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## Incidence of complications of herpes zoster in individuals on immunosuppressive therapy: A register-based population study

Sylvain Chawki, Ana Maria Vilcu, Cindy Etienne, Flora Finet, Thierry Blanchon, Cécile Souty, Thomas M. Hanslik

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1 **Title:**

2 Incidence of complications of herpes zoster in individuals on immunosuppressive  
3 therapy: a register-based population study

4

5 **Authors:**

6 Sylvain Chawki<sup>1</sup>, Ana-Maria Vilcu<sup>2</sup>, Cindy Etienne<sup>3,4</sup>, Flora Finet<sup>3,4</sup>, Thierry Blanchon<sup>2</sup>,  
7 Cecile Souty<sup>2</sup>, Thomas Hanslik<sup>2,3,4</sup>.

8

9 1- Université de Paris, INSERM, Institut Universitaire d'Hématologie, U-944, Paris,  
10 France

11 2- Sorbonne Université, INSERM, Institut Pierre Louis d'épidémiologie et de Santé  
12 Publique (IPLESP UMRS 1136), Paris, France

13 3- Université de Versailles Saint-Quentin-en-Yvelines, UVSQ, UFR de Médecine,  
14 Versailles, France

15 4- Assistance Publique - Hôpitaux de Paris (APHP), Hôpital Ambroise Paré, Service  
16 de Médecine Interne, Boulogne Billancourt, France

17

18 **Corresponding author:** Dr Sylvain Chawki, INSERM U-944, Institut Universitaire  
19 d'Hématologie, Hôpital Saint Louis, 16 rue de la Grange aux Belles, 75010 Paris, France.

20 E-mail: [sylvain.chawki@aphp.fr](mailto:sylvain.chawki@aphp.fr). Phone: +33(0)153724051. Fax: +33(0)142494043

21 **Alternate corresponding author:** Pr Thomas Hanslik, Hôpital Ambroise Paré, Service de  
22 Médecine Interne, 9 avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France.

23 E-mail: [thomas.hanslik@aphp.fr](mailto:thomas.hanslik@aphp.fr). Phone: +33(0)149095000.

24

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27

28 **Running title:**

29 Complicated zoster and immunosuppression

30

31 **Highlights:**

32 - Complications of herpes zoster are over three times more frequent in individuals  
33 exposed to immunosuppressive therapy.

34 - Exposed individuals showed more persistent postherpetic neuralgia.

35 - Complicated zoster occurred after a median of one year of immunosuppressants.

36

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## 1 **Introduction**

2           Herpes zoster (HZ) is a common viral disease with a potential severe burden.  
3 Acute and postherpetic complications can lead to long-lasting alterations of the quality  
4 of life in those affected(1–8). The most frequent complication is post herpetic neuralgia  
5 (PHN) which can start with the first symptoms of zoster and can last for an  
6 unpredictable period of time(9,10). PHN could induce iatrogenic harm in the elderly  
7 through prescription of antiepileptic drugs and/or opioids(6,11). Other complications  
8 such as cutaneous dissemination, encephalitis or life-threatening visceral involvement  
9 can also occur(12–14).

10           HZ incidence in industrialized countries is estimated around 1.4 to 4.8/1000  
11 person-year(8,15–20). It increases with age, reaching up to 10.0/1000 in people over 50  
12 years of age(8,15,17–23). Incidence has also been shown to increase with exposure to  
13 immunosuppressive therapy, although this increase has rarely been evaluated on a  
14 population based basis(10,14,24–30). Moreover, it remains uncertain whether the rate  
15 of complications also increases in the context of drug-induced  
16 immunosuppression(9,14,25,31,32).

17           To evaluate whether complicated zoster (CZ) is more frequent in patients with  
18 drug-induced immunosuppression, we carried out an observational, 13-year  
19 retrospective analysis, from a sample of a national healthcare system claims database of  
20 adult patients treated for complicated zoster, *i.e.* PHN and/or hospitalization for HZ.

## 21 **Material and Methods**

22 This study is an observational, 13-year retrospective analysis from 2006 to 2018.

### 23 Data sources and study population

24 Our study is based on the Echantillon généraliste de bénéficiaires (EGB) a healthcare  
25 claims database. The EGB is a 1/97th random permanent sample of the beneficiaries of  
26 the French healthcare insurance system - which covers more than 97.5% of the French  
27 population. It is an open cohort allowing a 20-year follow-up. The EGB was previously  
28 reported as significantly representative of the French population for age, gender,  
29 occupation and medical expenses(33,34). Details on the constitution of the EGB can be  
30 found elsewhere(35). The EGB includes medication and number of units dispensed by  
31 community pharmacies to individuals, but does not include diagnosis nor precise dosage  
32 prescribed. The EGB is linked to the PMSI database, which includes all hospital discharge  
33 data in France, in both the public and private sectors. It includes the date of admission,  
34 duration of stay and medical diagnosis coded according to the International  
35 Classification of Diseases and Related Health Problems 10<sup>th</sup> Edition (ICD-10).

36 All adults  $\geq 18$  years old included in the EGB and with at least one year of history in the  
37 database from 01/01/2006 to 12/31/2018 were eligible for inclusion.

### 38 Definition of complicated zoster

39 Based on medications dispensed in the EGB database and medical diagnosis during  
40 hospitalization (ICD-10 codes) in the PMSI database, incident CZ cases were identified as  
41 either:

- 42 1) a hospitalization with a diagnosis of HZ or PHN, as established by any of the  
43 following ICD-10 codes: B02; B020 through B023; B027 through B029; G530, as  
44 main, related or associated diagnosis.

45 2) a PHN, defined by a first single dispensation of at least 20g of valacyclovir (VCV)  
46 followed less than 4 weeks later by a dispensation of one of the following  
47 analgesics usually used for the treatment of PHN: topical lidocaine;  
48 carbamazepine; gabapentin; pregabalin; imipramine; clomipramine;  
49 amitriptyline; capsaicin(6,13,36). We excluded individuals with dispensations of  
50 VCV or specific analgesics listed in the preceding year, in order to avoid potential  
51 confusion with usual treatment. Persistent PHN was determined every three  
52 months, based on specific analgesics dispensation after the initial 4 weeks period  
53 after VCV dispensation. We only focused on VCV as previous study performed in  
54 France showed that other antivirals are used only marginally(4,15).

55 When an individual had both criteria for hospitalization and PHN, we only considered  
56 the event occurring first.

#### 57 Definition of immunosuppression

58 Based on medication dispensation, we defined the immunosuppression period based on  
59 the dispensation of either:

- 60 a) any immunosuppressive therapy with drugs included in the ATC L04  
61 (immunosuppressants) or L01AA01 (oral cyclophosphamide)
- 62 b) A dose and duration of corticosteroids necessary to substantially raise risk of  
63 infection was defined by an equivalent of 10mg of prednisone per day(37,38) for  
64 a minimum of three dispensations, indicating an uninterrupted period treatment  
65 of at least one month. The treatment period covered by a corticosteroid  
66 dispensation was estimated as the dispensed volume divided by the assumed  
67 daily dose (one month grace period allowed between two dispensations).

68 In order to account for residual immunosuppression even after stopping the drug, we  
69 added a 6-month period of immunosuppression after the last dispensation of any  
70 immunosuppressive therapy.

71 A CZ was recorded as occurring in the exposed to immunosuppressive therapy group  
72 only if it happened during an immunosuppression period, at least two weeks after the  
73 beginning of the immunosuppressive therapy.

#### 74 Statistical analysis

75 The incidence of complicated zoster over the period was estimated by dividing the  
76 number of CZ events by the population size. The population size was calculated by year  
77 for three categories: overall, exposed individuals to immunosuppressive therapy (EI)  
78 and non-exposed individuals (NEI) to immunosuppressive therapy. A risk ratio to  
79 compare incidences between EI and NEI was performed.

80 CZ events included in the study were described. Categorical variables are presented as  
81 “Absolute number (percentage)” and quantitative variable as “Mean (standard  
82 deviation)”. For PHN events, a survival analysis using the Kaplan-Meier method was  
83 performed to account for PHN persistence.

84 Statistical significance was defined for a p-value inferior to 0.05.

#### 85 Ethics and consent

86 National Institute for Health and Medical Research (INSERM) agreement for the  
87 research protocol was given on 11/20/2020. Neither approval by an ethics committee  
88 nor request from national commissions for individual data protection were required,  
89 according to the French law, to access restricted access database of anonymously  
90 recorded data. Access to the EGB database is possible only through a secured connection  
91 to a specific server. Data are accessible online and are analyzed by the software SAS  
92 Enterprise Guide version 4.3 (Copyright © 2006–2010, SAS Institute Inc., Cary, NC, USA).

93 **Results**

94 Study population

95 A total of 616,237 individual in the EGB were eligible for inclusion in the study. Among  
96 them, 3065 patients with CZ were identified: 624 through hospitalization for zoster and  
97 2441 through dispensation of drug for PHN treatment. Reasons for hospitalization were  
98 mostly herpes zoster (B0.29) in 337 cases (54.0%), followed by neuro-ocular  
99 manifestations (n=173 ; 27.7%) (Table 2).

100 Overall in the eligible study population, 40,063 individuals had a least one exposure to  
101 high dose/prolonged corticosteroids and 8,952 patients had at least one exposure to an  
102 immunosuppressive therapy, accounting for a total of 44,404 individuals exposed to  
103 immunosuppressive therapy and/or corticosteroid therapy. Among them, CZ occurred  
104 in 227 individuals.

105 Mean age of individuals with CZ was 66.1 years ( $\pm 17.0$  SD) overall and 66.0 years ( $\pm 15.9$   
106 SD) and 66.1 years ( $\pm 17.1$  SD) in EI and NEI, respectively. Sex ratio for female was 1.6  
107 overall and 1.4 and 1.6 in EI and NEI, respectively (Table 1).

108

109 Complicated zoster incidence

110 Overall CZ incidence rate was 54.6 per 100,000 person-year (95%CI=[52.6-56.5]). In  
111 NEI, CZ incidence rate was 51.7 per 100,000 person-year (95%CI=[49.8-53.6]) whereas  
112 in EI CZ incidence rate reached 178 per 100,000 person-year (95%CI=[154.9-201.1]),  
113 which accounted for a risk ratio of 3.44 (95%CI=[3.01-3.94]). Incidences according to  
114 age in both populations are summarized in the supplemental figure.

115 Hospitalization occurred in EI in 95 cases (41.9%) and in NEI in 529 cases (18.6%).

116 Mean hospitalization duration was 13.8 days ( $\pm 15.3$  SD ; 95%CI=[10.7-16.9]) and 11.8  
117 days ( $\pm 16.3$  SD ; 95%CI=[10.4-13.2]) in EI and NEI, respectively (Table 1). Autoimmune



118 and rheumatological diseases codes associated with hospitalization for complicated  
119 zoster in the exposed individuals are summarized in the supplemental table.

120

#### 121 Persistence of neuralgia

122 In the 2441 PHN individuals identified by the prescription of drugs, treatment persisted  
123 more than 3 months, 6 months and 9 months in 563 (23.1%), 253 (10.4%) and 158  
124 (6.5%) of cases, respectively (Table 1). Over all the study period, the Kaplan-Meier  
125 survival analysis of PHN persistence in each group showed a tendency towards a  
126 quicker resolution of PHN in NEI compared to EI ( $p=0.12$ ) (Figure 1). At 3 months, PHN  
127 persisted in 43 cases (32.6%) in EI and in 520 cases (22.5%) in NEI ( $p=0.01$ ) (Table 1).

128

#### 129 Specific analgesics used

130 The analgesic specific for PHN the most prescribed was pregabalin ( $n= 1315 ; 53.9 \%$ ) in  
131 both EI ( $n=77 ; 50\%$ ) and NEI ( $n=1208 ; 46.7\%$ ). Other analgesics used are summarized  
132 in Table 3. More than one analgesic was prescribed in 18 cases (13.6%) in EI patients  
133 and in 305 cases (13.2%) in NEI. When excluding lidocaine patches from this definition,  
134 the results were 7 (5.3%) and 96 (4.2%), respectively. Level II opioids (*i.e.* tramadol and  
135 codeine) were dispensed in 44 cases (33.3%) and 814 cases (35.2%) in EI and NEI,  
136 respectively. Additionally, level III opioids according to the WHO analgesic ladder(39)  
137 (morphine, hydromorphone, oxycodone or fentanyl) were initially prescribed in 13  
138 cases (12.9%) in EI against 97 cases (4.2%) in NEI.

139

#### 140 Immunosuppressants and corticosteroids used

141 In the exposed group, individuals presented a complicated zoster after a median of 11.7  
142 months (interquartile range [5.3-49.9]). The main immunosuppressive therapy used

143 was corticosteroids alone (n=127; 55.9%) followed by corticosteroids in combination  
144 with an immunosuppressant (n=61 ; 26.9%) (Table 4). Among patients on  
145 corticosteroids we identified 188 events of CZ and 100 among patients on  
146 immunosuppressive therapy, with incidence rates of 178.9 per 100,000 person-year  
147 (95%CI=[152.7-205.1]) and 241.1 per 100,000 person-year (95%CI=[193.9-288.3]),  
148 respectively. The main immunosuppressant used was methotrexate (n=37 ; 16.3%)  
149 followed by mycophenolate acid (n=32 ; 14.1%) and calcineurin inhibitors (n=29 ;  
150 12.8%) (Table 4).

151 **Discussion**

152 In this observational 13-year retrospective analysis from a claims database, adult  
153 individuals exposed to immunosuppressive therapy were three times more prone to  
154 complicated zoster compared to non-exposed individuals.

155 Although HZ is more frequent with age and immunosuppression, its complications (*i.e.*  
156 PHN and/or hospitalization) in immunosuppressed individuals remain poorly  
157 evaluated(8,10,14,20,21,24–30).

158

159 In our analysis, we observed that CZ was three times more frequent in EI than NEI,  
160 despite a similar sex ratio and age. A higher rate of hospitalization and PHN was  
161 noteworthy in EI, in each age class. These results are in line with previous studies that  
162 suggest more frequent occurrences of HZ complications with exposure to  
163 immunosuppression. Indeed, Schröder et al. reported, based on German claims data,  
164 that CZ was higher in the context of immunosuppression. According to the incidence  
165 rate they published for HZ and HZ without complication, CZ incidence was  
166 approximately 190 per 100,000 person-year in immunocompromised individuals and  
167 80 per 100,000 person-year in immunocompetent individuals, which is comparable to  
168 our findings. They also reported a prevalence of 22.5% of PHN (defined by dispensation  
169 of specific pain medication in the quarter of HZ or the following one) in  
170 immunocompetent and 33.8% in immunocompromised. Similarly, a population-based  
171 study reported higher incidence of non-pain complications of HZ in  
172 immunocompromised, with 21% in immunocompetent individuals and 48% in  
173 immunocompromised ( $p<.001$ )(20). In a recent meta-analysis and a systemic review  
174 Marra et al. studied the association between immunosuppressive therapy in  
175 autoimmune diseases and HZ outcome. They described an increased risk of HZ with

176 non-biologic DMARDs (OR = 1.21;CI<sub>95%</sub>=1.39-1.81) and corticosteroids (OR =  
177 1.73;CI<sub>95%</sub>=1.57-1.89) compared to immunocompetent(21,30).

178

179 To the best of our knowledge persistence of PHN has not been previously compared in  
180 NEI and EI. We observed a significantly higher proportion of persistence of specific  
181 neuropathic pain management therapy at 3 months in EI compared to NEI and a  
182 tendency, although not statistically significant, towards a quicker resolution of PHN in  
183 NEI overall. This suggests that immunosuppressive therapy might delay clearance of  
184 neuralgia in HZ. Overall, in immunocompetent individuals, PHN at 6 months is reported  
185 in 8.5 to 18%(1–4,20). PHN definition does not reach a broad consensus within the  
186 medical community. HZ-related pain prevalence decreases with time. HZ-related pain  
187 has been reported to be present in 79.6% of individuals at day 0, 8.5% at 6 months and  
188 6% after a year(4). Comparably, Bricout et al. reported HZ-related pain in 89.6% of  
189 patients initially and 9.2% after 6 months(1). When applied to the incidence of HZ  
190 estimated in a French general practitioners surveillance network(15), these proportions  
191 would result in an incidence estimate of PHN between 35 and 342 per 100,000 person-  
192 year, in line with the overall incidence of CZ provided here (54.6 per 100,000 person-  
193 year).

194

195 In the context of CZ, we identified individuals through hospitalization in 41.9% of cases  
196 for EI compared to 18.6% in NEI. Although it could be argued that hospitalization is  
197 more broadly recommended in EI with HZ, Schröder et al. reported only 10% of  
198 hospitalization in EI with HZ(10,40). These figures cannot be evaluated in our study but  
199 such a low rate suggests that overcautious hospitalization is uncommon for HZ in EI.

200 Only a few studies provide evidence for the persistence of pain medication over 12  
201 months after the episode of HZ in both immunocompetent and immunosuppressed  
202 individuals, our study provides new insights into the persistence of pain even after HZ  
203 resolution and the potential indication for VZV prophylaxis(20).

204 We observed a higher use of level III opioids in the EI group but were unable to relate  
205 that exclusively to CZ severity as we did not exclude individuals with prior exposition to  
206 opioids.

207

208 Our work shows some limitations. First, diagnoses were not available, thus assessment  
209 of CZ relied on drug dispensation and hospitalization data alone. Drugs used for CZ or  
210 PHN treatment are not disease specific. To overcome this limitation, we established  
211 strict definitions to avoid the risk of confounding inclusions of patient taking VCV for  
212 HSV or prophylaxis of VZV reactivation or treated for epilepsy or other neurological or  
213 psychiatric disorders overlapping the spectrum of drug used in PHN. These definitions  
214 excluded individuals with prior exposure to specific analgesics or VCV. Additionally, CZ  
215 identified through hospitalization were ascertained through the use of a specific and  
216 narrow range of hospitalization codes and only if hospitalization occurred as the first  
217 event, to retain incident cases of CZ. Finally, the fact that our findings agree with  
218 established HZ epidemiological data is validating our data to some extent. Indeed, the  
219 sex ratio, the increase in incidence according to age and the rates of PHN observed after  
220 6 and 12 months in the overall population are in the same range to those reported in  
221 previous epidemiological studies(1,4).

222 Second, for the definition of exposure to immunosuppressant, we are inferring that  
223 every medication dispensed were consumed for the supposed duration which can lead  
224 to potential overinterpretation.

225 Third, this was an observational retrospective study, based on a sample of France's  
226 healthcare medical consumption, thus inducing potential bias of non-  
227 representativeness. Nonetheless, the EGB is considered a representative sample of  
228 France's population.

229 Fourth, causal inference of the increase of CZ to drug-induced immunosuppression is  
230 limited by the fact that information on additional potential confounders or effect  
231 modifiers (*e.g.* sociodemographic characteristics, tobacco and alcohol consumption,  
232 comorbidities) were not available. However, drug-induced immunosuppression  
233 presents a strong plausibility for higher rates of complications of HZ and remains an  
234 easily identifiable proxy for practical purposes.

235 This study highlighted the fact that, in a real-life setting, drug-induced  
236 immunosuppression increases the risk of complicated herpes zoster and exposes  
237 patients to longer lasting PHN. The information provided in this study can help guide  
238 patients and physicians regarding decision of prophylaxis of HZ.

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241 **Conflict of Interest**

242 The authors have no conflict nor link or interest to declare with regards to that work.

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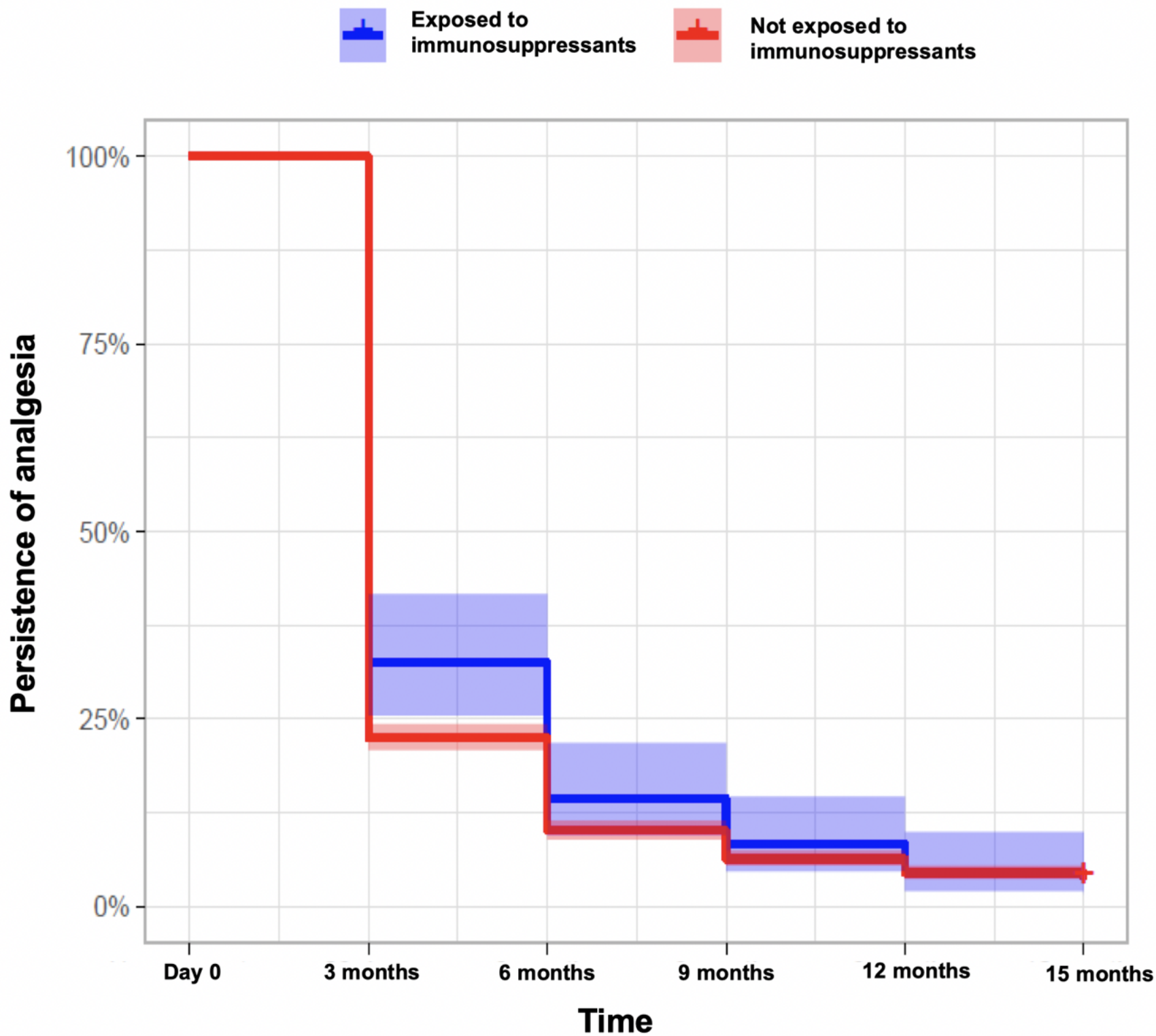
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**Figure 1. Kaplan-Meier survival plot of the persistence of post-herpetic neuralgia according to exposure to immunosuppressants**



1 **Tables and figures:**

2 **Table 1 . Characteristics of patients with complicated zoster, overall and according to exposure to immunosuppressants**

<b>Characteristic</b>	<b>All population (n= 3065; 100%)</b>	<b>Exposed to immunosuppressants (n= 227; 7.4%)</b>	<b>Not exposed to immunosuppressants (n=2838 ; 92.6%)</b>
Age (years), mean (SD)	66.1 (17.0)	66.0 (15.9)	66.1 (17.1)
Sex (male), n (%)	1179 (38.5)	94 (41.4)	1085 (38.2)
Hospitalization as identifying factor, n (%)	624 (20.4)	95 (41.9)	529 (18.6)
<i>Hospitalization duration (days), mean (SD ; [95%CI])</i>	<i>12.1 (16.6 ; [10.8-13.4])</i>	<i>13.8 (15.3 ; [10.7-16.9])</i>	<i>11.8 (16.8 ; [10.4-13.2])</i>
Neuralgia as identifying factor, n (%)	2441 (79.6)	132 (58.1)	2309 (81.4)
<i>3-month persistent neuralgia, n (%)</i>	<i>56 (23.1)</i>	<i>43 (32.6)</i>	<i>520 (22.5)</i>
<i>6-month persistent neuralgia, n (%)</i>	<i>253 (10.4)</i>	<i>19 (14.4)</i>	<i>234 (10.1)</i>
<i>9-month persistent neuralgia, n (%)</i>	<i>158 (6.5)</i>	<i>11 (8.3)</i>	<i>147 (6.4)</i>
<i>12-month persistent neuralgia, n (%)</i>	<i>110 (4.5)</i>	<i>6 (4.5)</i>	<i>104 (4.5)</i>
<i>15-month persistent neuralgia, n (%)</i>	<i>90 (3.7)</i>	<i>5 (3.8)</i>	<i>85 (3.7)</i>

3

4 **Table 2 . Reasons for hospitalization for herpes zoster, overall and according to**  
 5 **exposure to immunosuppressants**

<b>Reason for hospitalization</b>	<b>All population n (%)</b>	<b>Exposed to immunosuppressants n (%)</b>	<b>Not exposed to immunosuppressants n (%)</b>
Herpes zoster	337 (54.0)	52 (54.7)	285 (45.7)
Ocular herpes zoster	82 (13.1)	11 (11.6)	71 (11.4)
Neuralgia	76 (12.2)	6 (6.3)	70 (11.2)
Disseminated	31 (5.0)	8 (8.4)	23 (3.7)
Meningitis, encephalitis or both	16 (2.6)	0 (0.0)	16 (2.6)
Other complications	8 (13.6)	18 (19.0)	67 (10.7)

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7

8 **Table 3.: Specific analgesics dispensed initially to identify complicated zoster**  
 9 **according to exposure to immunosuppressants**

Analgesic	Exposed to immunosuppressants	Not exposed to immunosuppressants
	n (%)	n (%)
Pregabalin	77 (50)	1238 (46.7)
Lidocaine	28 (18.2)	617 (23.3)
Amitriptyline	24 (15.6)	370 (14)
Gabapentin	21 (13.6)	353 (13.3)
Carbamazepine	4 (2.6)	58 (2.2)
Clomipramine	0 (0)	16 (.6)

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12 **Table 4. Distribution of immunosuppressive drugs used by the patients in the**  
 13 **group exposed to immunosuppressive therapy**

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<b>Immunosuppressive drug</b>	<b>n (%)</b>
Corticosteroids alone	127 (55.9)
Corticosteroids in combination with an immunosuppressant (or more than one)	52 (22.9)
Immunosuppressant alone	39 (17.2)
<b>Immunosuppressants used</b>	
Methotrexate	37 (16.3)
<i>Methotrexate and corticosteroids</i>	<i>17 (7.5)</i>
Mycophenolate acid	32 (14.1)
<i>Mycophenolate acid and corticosteroids</i>	<i>24 (10.6)</i>
Calcineurin inhibitors	29 (12.8)
<i>Calcineurin inhibitors and corticosteroids</i>	<i>16 (7.0)</i>
TNFalpha inhibitors	10 (4.4)
Azathioprine	8 (3.5)
Cyclophosphamide	5 (2.2)
Interleukines inhibitors*	3 (1.3)
Others#	8 (3.5)

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16 \*Secukinumab (n=1); Tocilizumab (n=1); Ustekinumab (n=1)

17 #Apremilast (n=1); everolimus (n=1); leflunomide (n=4); sirolimus (n=1), teriflunomide  
 18 (n=1)