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Commentary

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

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SUMMARY

Objectives: Herpes zoster (HZ) exposes to alterations of the quality-of-life. HZ is more frequent in immunocompromised individuals, but whether immunosuppression is associated with a higher rate of complications is not well documented. We aimed to assess association between drug-induced immunosuppression and HZ complications.

Methods: Data from a sample of the French healthcare claims from 01/01/2006 to 12/31/2018 were analyzed. Complicated zoster (CZ) was defined as a hospitalization with a code for HZ or the first-time dispensation of high-dose valacyclovir and specific neuralgia analgesics. Drug-induced immunosuppression was identified through medication dispensation. Risk ratios were calculated to compare incidences in exposed individuals (EI) and non-exposed to immunosuppressive therapy (NEI).

Results: We identified 227 and 2838 CZ, accounting for an incidence of 178 per 100,000 person-year (95%CI[154.9–201.1]) and 51.7 per 100,000 person-year (95%CI[49.8–53.6]), in EI and NEI, respectively (risk ratio: 3.44 (95%CI[3.01–3.94]). Mean age was 66 years in both groups. CZ occurred after a median of 11.7 months (IQR[5.3–49.9]) of immunosuppressive therapy. Post-herpetic neuralgia (PHN) lasted at least 3 months in 32.6% and 22.5% of cases in EI and NEI, respectively (p=.01).

Conclusions: Drug-induced immunosuppression increases the risk of CZ and exposes to longer-lasting PHN. Figures provided in this study could help guide prophylaxis of HZ.

Introduction

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

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

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

Material and methods

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

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Data sources and study population

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

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

Definition of complicated zoster

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

1) a hospitalization with a diagnosis of HZ or PHN, as established by any of the following ICD-10 codes: B02; B020 through B023; B027 through B029; G530, as main, related or associated diagnosis.
2) a PHN, defined by a first single dispensation of at least 20 g of valacyclovir (VCV) followed less than 4 weeks later by a dispensation of one of the following analgesics usually used for the treatment of PHN: topical lidocaine; carbamazepine; gabapentin; pregabalin; imipramine; clomipramine; amitriptyline; capsaicin [6,13,36]. We excluded individuals with dispensations of VCV or specific analgesics listed in the preceding year, in order to avoid potential confusion with usual treatment. Persistent PHN was determined every three months, based on specific analgesics dispensation after the initial 4 weeks period after VCV dispensation. We only focused on VCV as previous study performed in France showed that other antivirals are used only marginally [4,15].

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

Definition of immunosuppression

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

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

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

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

Statistical analysis

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

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

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

Ethics and consent

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

Results

Study population

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

Overall in the eligible study population, 40,063 individuals had a least one exposure to high dose/prolonged corticosteroids and 8952 patients had at least one exposure to an immunosuppressive therapy, accounting for a total of 44,404 individuals exposed to immunosuppressive therapy and/or corticosteroid therapy. Among them, CZ occurred in 227 individuals.

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

Complicated zoster incidence

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

Hospitalization occurred in EI in 95 cases (41.9%) and in NEI in 529 cases (18.6%). Mean hospitalization duration was 13.8 days (± 15.3 SD; 95%CI=[10.7–16.9]) and 11.8 days (± 16.3 SD;

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

Characteristic	All population (n = 3065; 100%)	Exposed to immunosuppressants (n = 227; 7.4%)	Not exposed to immunosuppressants (n = 2838; 92.6%)
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)
Hospitalization duration (days), mean (SD; [95%CI])	*12.1 (16.6; [10.8–13.4])*	*13.8 (15.3; [10.7–16.9])*	*11.8 (16.8; [10.4–13.2])*
Neuralgia as identifying factor, n (%)	2441 (79.6)	132 (58.1)	2309 (81.4)
3-month persistent neuralgia, n (%)	*56 (23.1)*	*43 (32.6)*	*520 (22.5)*
6-month persistent neuralgia, n (%)	*253 (10.4)*	*19 (14.4)*	*234 (10.1)*
9-month persistent neuralgia, n (%)	*158 (6.5)*	*11 (8.3)*	*147 (6.4)*
12-month persistent neuralgia, n (%)	*110 (4.5)*	*6 (4.5)*	*104 (4.5)*
15-month persistent neuralgia, n (%)	*90 (3.7)*	*5 (3.8)*	*85 (3.7)*

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

Reason for hospitalization	All population n (%)	Exposed to immunosuppressants n (%)	Not exposed to immunosuppressants n (%)
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)

Table 3
Specific analgesics dispensed initially to identify complicated zoster according to exposure to immunosuppressants.

Analgesic	Exposed to immunosuppressants n (%)	Not exposed to immunosuppressants 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 (0.6)

95%CI=[10.4–13.2]) in EI and NEI, respectively (Table 1). Autoimmune and rheumatological diseases codes associated with hospitalization for complicated zoster in the exposed individuals are summarized in the supplemental table.

Persistence of neuralgia

In the 2441 PHN individuals identified by the prescription of drugs, treatment persisted more than 3 months, 6 months and 9 months in 563 (23.1%), 253 (10.4%) and 158 (6.5%) of cases, respectively (Table 1). Over all the study period, the Kaplan-Meier survival analysis of PHN persistence in each group showed a tendency towards a quicker resolution of PHN in NEI compared to EI (p=.12) (Fig. 1). At 3 months, PHN persisted in 43 cases (32.6%) in EI and in 520 cases (22.5%) in NEI (p=.01) (Table 1).

Specific analgesics used

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

Immunosuppressants and corticosteroids used

In the exposed group, individuals presented a complicated zoster after a median of 11.7 months (interquartile range [5.3–49.9]). The main immunosuppressive therapy used was corticosteroids alone (n = 127; 55.9%) followed by corticosteroids in combination with an immunosuppressant (n = 61; 26.9%) (Table 4). Among patients on corticosteroids we identified 188 events of CZ and 100 among patients on immunosuppressive therapy, with incidence rates of 178.9 per 100,000 person-year (95%CI=[152.7–205.1]) and 241.1 per 100,000 person-year (95%CI=[193.9–288.3]), respectively. The main immunosuppressant used was methotrexate (n = 37; 16.3%) followed by mycophenolate acid (n = 32; 14.1%) and calcineurin inhibitors (n = 29; 12.8%) (Table 4).

Discussion

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

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

In our analysis, we observed that CZ was three times more frequent in EI than NEI, despite a similar sex ratio and age. A

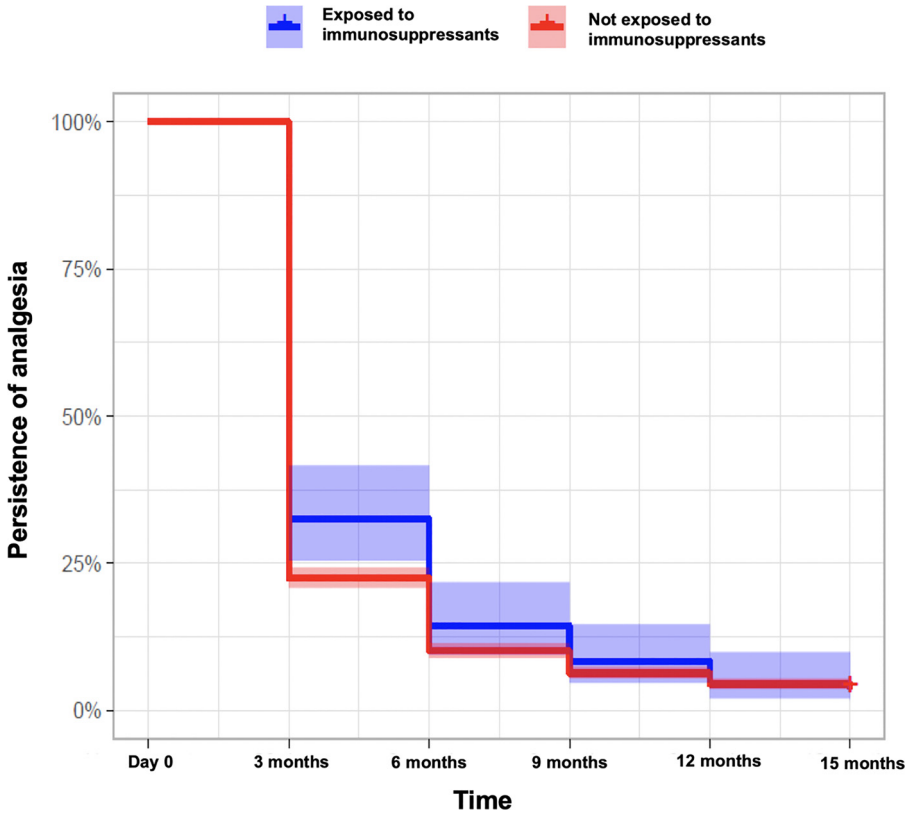

Fig. 1. Kaplan - Meier survival plot of the persistence of post-herpetic neuralgia according to exposure to immunosuppressants.

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

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

*Secukinumab ($n = 1$); Tocilizumab ($n = 1$); Ustekinumab ($n = 1$).
#Apremilast ($n = 1$); everolimus ($n = 1$); leflunomide ($n = 4$); sirolimus ($n = 1$), teriflunomide ($n = 1$).

higher rate of hospitalization and PHN was noteworthy in EI, in each age class. These results are in line with previous studies that suggest more frequent occurrences of HZ complications with exposure to immunosuppression. Indeed, Schröder et al. reported, based on German claims data, that CZ was higher in the context of immunosuppression. According to the incidence rate they published for HZ and HZ without complication, CZ incidence was approximately 190 per 100,000 person-year in immunocompromised individuals and 80 per 100,000 person-year in immunocompetent individuals, which is comparable to our findings. They also reported a prevalence of 22.5% of PHN (defined by dispensation of specific pain medication in the quarter of HZ or the following one) in immunocompetent and 33.8% in immunocompromised. Similarly, a population-based study reported higher incidence of non-pain complications of HZ in immunocompromised, with 21% in immunocompetent individuals and 48% in immunocompromised ($p<.001$) [20]. In a recent meta-analysis and a systemic review Marra et al. studied the association between immunosuppressive therapy in autoimmune diseases and HZ outcome. They described an increased risk of HZ with non-biologic DMARDs (OR = 1.21;$CI_{95\%}$=1.39–1.81) and corticosteroids (OR = 1.73;$CI_{95\%}$=1.57–1.89) compared to immunocompetent [21,30].

To the best of our knowledge persistence of PHN has not been previously compared in NEI and EI. We observed a significantly higher proportion of persistence of specific neuropathic pain management therapy at 3 months in EI compared to NEI and a ten-

dency, although not statistically significant, towards a quicker resolution of PHN in NEI overall. This suggests that immunosuppressive therapy might delay clearance of neuralgia in HZ. Overall, in immunocompetent individuals, PHN at 6 months is reported in 8.5 to 18% [1-4,20]. PHN definition does not reach a broad consensus within the medical community. HZ-related pain prevalence decreases with time. HZ-related pain has been reported to be present in 79.6% of individuals at day 0, 8.5% at 6 months and 6% after a year [4]. Comparably, Bricout et al. reported HZ-related pain in 89.6% of patients initially and 9.2% after 6 months [1]. When applied to the incidence of HZ estimated in a French general practitioners surveillance network [15], these proportions would result in an incidence estimate of PHN between 35 and 342 per 100,000 person-year, in line with the overall incidence of CZ provided here (54.6 per 100,000 person-year).

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

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

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

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

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

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

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

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

Declaration of competing interest

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.01.003.

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