at the National Institutes of Health. It was a randomized, double-blind, controlled study on 40 SLE patients who received an intramuscular inoculation of either pneumococcal vaccine (14 purified capsular antigens) or placebo (quality score 6) [7]. Unfortunately, the authors did not mention the origin and number of normal healthy subjects used as controls. Patients were all in a relatively stable course of the disease and no one was receiving cytotoxic drugs. In the four-week follow-up, using a composite lupus activity index, no clinical and serologic difference was detected between placebo and vaccine-treated patients. Vaccinated patients showed a statistically significant increase in antibody concentrations to 12 type-specific capsular antigens compared with the pre-vaccine levels, even though the mean titre was significantly lower than in normal healthy controls (SLE patients: GMTs pre-vaccination 177 ng/ml, post-vaccination 1045 ng/ml; normal healthy controls: GMTs pre-vaccination 373 ng/ml, post-vaccination 1758 ng/ml, $p < 0.001$). However, the ratios of post- to pre-vaccine antibody concentrations were similar between SLE patients (5.7) and normal controls (4.7) [7].

Soon after, Jarrett and co-workers immunized with pneumococcal vaccine 38 SLE patients (cases) [45]. Twenty-three SLE patients who refused vaccination, 17 historical and five contemporaneous vaccinated healthy volunteers served as controls (quality score 6). During the six-month follow-up, the incidence of disease flare-ups was similar in cases and controls. There was one death in vaccinated patients (fatal myocarditis after three weeks) and one death in controls (pneumococcal meningitis). With regard to the immunogenicity, one month after the vaccination the mean antibody level to all 12 serotypes tested was significant lower in SLE patients (918 ± 405 ng/ml) in comparison to normal controls (1787 ± 694 ng/ml), $p < 0.001$, even though the supposed protective GMTs (greater than 300 ng/ml) was achieved in 36/38 (95%) patients. In addition, no significant difference in antibody titre among patients on low dose prednisone and patients on prednisone plus azathioprine was demonstrated [45]. The follow-up of 19 out of 38 SLE vaccinated patients and of five healthy volunteers at one, two, and three years revealed a lower mean antibody level in the SLE patients, although the difference was statistically significant only at the first year. At three years, eight out of 19 SLE patients presented GMTs below the level considered to be protective, while all the controls were above this level

Table 3. Safety and Immunogenicity of Pneumococcal Vaccination in SLE Patients

Authors	Type of Study	Subjects	Follow-Up	Safety	Immunogenicity*	Quality Score [‡]
Klippel <i>et al.</i> 1979 ^a	Randomized, double-blind, controlled	20 SLE cases; 20 SLE controls; healthy controls (not specified)	4 weeks	No differences	Quite similar	6
Jarrett <i>et al.</i> 1980 ^b McDonald <i>et al.</i> 1984 ^c	Controlled	38 SLE cases; 23 SLE controls; 22 healthy controls	6 months	3 flare-ups in cases; 2 flare-ups in controls	Reduced	6
Lipnick <i>et al.</i> 1985 ^d	Randomized, double-blind, controlled	60 SLE not receiving cytotoxics; 17 SLE receiving cytotoxics	6 months	no differences	Similar	6
Battafarano <i>et al.</i> 1998 ^e	Uncontrolled	73 SLE	12 weeks	No flare-ups; no increased SLEDAI	4-fold increase in total anti-pneumococcal titre in 47% patients	5
Elkayam <i>et al.</i> 2002 ^f	Controlled	24 SLE patients; 42 RA patients; 20 healthy controls	4 weeks	1 pleuritic pain; no increased SLEDAI	Reduced in SLE and RA patients	6
Tarijan <i>et al.</i> 2002 ^g	Controlled	18 SLE patients; 9 healthy controls	4 weeks	No flare-ups; no increased SLEDAI	Reduced in the 6 cases studied	3

a: [7]; b: [45]; c: [46]; d: [51]; e: [52]; f: [53]; g: [55].

*Seroconversion (twofold or greater increase in antibody titres) or geometric mean antibody titres compared with normal control subjects.

[‡]Total quality score 0-8: studies were classified as high (score >6), medium (score 4-6), or low quality (score <4).

[46]. One vaccinated patient developed pneumococcal pneumonia two months after the three-year follow-up. Her three-year antibody titre against pneumococcal capsular antigen type 14, the type isolated from her blood cultures, was lower than the level measured in normal healthy controls. In addition, the authors studied 18 pneumococcal vaccinated SLE patients, 8 non-vaccinated SLE patients and 7 normal healthy subjects to determine whether they would develop, *in vivo*, a specific or polyclonal B cell response to antigenic stimulation [47]. Antibody concentrations versus several antigens (rubella, rubeola, A- and B- blood group antigens), total immunoglobulin, and immune complex levels were monitored. In contrast with previous reports, only a specific antibody response was demonstrated [48-50]. Unfortunately, these studies lacked a valid disease activity index to evaluate the effect of vaccination on the overall SLE activity, and the number of controls in the long time follow-up was too small.

In 1985 Lipnick and colleagues studied the effect of oral cyclophosphamide and/or azathioprine therapy on the immunogenicity of a 14-valent pneumococcal vaccine in SLE patients in a six-month, placebo controlled, randomized, double blind study (quality score 6). Seventy-seven SLE patients were stratified into noncytotoxic group (N=60) or cytotoxic treated group (N=17), and randomized to receive pneumococcal vaccine or placebo. The results of this study demonstrated that oral cyclophosphamide, azathioprine, or a combination of the two drugs given in low doses had no effect on immunization with pneumococcal vaccine [51].

Battafarano and co-workers carried out a study on 73 SLE patients to determine the safety and the immunogenicity of the combined administration of three vaccines: tetanus toxoid (TT), pneumococcal and *Haemophilus influenzae* type B (HIB) vaccines (quality score 5) [52]. Neither SLE control group nor healthy subjects were included in the study. The majority of enrolled patients had a mild form of the disease and only four (5%) had renal disease at the time of vaccination. During the 12-week follow-up no clinical flare-up occurred among the vaccinated patients and disease activity scores (SLEDAI or LACC) did not increase signifi-

cantly. So multiple, simultaneous immunizations resulted safe in SLE patients. Regarding the immunogenicity, 47% of SLE patients developed a 4-fold increase in total anti-pneumococcal antibody titre. However, there was a trend towards decreased antibody response in patients receiving immunosuppressive therapy (cyclophosphamide, azathioprine and prednisone) or with active disease, although the difference was not statistically significant [52].

In a recent study, Elkayam and colleagues immunized 24 SLE patients, 42 RA patients, and 20 healthy control subjects with a 23-valent pneumococcal vaccine (quality score 6) [53-54]. With regard to the safety, no significant difference in clinical or laboratory features (including autoantibodies) was observed after the immunization, and only one SLE patient developed a disease flare-up (pleuritic pain) soon after the immunization. Overall, one month after immunization, both RA and SLE patients showed a significant increase in the mean capsular pneumococcal antibody titre, and immunosuppressive drugs were not significantly associated with the immune response. Nevertheless, a substantial proportion of patients presented a poor response to the vaccine: 20.8% of SLE patients and 33.3% of RA patients responded either to none or only to one of the seven pneumococcal serotypes tested. Conversely, none of the healthy control subjects failed to respond to the vaccination ($p=0.004$) [53].

In 2002, a Hungarian group enrolled 18 SLE patients and nine healthy women to investigate the early immunological effects of a 23-valent pneumococcal vaccine (quality score 3) [55]. During the four-week follow-up no disease flare-up occurred, all side effects were mild, the SLEDAI score remained almost the same, and treatment modifications were not required. The antigen-specific response against two antigens (6B, 23F) in six SLE patients resulted similar for IgM and weaker for IgG in comparison with six healthy subjects. However, the very small number of cases and controls tested makes it difficult to interpret these data.

In conclusion, results from five medium quality score studies, and one low quality score study suggest that SLE

patients can be safely and successfully immunized against pneumococcus, although with a lower rate of seroconversion compared to normal subjects and immunosuppressive drugs were not significantly associated with the immune response. Moreover, multiple simultaneous immunizations seem not to impair the safety and the therapy does not significantly influence the immunogenicity.

SLE and Tetanus Toxoid (TT) Vaccination

The safety and the immunogenicity of TT vaccination in SLE patients have been assessed in two studies, including 97 vaccinated patients [52, 56].

Devey and colleagues enrolled 24 SLE patients, 29 RA patients and 33 healthy subjects to study the amount, the affinity and the IgG subclasses of antibody response two-three weeks after TT vaccination (quality score 5) [56]. Only patients receiving prednisolone (<15mg/day) and no immunosuppressive drugs were included in the study. All groups presented a post vaccination significant increase in the mean anti-TT antibody level; the immunization was not successful only in two healthy controls, one RA patient and one SLE patient. Thirty-nine percent of SLE patients developed very high affinity antibodies compared to 15% in healthy subjects, while RA patients presented significantly lower affinity values compared with the other 2 groups [56].

In the above mentioned report by Battafarano and colleagues, the authors found the simultaneous administration of TT, pneumococcal and *Haemophilus influenzae* type B vaccines to be safe in 73 consecutive SLE patients followed for 12 weeks [52]. Among the 36 patients without protective antibody levels of anti-TT at baseline, 76% developed protective levels after immunization.

Despite these two encouraging investigations, the available data are still inadequate to fully support the safety and immunogenicity of tetanus toxoid in SLE patients.

SLE and Hepatitis B Virus Vaccination

Hepatitis B virus vaccine was initially recommended for adults or children at high risk of HBV infection [57]. More recently, since vaccination programmes had a less-than-optimal impact on the incidence of HBV infection, immunization strategies including universal immunization of infants have been developed [58-62].

Only a few reports have been published on SLE and HBV vaccination.

The first was a case-control study published as an abstract, testing the safety and the immunogenicity of three-dose series of HBV vaccine in 14 SLE patients with mild disease [63]. No disease flare-up occurred, and SLE patients showed a significantly lower immune response in comparison with 14 normal subjects [63].

Senécal and co-workers reported a case of severe disease exacerbation in a 21-year-old female with SLE, who had been in remission for more than three years, nine days after the second injection of HBV vaccine [64]. Maillefert *et al.* described three patients (two females, one male, aged 19, 23, and 22, respectively) who developed exacerbation of SLE one week, one month, and a few days after HBV immunization [65].

Although the last papers underlined a potential causal role of HBV immunization in exacerbating SLE disease, the relationship could be merely coincidental. On the other hand, SLE patients seem to develop a lower specific immune response compared to normal subjects. Therefore, randomized, double-blind, placebo controlled studies should be performed to assess risk/benefit ratio of HBV vaccine in SLE patients.

RHEUMATOID ARTHRITIS

Rheumatoid Arthritis and Infections

Several studies have reported increased mortality associated with infection in RA patients [66,67]. It has been estimated that the risk of developing an infection in patients affected by RA is double when compared with age- and sex-matched subjects [68]. The susceptibility to infectious diseases may be due to leukocytopenia, dependent on the disease or related to the therapy, or to the observed contraction of the T-cell receptor repertoire [69]. Furthermore, the severity of the disease itself has been shown to correlate with the infection rate [70]. Several other factors such as skin lesions, invasive investigations and immobility due to the damage of the articular surface, may favour articular and cutaneous infections [71]. Finally, glucocorticoid therapy may contribute to the development of infections, while controversial results are reported about the influence of disease-modifying anti-rheumatic drugs (DMARDs) [71]. With regard to VPDs, it is well known that RA patients have an increased mortality due to infectious respiratory diseases. In addition, reports of serious infections due to *S. pneumoniae* during anti-TNF α blocking therapy have been described [72,73].

Rheumatoid Arthritis After Vaccinations

Several cases of arthritis have been described after immunization, mostly following HBV vaccination [74-76].

Gross and colleagues described three cases of arthritis onset after HBV vaccination, two patients showed a clinical pattern resembling reactive arthritis, the other one fulfilled ACR criteria for RA [74]. The third patient expressed HLA DR-4, a genotype frequently associated with RA, therefore HBV vaccination might have triggered RA in this genetically predisposed woman [74].

In another report oligoarthritis started in a 49 year old, previously healthy woman, within 24 hours from the first administration of HBV vaccine, and rapidly developed into a symmetrical arthritis. This patient, as well, presented a DR4 genotype [75]. Pope and co-workers reported a cluster of five fire-fighters who developed persistent arthritis after recombinant HBV vaccine [76]. Four of them satisfied ACR revised criteria for RA [77]. The authors also described six sporadic cases of arthritis post-HBV vaccine: six young women, all working in the health care service who presented joint symptoms a week after the second or third inoculation. Genetic investigation of the patients showed HLA DR-4 genotype in 5/11 and HLA DR-1 in 6/11. The latest report describes RA development in six women one, two, three, ten, eighteen, twenty days, respectively, after HBV immunization [78].

Despite the wide diffusion of HBV vaccination programmes, only a few cases of RA onset after vaccination

have been reported in the medical literature. HLA DR-4 genotype may represent a permissive background for the development of arthritis triggered by HBV vaccine. However, as stated above for systemic lupus erythematosus, it is possible that the recorded cases of RA after vaccination represent only a coincidental finding. Prospective studies could elucidate the causal relationship and allow larger genetic studies in order to perform a safer vaccination.

Vaccinations in RA Patients

RA and Influenza Vaccination

Five studies, only one of whom with a randomized controlled design, investigated the safety and the immunogenicity of influenza immunization in RA patients (Table 4).

Herron's case-control study, mentioned above in the section on SLE and influenza vaccination, included 17 RA patients, none of whom acutely ill, who received a bivalent influenza vaccine (A/New Jersey/76 and A/Victoria/75) [6]. Six out of 17 RA patients presented a disease flare-up during the first three weeks of study; this high rate of exacerbations induced the authors to continue the follow-up for additional three weeks after the four months planned follow-up of. Disease flare-up occurred in a proportion similar to the first three-week period, so it seemed unlikely that the flare-ups during the first period could be due to the vaccination. Regarding the immunogenicity, seroconversion rate for A/Victoria/75 in RA patients (65%) was comparable with the normal controls (69%), while for A/New Jersey/76 was slightly lower (65% versus 87%). In addition the mean antibody increase was lower in patients treated with glucocorticoids, even though the difference reached statistical significance only for A/New Jersey/76 in those younger than 57 [6]. No RA control patients (non-vaccinated) were included in this study and this limitation compromises the power of safety assessment.

Later, Chalmers and colleagues tested, in a randomized placebo controlled study, the safety and immunogenicity of a trivalent influenza vaccine (A/Taiwan/1/86(H1N1), A/Beijing/353/89(H3N2), B/Panama/45/90) in one hundred and twenty-six RA patients stratified into three groups according to their therapy and influenza immunization in the previous

previous 24 months (quality score 6) [79]. Within each group, patients were randomized to receive vaccine or placebo. Sixty-four healthy subjects were also vaccinated. After one month ten RA patients presented flares-ups of the disease, and they were equally distributed among vaccine and placebo treated patients. With regard to the immunogenicity, after a four-week follow-up the antibody response to the vaccine was similar between patients and controls regardless of immunosuppressive therapy or glucocorticoid dose [79].

Cimmino and colleagues reported in a letter the results of a retrospective study on 30 RA patients who received influenza vaccination [80]. In the month after immunization six patients reported a disease flare-up, a figure similar to the expected rate of spontaneous exacerbation. However, the results of this uncontrolled, retrospective study do not allow any generalizations.

Van der Bijl and colleagues reported, as an abstract, the results of a study on 113 patients (71% with RA, 19% with Crohn's disease, 10% with other autoimmune diseases) and 18 healthy controls immunized with a trivalent influenza vaccine [81]. Patients treated with TNF α blocking agents (N=65) (TNF α + group) significantly failed in developing antibody response compared with TNF α - group and healthy controls ($p < 0.05$).

Recently, Fomin and colleagues have evaluated the safety and the immunogenicity of influenza vaccination in RA patients as well as the effect of DMARDs, including TNF α blocking agents, on the immunogenicity of the vaccine (quality score 6) [82]. Eighty-two RA patients and 30 healthy personnel were vaccinated with a trivalent influenza vaccine: B/Hong Kong/330/2001 (HK), A/Panama/2007/99 (PAN) and A/New Caledonian/20/99(NC). At the time of vaccination, 56 out of 82 RA patients were treated with methotrexate, 22 received infliximab (INF) and five were on etanercept (ETA) for at least 3 months. During the six-week follow-up influenza vaccination resulted safe in RA patients. Regarding the immunogenicity, both RA patients and controls had significant increases of their GMTs against each antigen tested. For the HK antigen the rise was significantly higher in the healthy group ($p = 0.004$). A satisfactory humoral response was defined as ≥ 4 -fold rise in hemagglutina-

Table 4. Safety and Immunogenicity of Influenza Vaccination in RA Patients

Authors	Type of Study	Subjects	Follow-Up (Weeks)	Safety	Immunogenicity	Quality Score ^{&}
Herron <i>et al.</i> 1979 ^a	Controlled	17 RA patients; 32 healthy controls	16	6 flare-ups	Quite similar *	6
Chalmers <i>et al.</i> 1994 ^b	Randomized, controlled	126 RA patients; 64 healthy controls	4	No differences	Similar*	6
Cimmino <i>et al.</i> 1995 ^c	Retrospective	30 RA patients	4	6 flare-ups	Not specified	3
Fomin <i>et al.</i> 2006 ^d	Controlled	82 RA patients; 30 healthy controls	6	No major flare-ups	Slightly reduced*	6
Del Porto <i>et al.</i> 2006 ^e	Controlled	10 RA cases; 10 RA controls; 10 healthy controls	24	2 flare-ups in cases, 3 in controls	Quite similar [§]	4

a: [6]; b: [79]; c: [80]; d: [82]; e: [44].

[†]Seroconversion (fourfold or greater increase in antibody titres) or geometric mean antibody titres compared with normal control subjects.

[‡]Seroprotection rate exceeding 70% and/or a seroconversion rate exceeding 40% and/or a seroconversion factor exceeding 2.5.

[&]Total quality score 0-8: studies were classified as high (score >6), medium (score 4-6), or low quality (score <4).

tion-inhibition (HI) antibodies 6 weeks after vaccination or a rise to HI levels of $>1/40$ in subjects with nonprotective baseline levels of $< 1/40$. The percentage of responders in RA patients for HK was significantly lower than in controls (67% vs. 87%, respectively) ($p=0.05$). The proportion of responders was similar for PAN (53% vs. 54%) and NC (53% vs. 68%). The immune response was not affected by the use of commonly administered DMARDS, including methotrexate, INF and ETA [82].

Moreover, in the study mentioned above in the session on SLE and influenza vaccination [44], 10 RA patients (two of them treated with TNF α blockers) with a DAS 28 <4 and/or a stable disease underwent trivalent influenza immunization (A/New Caledonia/20/99, A/Moscow/10/99, and B/Shangdong/7/97). The authors observed 2 flare-ups in the cases and 3 in the ten AR patients used as controls. The vaccination resulted immunogenic in RA patients; a significant seroprotection factor was reached for all the 3 antigens [44].

In conclusion, results from four medium quality studies and one low quality score study indicate that influenza vaccine in RA patients seems to be safe and immunogenic in most cases, regardless of immunosuppressive therapy. However, studies in this field are limited, and the effect of TNF α -blockers on the immune response is still controversial.

RA and Pneumococcal Vaccination

The Advisory Committee on Immunization Practices recommends pneumococcal vaccination in patients suffering from chronic diseases [20]. A few studies investigated the safety and the immunogenicity of influenza immunization in RA patients (Table 5).

Elkayam and colleagues firstly assessed the safety and the immunogenicity of pneumococcal vaccination in RA patients [53]. This study (quality score 6) has been mentioned above, in the section on SLE and pneumococcal vaccine. The 23-valent pneumococcal vaccine used in 42 consecutive RA patients was found to be safe and well-tolerated. In fact, RA patients presented significantly fewer tender joints two months after vaccination. Regarding the immunogenicity, one month after vaccination RA patients showed a significant increase in mean antibody levels to all the seven pneumococcal serotypes tested. Nevertheless, one-third of patients presented an extremely poor antibody response, but the authors did not identify any predictive parameter of impaired response [53].

Recently the same authors studied the effect of TNF α blocking agents on human immune responses to pneumococcal vaccination (quality score 4) [83]. They evaluated the immunogenicity of the 23-valent pneumococcal vaccine in a small heterogeneous population of rheumatic patients (11 RA patients and 5 patients with Ankylosing Spondylitis) on anti-TNF α therapies. All cases were treated with either intravenous INF (N=12) or subcutaneous ETA (N=4). The control group consisted of 17 RA patients treated with anti-inflammatory medications and DMARDS other than TNF α blocking agents. One month after vaccination, both groups had statistically significant increases in GMTs for the specific antibodies, and in mean fold-increases in antibody levels for all seven serotypes tested. Significant percentage of patients in each group failed to develop an immune response. Apart from responses to serotype 14, the TNF α blockade-treated patients presented lower antibody increase for the serotypes tested and, less than half of them achieved a twofold increase [83]. As noted by the same authors, the major flaws of the study were the small number of enrolled patients, the heterogeneity of their rheumatic diseases and anti-TNF α therapy.

Visvanathan and co-workers reported [84], as an abstract, the administration of pneumococcal polyvalent vaccine in 70 patients with Early Rheumatoid Arthritis enrolled in the ASPIRE trial [85]. Twenty patients were treated with INF 3 mg/Kg in association with methotrexate (MTX), 36 patients with INF 6 mg/Kg plus MTX and 14 patients with placebo plus MTX. Patients were vaccinated 34 weeks after the beginning of the treatment; antibody titre specific for 12 serotypes was measured four weeks later. Antibody response was considered a 2-fold increase in antibody titre in at least six of the 12 serotypes tested. The percentage of patients with antibody response was similar in the three groups (20% INF 3 mg/Kg plus MTX, 25% INF 6 mg/Kg plus MTX, and 21.4% MTX alone). There was a great variability of antibody response rates to the different serotypes among the patients, but INF did not appear to impair the immune response [84].

In another study (quality score 5) 149 RA patients and 47 healthy sex-matched controls were immunized with a 23-valent pneumococcal vaccine [86]. Patients were stratified in 3 groups according to their therapies (TNF α blockers without MTX, TNF α blockers plus MTX, MTX), a total of 112 patients were treated with TNF α blockers (64 with INF and 48 with ETA). Post-vaccination antibody titre against the antigens 23F and 6B rose significantly in all groups. Immuniza-

Table 5. Safety and Immunogenicity of Pneumococcal Vaccination in RA Patients

Authors	Type of Study	Subjects	Follow-Up (Weeks)	Safety	Immunogenicity*	Quality Score [§]
Elkayam <i>et al.</i> 2002 ^a	Controlled	42 RA patients; 20 healthy controls	8 (safety); 4 (immunogenicity)	No flare-ups	Reduced in RA patients	6
Elkayam <i>et al.</i> 2004 ^b	Controlled	11 RA patients and 5 Ankylosing Spondylitis patients on anti-TNF α ; 17 RA on DMARDS	4	Not reported	Reduced in each group, mostly in anti-TNF α treated patients	4
Kapetanovic <i>et al.</i> 2006 ^c	Controlled	149 RA patients; 47 healthy controls	4/6	Not reported	Similar in patients on anti-TNF α and healthy controls. Reduced in patients on MTX	5

a: [53]; b: [83]; c: [86].

*Seroconversion (twofold or greater increase in antibody titres) or geometric mean antibody titres compared with normal control subjects.

[§]Total quality score 0-8: studies were classified as high (score >6), medium (score 4-6), or low quality (score <4).

tion responses, i.e. the ratios between post- and pre-vaccination antibody concentrations, as well as ≥ 2 -fold increase of the antibody titre were highest for TNF α blockers without MTX and lowest for MTX. Patients treated with TNF α blockers and healthy controls showed similar responses to vaccination [86].

In conclusion, medium quality studies showed that pneumococcal vaccine can induce statistically significant humoral responses in RA patients; nevertheless, a substantial proportion of patients presented a poor response to the vaccine. The influence of TNF α blocking therapy in RA patients immunized with pneumococcal vaccination has to be established, and few recent observations need to be supported by larger, well-designed studies.

RA and Hepatitis B Virus Vaccination

So far only one study has been published on the safety and the immunogenicity of vaccination against HBV in RA patients [81]. In this cohort study, 44 RA patients were enrolled, 22 of them received three doses of recombinant HBV vaccine and the other 22 were studied as controls (quality score 6). During the observation period of seven months the vaccine did not induce major side effects and was not associated with a significant worsening in any clinical or laboratory measures of disease. Seroconversion (antibody titre after vaccination greater than 10 IU/L) resulted in 15/22 (68%) RA patients and was lower than expected in young healthy adults (85%). Lack of immune response was significantly associated with older age and increased daytime pain at vaccination, not with the use of glucocorticoids and DMARDs [87]. The major limit of this investigation was the absence of age- and sex- matched normal healthy controls.

VACCINATION IN PATIENTS WITH SJOGREN'S SYNDROME

Patients with Sjogren's syndrome (SS) may present recurrent attacks of bronchitis and pneumonia due to dryness of tracheobronchial mucosa.

Only one significant study about SS and vaccination has been published. Karsh and colleagues carried out a double-blind randomized trial to assess the safety and the immunogenicity of pneumococcal vaccination in SS patients (quality score 5) [88]. Thirty-two SS patients were enrolled and randomized to receive a 14-valent pneumococcal vaccine or placebo. During the six-month follow-up no clinical or serologic evidence of disease exacerbation occurred in each group. After one month, SS vaccinated patients developed significant increase of antibody titre to all the 12 serotypes tested, and, after six months, GMTs remained significantly increased for eight of the 12 serotypes [88]. Even though this study included a small number of patients, it seems to indicate that SS patients may benefit from pneumococcal vaccination without safety concerns. Larger well-designed studies could support this preliminary observation.

VACCINATION IN CHILDREN WITH RHEUMATIC DISEASES

Infections, even though rare, are the most common cause of death in children with chronic arthritis in North America, and the concomitant use of steroids may favour the development of complications after influenza infection [89]. The

Canadian 1991 Influenza vaccination guidelines recommended influenza vaccination for immunocompromised or immunodeficient children and for children taking acetylsalicylic acid for prolonged periods (risk of Reye's syndrome in the presence of influenza or chicken-pox) [90].

Two studies, including 104 children, evaluated influenza vaccination in children with rheumatic diseases.

In 1993 Malleson and colleagues published the results of an open study designed to assess the safety and the immunogenicity of a trivalent influenza vaccine (A/Taiwan/1/86-H1N1, A/Beijing/353/89-H3N2-like strain and B/Panama/45/90) in 34 children with chronic arthritis (mean age 12.8 years, range 3-22 years): 22 with JRA, two Mixed Connective Tissue Disease, two Juvenile Psoriatic Arthritis, eight Spondyloarthropathy (quality score 3) [91]. The control group included 13 healthy subjects. There was no difference between mean disease activities assessed at vaccination and four to six weeks later, with more children improving than deteriorating. A rise from < 20 to ≥ 40 or a fourfold rise in antibody titres was registered in 39% of patients for A/Taiwan, 85% for A/Beijing, 64% for B/Panama; in 60% of controls for A/Taiwan, 70% for A/Beijing, 50% for B/Panama. Pre-immunization titres, seroresponse rates and final titres were comparable between the groups, and immune response did not seem to be influenced by the concomitant use of glucocorticoids or DMARDs [91]. The major limitations of this study were the small sample of heterogeneous patients, and the high number of patients lost in the follow-up.

Analogous results have been reported in a recent study carried out in Greece. An expected influenza epidemic for the 1999-2000 winter season led to immunize 70 children with chronic rheumatic diseases with a trivalent influenza vaccine (A/Beijing, A/Sydney, and B/Beijing) (quality score 3) [92]. The children enrolled included 49 Juvenile Idiopathic Arthritis (JIA), 11 SLE and 10 other rheumatic diseases (three Juvenile Dermatomyositis, three Systemic Vasculitis, two Mixed Connective Tissue Disease, one Behçet Disease, one Idiopathic Recurrent Pericarditis) and all patients were on immunosuppressive therapy for more than six months. At the time of immunization 17 out of 70 children had active disease. Disease activity and the main laboratory indices were recorded at study entry, and one, three and six months after vaccination. Children were divided into four groups according to their therapy (prednisone alone, prednisone plus one DMARD, prednisone plus two DMARDs, one or more DMARDs without prednisone). Five healthy young siblings were vaccinated as controls. No worsening of disease activity or flare-ups was detected at any reassessment; no increase in autoantibody titres was demonstrated. The majority of patients developed protective antibody titres to all three strains (97,1% to A/Beijing, 100% to A/Sydney and 80% to B/Beijing) regardless of their age, therapy and type of rheumatic disease. The response was similar to that reported in the medical literature for healthy children [93-94]. Fifteen patients (13 JIA, one SLE, and one Systemic Vasculitis) did not develop protective titres of antibodies, mainly to B/Beijing, despite two doses of vaccine. They did not show any peculiar clinical or demographic feature. The absence of any "flu-like illness" during the six-month post-immuni-

Table 6. Recommendations for Vaccinations in Patients with SLE and RA

Vaccine	Systemic Lupus Erythematosus	Rheumatoid Arthritis
Influenza Safety Immunogenicity	Recommended* Good Slightly reduced, mostly in patients receiving glucocorticoids or immunosuppressive agents	Recommended* Good Quite similar to healthy subjects
Pneumococcal Safety Immunogenicity	Recommended* Good Reduced	Recommended* Good Reduced
Hepatitis B virus Safety Immunogenicity	To consider case by case Still to be defined Reduced	To consider case by case Still to be defined Reduced

*According to the Advisory Committee on Immunization Practices recommendations [5].

zation period (parents' observation) was an indirect evidence of the clinical efficacy of the vaccination [92].

These two low quality score studies on influenza vaccination enrolled heterogeneous groups of children with rheumatic disorders, neither of them included a control group of non-vaccinated patients, and even though the results are encouraging, larger randomized controlled studies will be needed.

Recently, 39 children with JIA, and 41 sex and age-matched healthy controls have been included in a cohort study to assess the immunogenicity of HBV immunization (quality score 6) [95]. Children were screened each month for clinical status, and laboratory tests. No disease flare ups occurred among patients and all JIA patients but one (97%) developed a seroconversion (antibody titre above 10 mIU/ml), but GMTs resulted significantly lower in JIA patients than in controls. Therapy did not significantly influence the antibody response. In this study HBV vaccine resulted safe and immunogenic, however, as stated by the same authors, the major limitations were the lack of blind design and the enrolment of JIA patients in remission. Larger randomized, double-blind, controlled studies will be needed to confirm these preliminary results.

CONCLUSIONS

The development of rheumatic diseases after immunization has been reported in the medical literature. Whether these cases represent a coincidental finding or a cause-and-effect relationship has to be established. Large prospective studies could elucidate the causal relationship and allow genetic studies in order to perform a safer vaccination.

Infections remain an important cause of morbidity and mortality in patients with rheumatic diseases. Influenza and pneumococcal vaccines administered to SLE patients have found to be safe. These vaccinations are generally serologically effective, even though there is the possibility of inadequate response, especially in patients receiving immunosuppressive agents. In RA patients treated with DMARDs, immunization against influenza (recommended by the British Society for Rheumatology [96]) and pneumococcal can be considered safe and immunogenic in most cases. Further studies will be required to determine the efficacy of these vaccines in preventing influenza and pneumococcal infections in SLE and RA patients.

Studies on HBV vaccine in patients with rheumatic diseases are still limited, however, the world-wide campaign to

vaccinate all infants with HBV, hopefully, will obviate the need for consideration of adult vaccination in the future.

TT would remain the only urgent issue. As a matter of fact, TT vaccination should be performed in all adults, and adults should receive a booster every ten years [97]. However, the available data are still inadequate to support the safety and the immunogenicity of tetanus toxoid in patients with rheumatic diseases. Therefore, risk/benefit ratio of this immunization in rheumatic patients should be clarified by large well designed studies. Although the available evidence is insufficient to conclude that Tetanus Toxoid and HBV vaccines are safe and immunogenic in rheumatic patients, if a health care worker with rheumatic disease is occupationally exposed to blood products, or if a patient presents a tetanus-prone wound, it could be advisable to use these vaccines.

Finally, live-attenuated vaccines (i.e. measles, mumps, varicella, rubella, oral poliovirus, bacille Calmette-Guérin, Yellow fever and nasal spray influenza) should not be used to vaccinate rheumatic patients treated with immunosuppressive drugs or high dose of glucocorticoids, with the concern that an attenuated strain may be virulent in immunocompromised hosts, causing development of the vaccine associated disease [5,97]. Herpes zoster is a major cause of morbidity in patients with rheumatic diseases, nevertheless there are no data on the vaccination of people with rheumatic diseases with the varicella or the herpes zoster vaccine. A recent study showed the efficacy of live attenuated Oka/Merck VZV vaccine ("zoster vaccine") in adults over 60 in decreasing incidence and/or severity of herpes zoster and postherpetic neuralgia [98]. It could be considered to vaccinate patients with a history of Varicella infection candidated to receive immunosuppressive treatment.

In summary, influenza and pneumococcal immunizations in patients with SLE and RA can be recommended (Table 6). The decision whether to immunize patients with rheumatic diseases with other vaccines (HBV, TT), since there are no clear evidences of safety, should be based on patient-related risk factors, as well as on patient's informed choice.

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