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**Title:** Descriptive study of pneumococcal vaccination in cases of inflammatory disease: analysis of practices.

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## **1. Introduction**

Pneumococcal infections are common and potentially serious in immunocompromised patients with systemic or inflammatory diseases treated with immunosuppressive agents (IS). For several years, the *Haut Comité de la Santé Publique* (HCSP) has been publishing recommendations concerning a population considered to be at very high risk of infection [1]. Although in the general population the efficacy of the pneumococcal vaccine against invasive infections and pneumonia no longer needs to be demonstrated [2-6], its efficacy in immunocompromised patients is less well-defined due to (a) multifactorial immunosuppression intrinsic to the disease and/or secondary to treatments, which can potentially decrease vaccine response [7, 8] and (b) the fact that it is difficult to conduct clinical efficacy studies in small-scale heterogeneous populations. Pneumococcal vaccination (PV) is recommended due to a high risk of potentially serious infection [9], associated with an increased risk of death [10]. As inflammatory pathologies in general and autoimmune pathologies in particular have relatively low prevalence, there exist only a limited number of studies judging the effectiveness of this vaccination for conditions other than lupus and rheumatoid arthritis. That said, the results of these studies show a lower post-vaccine antibody level compared to the general population and a greater risk of invasive infection, which is nonetheless reduced by vaccination [11], thereby justifying the recommendations. While it seems difficult to influence the intrinsic causes of immunomodulation in these different pathologies, it remains possible to anticipate the immunosuppression secondary to IS and biotherapies (BT). Notwithstanding specific recommendations on the benefits of PV, vaccination coverage in this patient population remains low. The reasons given for insufficient vaccination are: (a) insufficient prescription by the specialist or general practitioner [12-14], (b) ideological obstacles among patients, which are often also observed in the general population, and (c) organizational obstacles in hospital care structures [15].

The main objective of our study, which is part of an analysis of professional practices, was to assess pneumococcal vaccination coverage in a day hospital for internal medicine and vascular disease, among patients with inflammatory diseases.

## **2. Patients and methods.**

Observational, descriptive, retrospective, and single-center study carried out in a day hospital unit (internal medicine-clinical immunology and vascular medicine) of Saint-André hospital at Bordeaux University Hospital, France.

### *2.1 Patients*

Patients over 18 years of age were included in the study consecutively during their day hospitalization between February 1 and April 30, 2018. Patients followed for a chronic inflammatory pathology and treated with an IS or BT were selected, regardless of age. The exclusion criteria from the study were no management for inflammatory disease and / or no treatment with IS or BT.

### *2.2 Data collection and judgment criteria*

Data collection was carried out from February 1 to April 30, 2018. The primary endpoint of the study was the existence or not of a 13-valent pneumococcal polysaccharide conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPV23) listed in the hospital computer file for each patient included in the study. When necessary, the attending physician was contacted to complete the collected information. We also provided information on the time elapsed between the date of vaccination with PCV13 and the start of the initial treatment (IS or BT), the objective being to estimate maximum potential vaccine efficacy. Arbitrarily, taking into account the mean time to effectiveness of PV, we preliminarily categorized the study population into 4 groups: *group 1*: vaccinated more than 3 weeks before the start of treatment; *group 2*: vaccinated within 3 weeks before the start of treatment; *group 3*: vaccinated after initiation of treatment or on the same day and *group 4*: no vaccination during treatment. The other variables studied were age and gender. We provided information on the vaccination time interval between PCV13 and PPV23 (less than or greater than 8 weeks). The different ISs reported in the study were: corticosteroids, methotrexate, azathioprine, cyclophosphamide, salazopyrin, mycophenolate mofetil, leflunomide. The relevant BT were rituximab, anti-TNF alpha, ustekinumab, eculizumab and tocilizumab. The data extracted from the hospital's computer file or obtained secondarily after telephone contact with the attending physician were anonymized and then collated in a secure and coded Excel file,

allowing quantitative data analysis. With reference to the *loi Jardé* and the *code de la santé publique*, this observational, descriptive, and non-interventional study was considered "out of scope" as it did not directly involve the human person.

### *2.3 Vaccination schedule.*

The recommended pneumococcal vaccination schedule (RVS) used in the study was that recommended at the time of the study according to the HCSP [1]. It consisted of an injection of PCV13 followed by an injection of PPV23 within a minimum of eight weeks. The PPV23 booster scheduled for 5 years after the first injection in the recommendations was not affected by our study.

## **3. Results**

### *3.1 Description of the population.*

During the inclusion period, 443 files were selected. One hundred and fifty patients were included in the study, treated with IS or BT for inflammatory disease with an indication for PV. There were 61 men (40.6%) and 89 women (59.3%), of average age ( $\pm$  DS):  $56.9 \pm 14.9$  years. Among the 293 patients excluded, 290 were not followed for an inflammatory disease and 3 (two cases of systemic lupus and one case of Sjogren's syndrome) had no indication for vaccination because they were treated only for lupus. Patients treated with hydroxychloroquine alone before initiating treatment with IS or BT were studied according to the start date of the first IS or BT treatment. The different treatments were distributed as follows: 32 biotherapies (21.3%), 93 immunosuppressants (62%) and 25 corticosteroids alone (16.7%) and are detailed in Table 1. During the 3 months of inclusion in the study, 31 different inflammatory pathologies were concerned. The pathologies were classified in order of decreasing frequency and reported according to initial treatment by IS or BT (Table 2).

### *3.2 Pneumococcal vaccination.*

Among the 150 patients, the PCV13 vaccination rate was distributed according to groups: 4% in group 1 (n = 6); 17.3% in group 2 (n = 26); 63.4% in group 3 (n = 95) and 15.3% in group 4 (n = 23). The PCV13 vaccination rate was 85% (127/150), 23 patients (15%) were not vaccinated with PCV13 (among the 23 patients not vaccinated with PCV13, none were vaccinated with PPV23). PCV13 vaccination was distributed as follows: 21.3% before start of treatment with IS

or BT and 63.4% after start of treatment. Seventy patients received RVS vaccination. The crude RVS vaccination rate (injection time between PCV13 and PPV23 at least equal to 8 weeks) in the study population was 46.7% (70/150). The RVS vaccination rate was 55.1% (70/127) in the patient population vaccinated with PCV13. Among the 127 patients, there were 7 missing data (without information on PPV23 vaccination). It appeared that among the patients vaccinated with PCV13 before the introduction of IS or BT treatment, 21.4% (15/70) had completed the RVS. Eighty-two patients were vaccinated with PPV23 and PCV13, i.e., 54.7% of the total study population (n = 150) and 64.5% of patients who received a first injection of PCV13 (n = 127). Only 70 had adhered to RVS (PPV23 at least 8 weeks after PCV13). Forty-five patients (35.5%) among the patients vaccinated with PCV13 (n = 127) vaccinated with PCV13 were not vaccinated with PPV23. Calculation of the time between PCV13 administration and the start of IS or BT treatment was performed to estimate the proportion of patients able to optimally benefit from the vaccine. The immunosuppressive therapies entailing vaccination after the start of treatment were mainly: anti-TNF alpha, methotrexate, cyclophosphamide, and azathioprine. The mean time to PCV13 vaccination compared to the introduction of the IS treatment proposed since the 2012 recommendations [20] in our study was  $34.8 \pm 24$  months with a median at 36 months [1-72].

Out of the 11 patients treated with rituximab, only 1 was vaccinated more than three weeks before start of treatment. Four were vaccinated within three weeks before and 4 were vaccinated after initiation of treatment. Regarding the 50 patients on methotrexate, only 1 was vaccinated more than 3 weeks before treatment initiation, only 1 was vaccinated during the 3 weeks before, and 39 were vaccinated after introduction of the treatment (65%). Six patients were not vaccinated (10%). Regarding the 4 patients on mycophenolate, none were vaccinated before initiation of treatment.

#### **4. Discussion.**

Other French studies have studied anti-pneumococcal vaccine coverage in immunocompromised or chronically ill patients. It remains low, with percentages varying from 15 to 53 [13, 16-19] depending on the judgment criterion used. Only one of these studies evaluated RVS, estimating the proportion of immunocompromised patients correctly vaccinated at 21.1% [13]. Our study shows higher pneumococcal vaccine coverage (around 46.7%). This could be explained by the location of the study at a venue where severely ill

patients are regularly followed several times a year for their biotherapy and/or additional examinations. More generally, it is important to consider the average time lapse before of PCV13 vaccination compared to the introduction of the IS or BT treatment recommended since the 2012 guidelines [20] in view of improving vaccination effectiveness. In our study, the overall figure is not very informative. It is estimated on average at  $34.8 \pm 24$  months with a median at 36 months [1-72], all patients combined, including the vaccinations carried out after introduction of the treatment, which may reflect an attempt to “catch up”. The exposure period under treatment is a period during which patients remain unprotected and run an increased risk of infection and a lower probability of protection following late vaccination. It is consequently important that the rate of anti-pneumococcal vaccination coverage be improved and that deadlines be respected, thereby reducing “catch-up” vaccination and ensuring better overall patient protection. The quality of vaccine coverage depends on the type of immunosuppressive therapy used and its impact on vaccine efficacy. Several studies have been published in recent years on the immunogenicity of vaccination according to the treatments used in autoimmune and inflammatory diseases. Biotherapies such as anti-TNF-alpha [21-23], tocilizumab [24], ustekinumab [25] ixekizumab [26] and belimumab [27, 28] do not seem to alter post-vaccination immune response. However, rituximab [29,31], abatacept [32,33] and tofacitinib [34] may decrease the immunogenicity of the pneumococcal vaccine, a factor justifying vaccination prior to their introduction. Regarding older immunosuppressants such as methotrexate [21], cyclophosphamide, mycophenolate, and azathioprine [35] decreased immunogenicity of the pneumococcal vaccine has been shown. The corticosteroids used in these different studies do not seem to modify vaccine response. In our study, three treatments (rituximab, methotrexate, and mycophenolate) were concerned by the need for vaccination with PCV13 before prescription of the immunosuppressive treatment. Out of the 11 patients treated with rituximab, only 1 (9.1%) was vaccinated more than 3 weeks before the initiation of treatment, receiving vaccination with PPV23 within 8 weeks. Six (54.5%) were vaccinated within the previous 3 weeks and 4 (36.4%) were vaccinated after initiation of treatment. Out of these 11 patients, only 1 (9.1%) was able to benefit from potentially optimal vaccine efficacy with initiation of treatment at least 4 weeks after vaccination, as recommended [36]. Out of the seven patients who received SVR, only one could be considered as optimal in terms of RVS (RVSO). In the context of this retrospective study, it was not possible to clearly determine the urgency of starting rituximab

treatment in the event of a life-threatening condition. Out of the 50 patients on methotrexate, only 1 (2%) was vaccinated more than 3 weeks before the initiation of treatment associated with PPV23 vaccination. One patient (2%) was vaccinated over 3 weeks before treatment, 1 patient (2%) within 3 weeks before treatment and 41/50 (82%) were vaccinated after initiation of treatment. Seven patients (14%) were not vaccinated. There are therefore only 4% (2/50) of patients treated with methotrexate who can be considered to have adhered to RVS. Out of the 6 patients treated with mycophenolate, only 1 (16.7%) was vaccinated before the initiation of treatment, and he did not receive vaccination with PPV23. One patient had not been vaccinated.

All in all, out of the 70 patients who received RVS, we can subtract 4 patients treated with rituximab, 20 treated with methotrexate and 3 treated with mycophenolate according to RVS but with non-optimal PCV13 vaccination. Only 33.8% (43/127) of the vaccinated patients and 28.7% of the entire study population in our study fully adhered to RVS. The results of our study highlight non-optimal pneumococcal vaccine management in many patients with inflammatory and/or autoimmune diseases who were being treated with IS or BT. Some studies have attributed insufficient vaccination to absence of prescription by the specialist or general practitioner [12–14]. It may also be associated with obstacles involving both patients and care centers, as has been observed in the general population [15].

Our study had several limitations. There may have been an information bias due to missing data, particularly on the date of PPV23 vaccination (absence of notification in the computerized medical file used by the specialist and the general practitioner alike). There may also have been a representativeness bias due to the small size of the study workforce. Finally, a selection bias may have occurred, as can be observed during any single-center study. Only a prospective study with adapted methodology, focusing only on new patients vaccinated and subsequently treated, would make it possible to better identify obstacles to pneumococcal vaccination and the means to have them bypassed.

This observational and retrospective study was based on an analysis of professional practices. It is therefore important to consider those needing improvement. The barriers to well-conducted pneumococcal vaccination in immunocompromised patients probably involve both patients and physicians. Given the risk of immediate complications of systemic inflammatory diseases upon diagnosis, treatment is often started immediately and despite knowledge of the recommendations, vaccination may be delayed in an emergency setting. The recommended



3-week time interval between vaccination with PCV13 and the start of IS or BT treatment may be difficult to meet in practice. The obstacles can also be organizational. Not all health centers are equipped to perform the first vaccination at the time of consultation. The HCSP recommendations can be difficult to implement for two main reasons: 1) the difficulty of carrying out the 2 injections 8 weeks apart, with intramuscular injection of PCV13 requiring nursing care 3 weeks before the initiation of the IS or BT treatment in patients with an active inflammatory disease requiring rapid treatment in an overactive hospital context, and 2) failure to carry out the pneumococcal vaccination at home, which is difficult to monitor. In addition to continued training of doctors, optimized computer prescription of vaccines enabling vaccination tracing and vaccination at the site of the consultation are avenues for improvement to be considered.

## **5. Conclusion.**

In line with previous studies, the pneumococcal vaccine coverage of patients with inflammatory disease treated with IS or BT appears insufficient. It is necessary to improve our practices within the framework of the working groups dedicated to PV. Optimization of this vaccination must be carried out both in hospitals and in the framework of city-hospital networks. Communication between hospital doctor and general practitioner must be improved. Information and continuing training in vaccinology for general practitioners should be continued.

**Disclosure of interest:** The authors declare that they have no competing interest.

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**Table 1.** Distribution of the different treatments (biotherapies, immunosuppressive agents and corticosteroids) among the 150 patients in the study.

<b>Study treatments</b>	<b>n (%)</b>
<b>Biotherapies</b>	<b>32 (21.3%)</b>
Anti-TNF alpha	18
Rituximab	11
Ustekinumab	1
Eculizumab	1
Tocilizumab	1
<b>Immunosuppressive agents</b>	<b>93 (62%)</b>
Methotrexate	50
Cyclophosphamide	22
Azathioprine	11
Mycophenolate mofetil	4
Salazopyrine	2
Leflunomide	2
<b>Corticoids alone</b>	<b>25 (16.7%)</b>

**Table 2.** Distribution of the various pathologies observed in the study grouped together according to the associated initial treatment. IS: immunosuppressive agents; BT: biotherapy; MTX: methotrexate; RTX: rituximab; anti-TNF $\alpha$ : anti-TNF-alpha. \* Ophthalmological pathologies: 6 idiopathic uveitis, 3 vasculitis, 2 Birdshot' diseases, 1 retinitis, 1 autoimmune disease, 1 inflammatory tumor, 1 episcleritis; \*\* Small vessel vasculitis: 3 polyangiitis with hypereosinophilia, 3 granulomatosis with polyangiitis, 3 microscopic polyangiitis, 2 ANCA vasculitis, 1 undetermined vasculitis; \*\*\* Spondyloarthropathies: 4 psoriatic, 2 IBD, 2 undetermined, 1 reaction to chlamydia.

Distribution of inflammatory and / or autoimmune pathologies	n	First treatment		
		Corticoïds (alone/+IS /+BT)	BT (anti-TNF $\alpha$ /RTX)	IS (MTX/autres)
Sarcoidosis	16	8 (2/5/1)	3 (3/0)	10 (8/2)
Inflammatory eye diseases*	14	7 (3/4/0)	2 (1/1)	9 (6/3)
Lupus	13	8 (0/2/2)		4 (2/2)
Rheumatoid arthritis (CCP+)	13	13 (0/10/3)	3 (2/1)	10 (10/0)
Giant cell arteritis	12	12 (12/0/0)		
Small vessels arteritis **	12	12 (0/8/4)	4 (0/4)	8 (1/7)
Spondylarthritis***	9		6 (6/0)	3 (2/1)
Ankylosis spondylitis	7		6 (6/0)	1 (1/0)
Behcet's disease	7		1 (0/0)	6 (4/2)
Rheumatoid arthritis (CCP -)	6			6 (6/0)
IgG4-related disease	6	3 (3/0/0)	2 (0/2)	1 (0/1)
Anti-synthetase syndrome	5	5 (0/5/0)		5 (1/4)
Crohn disease	4	2 (0/2/0)	1 (0/0)	3 (1/2)
Sjogren syndrome	3			1 (0/1)
Polyarthritis not classified	3		1 (0/0)	1 (1/0)
Polymyositis	2	1 (0/1/0)		2 (1/1)
Relapsing polychondritis	2			2 (1/1)
Periarteritis nodosa	2	1 (1/0/0)		1 (0/1)
Takayasu disease	2	1 (0/1/0)		2 (1/1)
Paroxysmal nocturnal hemoglobinuria	1			1 (0/1)
Myasthenia gravis	1			1 (0/1)
Auto-immune hemolytic anemia	1		1 (0/1)	
Amyloidosis	1	1 (0/1/0)		1 (0/1)
Still disease	1	1 (1/0/0)		
SAPHO	1			1 (0/1)
Rheumatoid arthritis + eosinophilic granulomatosis with polyangiitis	1	1 (0/1/0)		1 (0/1)
Erdheim-Chester disease	1	1 (1/0/0)		
Chronic parotitis	1	1 (1/0/0)		
Systemic scleroderma	1			1 (0/1)
IgA vasculitis	1	1 (1/0/0)		
Familial Mediterranean fever	1			1 (1/0)



**Table 3.** Recommended vaccination schedule (RVS) according to the inflammatory diseases in the 150 patients in the study.

<b>Disease</b>	<b>Number of patients</b>	<b>Number of patients vaccinated against pneumococcus according to SVR (%)</b>
Sarcoidosis	16	31
Lupus	13	15
Inflammatory eye disease	14	50)
Rheumatoid arthritis (CCP+)	13	61
Giant cell arteritis	12	16
Small vessels arteritis	12	66
Spondylarthritis	9	55
Ankylosis spondylitis	7	85
Behcet's disease	7	43
Rheumatoid arthritis (CCP -)	6	67
IGg4-related disease	6	0
Anti-synthetase syndrome	5	80
Crohn disease	4	75
Sjogren syndrome	3	100
Polyarthritis not classified	3	100
Polymyositis	2	50
Relapsing polychondritis	2	50
Periarteritis nodosa	2	0
Takayasu disease	2	50
Paroxysmal nocturnal hemoglobinuria	1	100
Myasthenia gravis	1	100
Auto-immune hemolytic anemia	1	0

Amyloidosis	1	100
Still disease	1	100
SAPHO	1	0
Rheumatoid arthritis + eosinophilic granulomatosis with polyangiitis	1	100
Erdheim-Chester disease	1	100
Chronic parotitis	1	100
Systemic scleroderma	1	100
IgA vasculitis	1	0
Familial Mediterranean fever	1	0