PAIN® 153 (2012) 342–349

PAIN®

www.elsevier.com/locate/pain

Patient perspective on herpes zoster and its complications: An observational prospective study in patients aged over 50 years in general practice

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 15 March 2011
Received in revised form 18 October 2011
Accepted 20 October 2011

Keywords:
Herpes zoster
Neuropathic pain
Postherpetic neuralgia
Quality of life

ABSTRACT

Understanding the effect of herpes zoster and zoster-related pain should inform care to improve health-related quality of life in elderly patients. A 12-month, longitudinal, prospective, multicenter observational study conducted in primary care in France enrolled patients aged ⩾50 years with acute eruptive herpes zoster. Patient-reported zoster-related pain was assessed by validated questionnaires (Douleur Neuropathique en 4 Questions [DN4], Zoster Brief Pain Inventory [ZBPI], and Neuropathic Pain Symptom Inventory [NPSI]) on days 0 and 15, and at months 1, 3, 6, 9, and 12. Health-related quality of life was assessed by the 12-item short-form health survey (SF-12) and the Hospital Anxiety and Depression scale on day 0 and at months 3, 6, and 12. Of 1358 patients included, 1032 completed follow-up. Mean ± standard deviation age was 67.7 ± 10.7 (range, 50–95) years; 62.2% were women. Most patients (94.1%) were prescribed antiviral drugs. The prevalence of zoster-related pain on day 0 and at months 3, 6, 9, and 12 was 79.6%, 11.6%, 8.5%, 7.4%, and 6.0%, respectively. Patients with persistent pain had lower scores on the physical and mental component summaries of the SF-12 and the ZBPI interference score than those without pain. By logistic regression analysis, main predictive factors on day 0 for postherpetic neuralgia at month 3 were age, male sex, ZBPI interference score, Physical Component Summary score of the SF-12, and neuropathic quality of pain (DN4 score ⩾4). Despite early diagnosis and treatment with antiviral agents, many patients with herpes zoster experience persistent pain and marked long-term reduction in health-related quality of life.

1. Introduction

Herpes zoster (HZ) and zoster-related pain are frequent causes of morbidity in the elderly [20]. HZ is caused by reactivation of varicella zoster virus from a latent infection in the sensory ganglia [1,18]. The acute phase of HZ is usually defined as ⩽30 days after rash onset, whereas the most common complication of HZ is postherpetic neuralgia (PHN), which is usually defined as chronic pain persisting for ⩾3 months after rash onset [32].

The lifetime risk of HZ is 25–30%, but this rises to 50% in those aged ⩾85 years [5,18,43]. Similarly, the risk of experiencing chronic zoster-related pain increases with age [14,18,37]. Despite therapy with antiviral agents, PHN has been reported to occur in 10–20% of all patients with HZ [14,21,36], but its incidence increases markedly in patients aged >60 years. However, few

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0304-3959/$36.00
doi:10.1016/j.pain.2011.10.026

long-term prospective longitudinal studies have been carried out, and these estimates are mostly based on retrospective studies. With the predicted worldwide increase in the number of people aged ⩾60 years in the coming decades [31], the number of people affected by HZ can also be expected to increase [19].

Early treatment of patients with acute HZ aims to accelerate rash healing, relieve pain, and reduce the number of complications [15]. Optimal care is summarized in recent guidelines recommending oral antiviral agents for 7 days in patients with HZ who are at risk of developing PHN (patients aged >50 years with severe acute pain, severe rash, or significant prodromal symptoms) [13]. These agents have shown efficacy in accelerating healing and decreasing the duration of pain if administered within 72 h of symptom onset [15,42] but will not necessarily prevent PHN [24]. Thus, the identification of predictive factors for the development of PHN remains of major clinical interest. In addition to antiviral therapy, most patients require analgesia, which may progress up the analgesic ladder to morphine in some cases [13,19].

Studies suggest that HZ and PHN can substantially impair health-related quality of life (HRQoL) [9,23,28]. Activities of daily living, psychological well-being, and social interaction may all be affected by acute and chronic zoster-related pain, which can also reduce the patient's ability to maintain an independent lifestyle [19,20,41]. Our understanding of the true long-term burden of illness experienced by patients with HZ and zoster-related pain (which is essential to initiatives to improve the delivery and coordination of care to these patients) remains limited as a result of a lack of long-term prospective data. A recent Canadian study of 261 patients recruited within 14 days of rash onset and followed for 6 months found that anxiety and depression, enjoyment of life, mood, and sleep were most frequently affected by PHN [11].

We carried out an observational, 12-month prospective study of a large cohort of primary-care patients aged ⩾50 years to evaluate, from the patient perspective, the real-life burden of HZ and its effect on HRQoL, in particular persistent zoster-related pain. We also aimed to identify factors that are predictive of persistent zoster-related pain.

2. Methods

2.1. Study design and patient population

This longitudinal, prospective, multicenter observational study was conducted in general practices in France. The study, managed by a multidisciplinary scientific committee, was carried out in accordance with the principles of the Declaration of Helsinki (2004). Ethical approval was provided by an independent review board. All patients provided written informed consent before enrollment.

Almost 30,000 family doctors (general practitioners [GPs]) across all regions of metropolitan France were randomly selected and invited by mail to participate in the study; 1759 agreed to take part.

Patients aged ⩾50 years with acute HZ in the eruptive phase (defined in this study as visible skin lesions at any stage of development) and presenting to the GP within 7 days of rash onset were eligible for inclusion in the study. Patients were invited to participate in the study at the first visit to the GP because of HZ (day 0). Participants were required to have a good understanding of French and to have telephone access. Patients who had experienced HZ in the previous 12 months were excluded from the study.

2.2. Assessments

At enrollment (day 0), GPs completed an inclusion form for each patient, on which they recorded the following: demographic details; history of the HZ episode (including the time interval between appearance of lesions and visit to the doctor); clinical features (including location and spread of skin lesions); stage of development and severity of lesions; and immunological status and zoster-related pain (defined as pain in the same area as the zoster rash). The 10-item Douleur Neuropathique en 4 Questions (DN4) questionnaire, which includes a sensory examination, was administered by GPs at first visit to diagnose neuropathic pain. Each item of this questionnaire requires a "yes" or "no" response (a score ⩾4 on a scale of 0 to 10 indicates neuropathic pain) [2]. Treatments prescribed for HZ were recorded. GPs were contacted by telephone at months 3, 6, and 12, and details of persistent zoster-related pain, clinical pathway, and treatments prescribed were obtained. PHN was defined as the persistence of pain of any intensity 3 months or more after the rash onset.

Table 1
Baseline characteristics of patients and herpes zoster.[a]

Characteristic	Age <70 y	Age ⩾70 y	Total population
No. of patients	745	609	1354
Age, y, mean ± SD	59.5 ± 5.8	77.7 ± 5.6	67.7 ± 10.7
Sex,%, M/F	38.8%/ 61.2%	36.7%/ 63.3%	37.8%/62.2%
Body mass index, mean ± SD	26.0 ± 4.4	26.1 ± 4.6	26.01 ± 4.5
DN4 score, mean ± SD	4.2 ± 1.9	4.1 ± 1.73	4.2 ± 1.91
DN4 ⩾4, n (%)	461 (62.6%)	367 (60.8%)	831 (61.8%)
NPSI, mean ± SD	31.9 ± 19.8	31.7 ± 19.3	31.8 ± 19.6
ZBPI, mean ± SD			
Worst pain score (0–10)	5.1 ± 2.7	5.4 ± 2.6	5.3 ± 2.6
ZBPI interference score	2.9 ± 2.3	3.3 ± 2.4	3.1 ± 2.4
SF-12, mean ± SD			
Physical Component Score	46.7 ± 8.9	40.2 ± 9.8	43.9 ± 9.8
Mental Component Score	42.1 ± 11.5	40.1 ± 10.7	41.2 ± 11.7
HADS, mean ± SD			
Depression	5.2 ± 4.3	7.6 ± 4.6	6.2 ±4.6
Anxiety	6.7 ± 4.6	7.3 ± 4.3	7.0 ± 4.4
Rash location, n (%)			
Thoracoabdominal	512 (68.8%)	408 (67.0%)	922 (68.0%)
Cranial and facial	124 (16.7%)	111 (18.2%)	235 (17.3%)
Limbs and girdles	76 (10.2%)	53 (8.7%)	130 (9.6%)
Combination or other location	32 (4.3%)	37 (6.1%)	69 (5.1%)
Description of rash, n (%)			
Extent			
Limited rash	409 (56.3%)	247 (42.1%)	657 (49.8%)
Extensive rash	318 (43.7%)	340 (57.9%)	661 (50.2%)
Severity of lesions			
Simple rash	663 (91.3%)	493 (84.0%)	1159 (88.0%)
Hemorrhagic appearance	43 (5.9%)	57 (9.7%)	101 (7.7%)
Necrotic appearance	10 (1.4%)	30 (5.1%)	40 (3.0%)
Comorbidities, n (%)	364 (49.1%)	465 (77.1%)	831 (61.6%)
Diabetes	60 (16.5%)	62 (13.3%)	122 (14.7%)
Cardiovascular disease	186 (51.1%)	337 (72.5%)	525 (63.2%)
Pulmonary disease	31 (8.5%)	54 (11.6%)	85 (10.2%)
Cancer	51 (14.0%)	40 (8.6%)	91 (11.0%)
Other chronic disease	120 (33%)	133 (28.6%)	253 (30.4%)

[a] DN4, Douleur Neuropathique en 4 Questions; range, 0–10; score ⩾4 indicates neuropathic pain; HADS, Hospital Anxiety and Depression Scale; range 0–21 for anxiety and depression; NPSI, Neuropathic Pain Symptom Inventory; range 0–100; SF-12, 12-item short-form health survey; score <50 indicates below-average health status; ZBPI, Zoster Brief Pain Inventory; range 0 ("no pain") to 10 ("pain as bad as you can imagine").

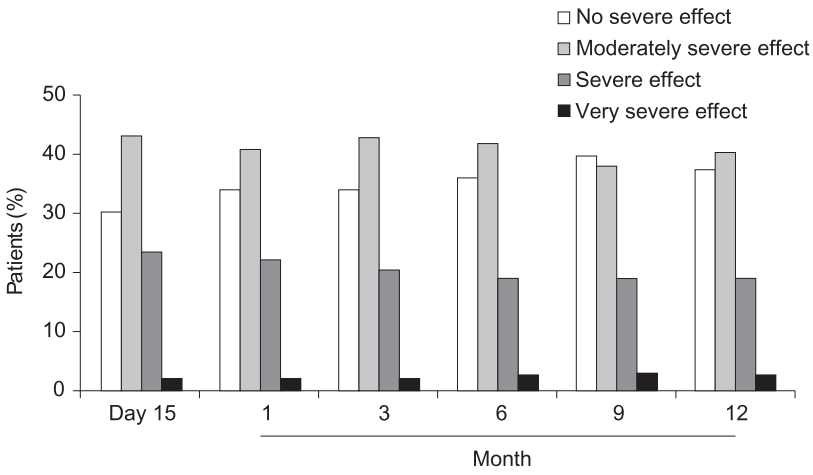

Fig. 1. Patient's perception of the effect of herpes zoster and zoster-related pain on daily life.

On day 0, all patients were asked to complete validated questionnaires for the assessment of pain symptoms and severity. The Zoster Brief Pain Inventory (ZBPI) [9,34] rates the severity of pain from 0 ("no pain") to 10 ("pain as bad as you can imagine") and the interference of pain on the activities of daily living from 0 ("does not interfere") to 10 ("completely interferes"). The Neuropathic Pain Symptom Inventory (NPSI) [3] assesses the severity of 10 symptoms of neuropathic pain on a rating scale from 0 ("no pain") to 10 ("worst pain imaginable") for each. General health was evaluated at baseline with the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores of the SF-12 [40]; a score of <50 indicates below-average health status. Mental well-being was assessed at baseline with the Hospital Anxiety and Depression Scale (HADS) [44]; a score of >8 indicates probable anxiety or depression, and a score of >10 indicates certain impairment of mood. Patients' reports of zoster-related pain were collected in follow-up telephone interviews conducted by trained interviewers with the ZBPI and NPSI on day 15, and at months 1, 3, 6, 9, and 12. Patients' perceptions of the effect of zoster and zoster-related pain on daily life were collected at the same time. Patient reports of HRQoL were obtained with the SF-12 and HADS during the interviews at months 3, 6, and 12.

2.3. Statistical analyses

The risk of developing chronic zoster-related pain in patients aged >50 years with HZ was assumed to be 5% on the basis of data from a study conducted in the Netherlands, selected as a result of its rigorous methodology [27]. This risk is at the lower end of most other observed ranges of the risk of zoster-related chronic pain [14,21,36]. The number of patients required to estimate this proportion, with a 95% confidence interval and a given precision, was calculated from the following equation:

$$n = p \times (1 - p) \times \left(\frac{1.96}{e}\right)^2$$

where P = proportion to estimate and e = estimate precision. To estimate a 5% proportion with an α risk of 5% and a precision of 1.4% required 931 patients.

Considering a questionnaire nonreturn or unusable rate of approximately 15% for this type of study, the number of patients required was estimated to be 1100.

All statistical analyses were undertaken by SAS software, version 8.02 (SAS, Cary, NC). Quantitative variables were described by size, mean, standard deviation (SD), median, and range. Qualitative variables were described by their size and the percentage of

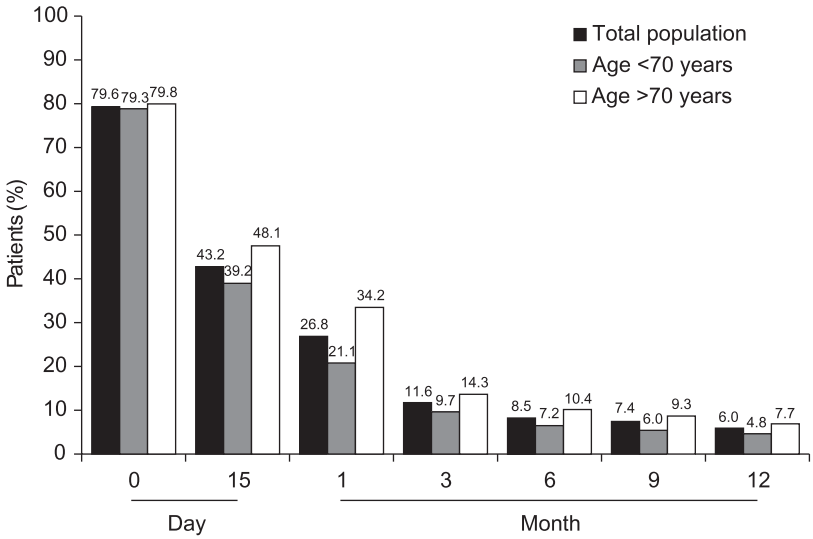

Fig. 2. Prevalence of zoster-related pain over 12 months of follow-up.

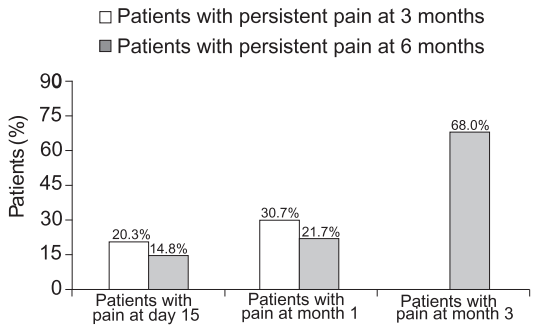

Fig. 3. Prevalence of postherpetic neuralgia at months 3 and 6 among patients with pain on day 15, and at months 1 and 3.

each modality. Missing data were not considered in the expression of the results. Changes from baseline in scores on the NPSI, ZBPI, SF-12, and HADS were compared by the paired Student's *t* test. If the conditions for this test were not met, the nonparametric Mann–Whitney–Wilcoxon test was used. If appropriate, 95% confidence intervals were calculated.

A logistic regression model was used to identify factors that may predict persistent zoster-related pain at ⩾3 months (ie, PHN). The outcome variable was the presence of zoster-related pain at ⩾3 months based on the answer to the question, "Do you still have pain associated with your shingles?" Univariate analysis was undertaken on each variable to identify possible associations with PHN.

Multivariate analysis was carried out by a stepwise selection process. Factors having a significant association with persistent zoster-related pain at month 3 (level of significance, 20%) on univariate analysis were entered into a logistic regression model as exploratory variables to identify possible predictors of PHN. The odds ratio for significant factors was calculated with 95% confidence intervals. Factors were selected by a backward calculation with an output threshold of 5%. A covariance analysis including all variables as fixed effects was used to identify possible predictors of the effect of the SF-12 PCS and MCS scores.

3. Results

3.1. Patient population

Between June 2007 and June 2008, 644 of the 1759 GPs across France who agreed to participate enrolled 1517 patients, of whom 1358 (89.5%) satisfied the inclusion criteria.

The mean age of participating GPs was 50.8 years (national mean, 50.4 years). The proportion of male GPs in the study (86.2%) was higher than the national proportion (68.8%) [10]. The regional distribution was close to that for GPs in France, with the exception of the Ile de France (Paris), in which the proportion of participants was low compared with the overall population [10].

Completed questionnaires were available for 1284 of 1358 (94.6%) patients on day 0, and for 1032 of 1358 (75.9%) patients at month 12. The mean ± SD age of patients at enrollment was 67.7 ± 10.7 (range 50–95) years, 44.9% of the population was aged ⩾70 years, and 17% were aged >80 years; 62.2% of patients were women; 23.3% of patients were working; and 97.1% lived at home or with close family or friends; and 2.7% were considered to be immunocompromised.

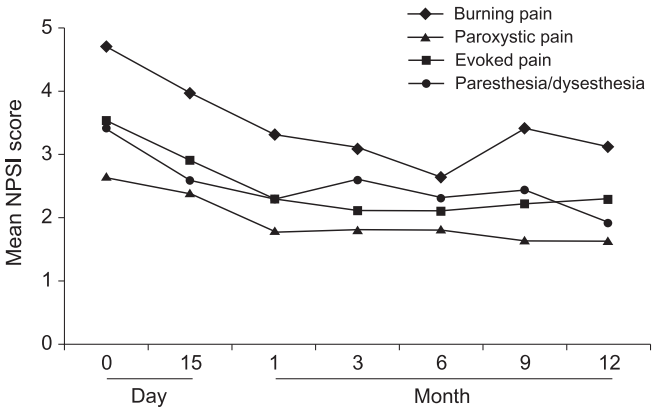

Fig. 4. Changes in NPSI subscores over 12 months of follow-up among patients with persistent pain. NPSI, Neuropathic Pain Symptom Inventory; range 0–100.

3.2. Clinical features and treatment of HZ

The mean ± SD time between onset of rash and the diagnosis of HZ was 2.6 ± 2.71 (median 2) days, and 77% of patients were diagnosed within 3 days of rash onset (based on patient report). Most patients (68.0%) had lesions on the trunk, most commonly in the thoracic region (47.6%). Rash distribution was similar in patients of all ages, but the proportions of patients with extensive rash, or with hemorrhagic or necrotic lesions, were higher in those aged ⩾70 years than in younger patients (Table 1). Antiviral drugs were prescribed to 94.1% of patients (systemic only 85%; topical only 1%; both systemic and topical 14%). Consistent with the recommendations of the French Society for Infectious Disease [30], the antiviral agents prescribed were valacyclovir (75.8%), acyclovir (12.5%), valacyclovir and acyclovir (10.1%), famciclovir (1.2%), and acyclovir and famciclovir (0.4%). Treatment was generally prescribed within 3 days after HZ onset (77% of patients), and the mean ± SD duration was 7.4 ± 2.0 (median 7) days. Analgesic agents were prescribed for 83.0% of patients. Anticonvulsant agents, tricyclic antidepressants, and other antidepressant agents were prescribed for 9.7%, 0.7%, and 0.4% of patients, respectively.

3.3. Zoster-related pain and HRQoL

On day 0, 79.6% of patients reported pain associated with HZ. The mean ± SD score on the DN4 questionnaire was 4.2 ± 1.9, and 61.8% of patients reported scores ⩾4. Of individual symptoms in the DN4 questionnaire, burning, allodynia, itching, and tingling were associated with the HZ rash on day 0 in 79.8%, 71.4%, 64.1%, and 58.0% of patients, respectively.

Zoster-related pain had a significant effect on patient HRQoL, from onset of the acute phase of the disease and during its evolution. At all time points, two-thirds of patients reporting persistent pain considered the effect of zoster-related pain on daily life to be "moderately severe" to "very severe," and one-quarter considered it "severe" or "very severe" (Fig. 1).

The prevalence of patient-reported pain declined over the first 6 months of follow-up but tended to stabilize thereafter, with similar proportions of patients reporting pain at months 6, 9, and 12 (8.5%, 7.4%, and 6.0%, respectively). Half of the patients describing pain at month 3 still had pain 12 months after onset (Fig. 2). At each time point, the prevalence of persistent pain was higher in patients aged ⩾70 years than in younger patients (Fig. 2). The difference was statistically significant at month 1 ($P < .001$), month 3 ($P = .02$), month 6 ($P = .04$), and month 9 ($P = .04$), but only close to significance at month 12 ($P = .06$).

The prevalence of patient-reported pain at months 3 and 6 was higher when established from patients who reported pain on day 15, and at months 1 and 3 (Fig. 3). More than two-thirds (68%) of patients with PHN at month 3 had persistent pain at month 6. The prevalence of pain was highest in the 91 (6.7%) patients with zoster ophthalmicus (20.3%, 16.2%, 15.7%, and 9.4% at months 3, 6, 9, and 12, respectively). The difference was statistically

significant at month 3 ($P = .02$), month 6 ($P = .02$), and month 9 ($P = .006$), but not at month 12 ($P = .235$).

Patients who had completed pain and HRQoL questionnaires at months 3, 6, 9, and 12 were compared with patients with incomplete data to enhance analysis on the global population. No difference was observed regarding proportion of patients with pain at each time (data not shown).

The NPSI identified burning as the predominant feature of neuropathic pain associated with HZ in patients with persistent pain at each time point (Fig. 4). Evoked pain usually resulted from light brushing and pressure.

In patients with persistent pain, the ZBPI interference score showed that HZ adversely affected general activity, sleep, and mood throughout the 12-month study period (Fig. 5). There was a worsening in the mean PCS score of the SF-12 from day 0 to month 12 in patients with persistent zoster-related pain (Fig. 6A), and they also had consistently lower scores on the MCS score than those without pain (Fig. 6B). Patients with persistent pain had higher scores for anxiety and depression on the HADS than those without pain at all time points (Fig. 6C and D).

The multivariate analysis identified that older age, male sex, decreased PCS, increased ZBPI score, and presence of comorbidities at baseline were predictive of the effect of HZ on the physical components (ie, decreased SF-12 PCS) at month 3 (Table 2). Regarding the effect on the mental component of quality of life (ie, SF-12 MCS), the predictive factors at baseline were higher average pain intensity, decreased MCS, and the presence of comorbidities (Table 2).

3.4. Predictive factors for persistent zoster-related pain

Univariate analyses found that potential predictive factors on day 0 for the persistence of pain at 3 months (ie, PHN) were older age, higher average pain intensity, higher NPSI total score, higher intensity of brush-evoked allodynia, DN4 score $\geqslant 4$, higher ZBPI interference score, and lower SF-12 PCS and MCS scores (Table 3). Multivariate analysis including these variables (Table 4) showed that independent predictive factors on day 0 for PHN were older age, male sex, DN4 $\geqslant 4$, higher ZBPI interference score, and lower PCS scores.

4. Discussion

To our knowledge, this is one of the largest prospective studies to evaluate the effect of HZ on daily life as perceived by the patient over 12 months. Although most patients (77%) received early treatment with antiviral drugs as recommended in the IHMF guidelines [13], HZ was described as a "painful and debilitating condition" (including during the acute phase) by a large proportion of patients, and zoster-related pain persisted for $\geqslant 12$ months in 6% of patients (8% of those aged $\geqslant 70$ years).

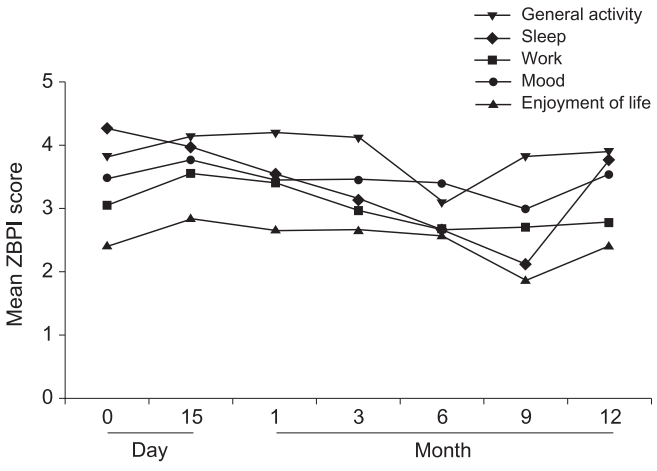

Fig. 5. Evolution of ZBPI scores over 12 months of follow-up among patients with persistent pain. ZBPI, Zoster Brief Pain Inventory; range 0 ("no pain") to 10 ("pain as bad as you can imagine").

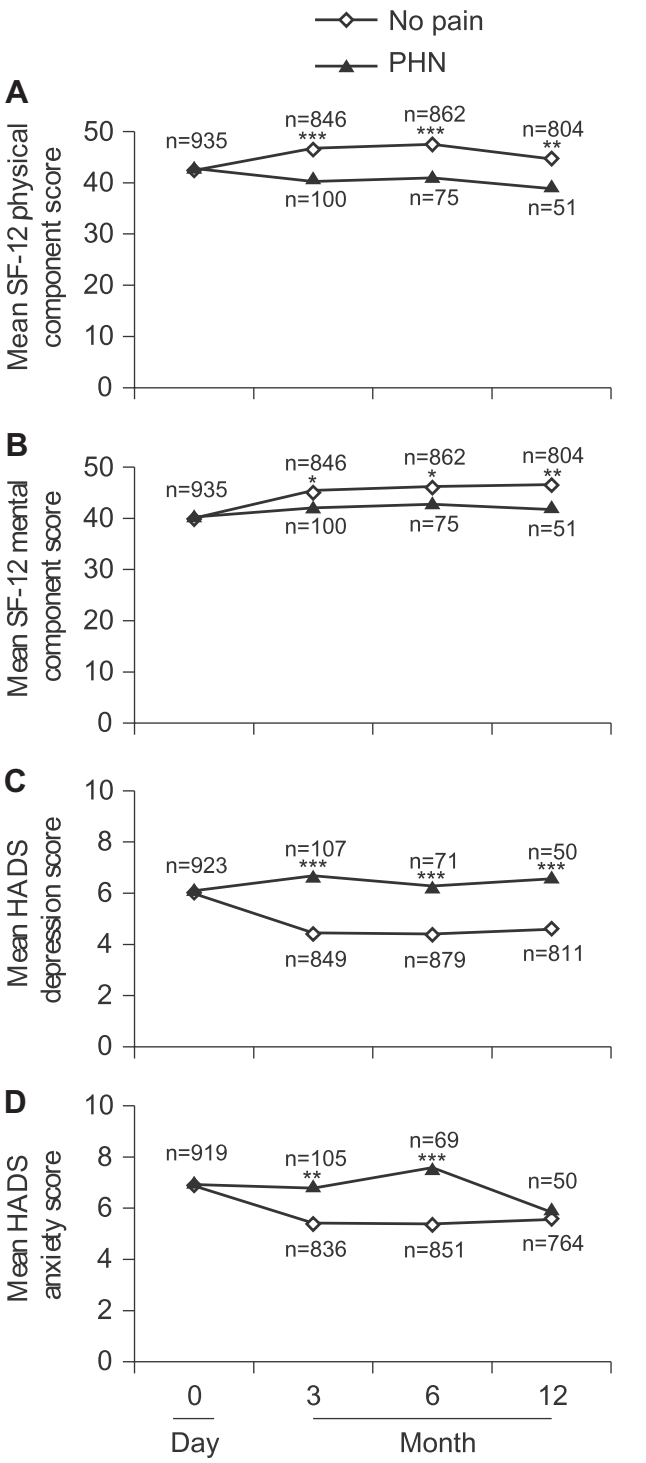

Fig. 6. Evolution of the mean Physical Component Summary score (PCS) (A) and Mental Component Summary (MCS) score (B) of the 12-item short-form health survey (SF-12) and of the anxiety (C) and depression (D) scores of the Hospital Anxiety and Depression Scale (HADS) over 12 months of follow-up in patients with or without postherpetic neuralgia (PHN). The number of patients in each group at each time point is indicated. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ for comparisons between patients with or without PHN.

Table 2
Multivariate analysis for the identification of potential predictive factors for the effect of herpes zoster on quality of life at 3 months.

Factor	PCS		MCS	
	F value	*P* value	*F* value	*P* value
Age, y	21.04	<.001	1.93	.165
Sex	4.44	.035	0.34	.558
Average pain intensity	1.34	.263	4.85	.008
PCS	113.32	<.001	0.01	.919
MCS	3.70	.054	79.58	.008
DN4 score	0.46	.500	0.74	.478
ZBPI interference score	9.37	.002	3.43	.064
comorbidities	7.27	.007	3.83	.050

PCS, Physical Component Summary; MCS, Mental Component Summary; DN4, Douleur Neuropathique en 4 Questions; ZBPI, Zoster Brief Pain Inventory.

Table 3
Univariate analyses to identify potential risk factors at day 0 that may be predictors of the presence of postherpetic neuralgia at 3 months.[a]

Day 0 criteria	Postherpetic neuralgia		*P* value
	Yes (n = 127)	No (n = 964)	
Age, n (%)			.021
<70 y	61 (48.0)	566 (58.8)	
⩾70 y	66 (52.0)	396 (41.2)	
Sex, n (%)			.062
Male	57 (44.9)	349 (36.4)	
Female	70 (55.1)	611 (63.6)	
Family situation, n (%)			.657
Married/cohabiting	82 (71.3)	549 (66.1)	
Single	8 (7.0)	57 (6.9)	
Divorced or separated	10 (8.7)	82 (9.9)	
Widowed	15 (13.0)	143 (17.2)	
Living arrangements, n (%)			.097
At home	115 (100.0)	808 (97.5)	
In an institutional facility	0 (0.0)	21 (2.5)	
Delay in diagnosis, n (%)			.086
⩽1 d	59 (46.8)	352 (37.0)	
1–2 d	20 (15.9)	235 (24.7)	
2–3 d	19 (15.1)	146 (15.4)	
>3 d	28 (22.2)	218 (22.9)	
Associated disease, n (%)			.099
Yes	86 (68.3)	581 (60,6)	
No	40 (31.7)	377 (39.4)	
Average pain intensity (ZBPI)			<.001
No.	113	803	
Mean ± SD	5.3 ± 2.39	4.1 ± 2.42	
Pressure allodynia (NPSI)			.058
No.	98	724	
Mean ± SD	4.9 ± 3.3	4.2 ± 2.99	
Brush-evoked allodynia (NPSI)			.008
No.	98	724	
Mean ± SD	4.7 ± 3.3	3.8 ± 3.0	
Global DN4 score, n (%)			<.001
⩾4	95 (74.8)	562 (58.4)	
<4	32 (25.2)	400 (41.6)	
NPSI score, n (%)			<.001
0–30	25 (34.2)	329 (52.7)	
40–70	44 (60.3)	288 (46.2)	
80–100	4 (5.5)	7 (1.1)	
ZBPI interference score, n (%)			<.001
0–3	30 (31.6)	431 (57.8)	
4–6	19 (20.0)	161 (21.6)	
7–10	46 (48.4)	154 (2.6)	
SF-12 Physical Component score			<.001
No.	88	685	
Mean ± SD	39.4 ± 10.14	44.7 ± 9.85	
SF-12 Mental Component score			.028
No.	88	685	
Mean ± SD	38.7 ± 10.49	41.6 ± 11.20	
Anxiety (HADS), n (%)			.350
No	52 (61.9)	461 (67.0)	
Yes	32 (38.1)	227 (33.0)	
Depression (HADS), n (%)			.074
No	49 (60.5)	487 (7.2)	
Yes	32 (39.5)	207 (29.8)	
Analgesic treatment, n (%)			.115
Yes	110 (86.6)	776 (8.6)	
No	17 (13.4)	187 (19.4)	

[a] DN4, Douleur Neuropathique en 4 Questions; range, 0–10; score ⩾4 indicates neuropathic pain; HADS, Hospital Anxiety and Depression Scale; range 0–21 for anxiety and depression; NPSI, Neuropathic Pain Symptom Inventory; range 0–100; SF-12, 12-item short-form health survey; score <50 indicates below-average health status; ZBPI, Zoster Brief Pain Inventory; range 0 ("no pain") to 10 ("pain as bad as you can imagine").

Rash distribution and pain severity in patients at enrollment were similar to those described in an epidemiological study of HZ in France [6]. As described in the literature [21], zoster ophthalmicus was associated with a higher risk of zoster-related pain. The proportions of patients with zoster-related pain at months 1, 3, and 6 reported here are similar to those of the placebo arm of the placebo arm of the prospective Shingles Prevention Study [29], although we should be cautious regarding such comparisons because different definitions of PHN were used in these 2 studies. In the present study, 77% of patients received antiviral therapy within 72 h of rash onset, compared with 65.9% of patients in the placebo arm of the Shingles Prevention Study [29]. This early initiation of treatment with antiviral and analgesic agents, in accordance with current recommendations, may also be responsible for the lower prevalence (11.6%) of persistent zoster-related pain at month 3 compared with reports of PHN in ⩾20% of elderly patients in other studies [11,12,17,35]. Although the present study was not designed to assess the efficacy of the antiviral therapy, our results confirm that, even with optimal early treatment, an important proportion of patients will develop PHN [24], with a major effect on the health and HRQoL of the elderly.

Consistent with previous studies, zoster-related pain was associated with marked reductions in HRQoL in the acute phase [6,9,11,23,26,33,34,41], and also in patients with persistent pain [6,9,11,28,35,38,39,41]. As reported previously, zoster-related pain interfered with general activity, sleep, and mood [6,11,25,28,41], and patients with more severe pain were more likely to report symptoms of anxiety and depression [28,32].

Identification of patients at the greatest risk of PHN can help to ensure that they receive optimal treatment to reduce that risk. Diagnosed neuropathic pain on day 0, as indicated by a DN4 questionnaire score ⩾4, was identified to be an independent predictor of persistent pain. Thus, it seems that pain quality, rather than just pain intensity, confers a greater risk of persistent zoster-related pain, as identified in previous studies. The DN4 questionnaire is simple to administer and could be used by GPs to identify patients with acute HZ who are at the greatest risk of developing PHN. Univariate analysis also identified average daily pain intensity, the ZBPI interference score (which measures effect of pain on daily activities), and the presence of allodynia as evaluated by the NPSI as potential predictors of PHN.

Several studies have found that older age is an important risk factor for PHN [7,8,11,16,22,27,39]. In the present study, age ⩾70 years was found to be an independent predictor of PHN. This age cutoff was selected for consistency with the efficacy analysis of the Shingles Prevention Study, which compared the incidence of HZ and PHN in 2 groups receiving a shingles (HZ) vaccine or a placebo [29].

The finding that male sex was an independent predictor of persistent zoster-related pain is in contrast to other studies, which found no difference between the sexes [7,16,27], or an increased risk in women [4,8,14,22]. Possible reasons include differences between studies in the number of patients surveyed and the methods used to evaluate pain.

Some important limitations of the study should be noted. Approximately 10% of invited GPs agreed to participate in the study, but this proportion is typical for observational studies. In

Table 4
Multivariate analysis showing independent risk factors for the development of postherpetic neuralgia.[a]

Factor	Odds ratio	95% confidence interval	*P* value
Sex (M vs F)	1.81	1.11–2.94	.015
Age	1.28	1.05–1.55	.013
DN4 score	1.78	1.03–3.06	.031
ZBPI interference score	1.18	1.05–1.31	.004
PCS	0.72	0.55–0.92	.011

[a] The multivariate analysis found that the following were independent risk factors for the development of postherpetic neuralgia: sex (male vs female), Douleur Neuropathique en 4 Questions (DN4) score ($\geqslant$4 vs <4), Zoster Brief Pain Inventory (ZBPI) score (as a continuous variable), and Physical Component Summary (PCS) score (as a continuous variable). The other variables included in the model were: Mental Component Summary (MCS) score ($P = .59$), intensity tactile allodynia from the NPSI ($P = .43$), and average pain intensity ($P = .54$), all expressed as continuous variables.

addition, identification of HZ was based on the GP's clinical evaluation, as the diagnosis is generally clinical and straightforward; in the Canadian prospective study, the presence of varicella zoster virus DNA confirmed the clinical diagnosis in 95% of the tested cases [11]. However, the present study also had several strengths. First, it involved >1300 participants, of whom 75.9% completed the 12-month follow-up. Indeed, the number of included patients was higher than planned, giving greater precision to the results. Second, the prospective design, in which patients were enrolled at HZ onset and followed over 12 months, enabled assessment of the evolution of zoster-related pain and its effect on HRQoL as perceived by the patient during the acute and chronic phases of disease. Third, the study used a precise definition of zoster-related pain (pain in the region of the HZ rash) to minimize the risk of confusion with comorbid pain conditions. Fourth, the use of several pain questionnaires that assign numerical values to different levels of pain severity allowed detailed evaluation of the various aspects of zoster-related pain, and there was good consistency between the results of the questionnaires. Finally, the study utilized self-reporting of zoster-related pain by patients, thereby avoiding the bias of misestimation by GPs; clearly patients are the best experts on their pain and its effect on daily life.

In summary, this large prospective cohort study demonstrated that even if patients with HZ receive the current standard of care (early diagnosis and treatment with antiviral agents), many will experience marked and often persistent pain that can significantly impair their functional status and HRQoL over the long term. Current strategies for the treatment of HZ and management of the associated pain are only partially effective, and this remains an area of unmet medical need [21]. This comprehensive evaluation from the patient's perspective over 12 months provides new information on the burden of HZ and PHN. It identified specific factors at presentation, including age $\geqslant$70 years, interference of pain on daily activities (ZBPI score), and neuropathic quality of pain (DN4 questionnaire), which may help identify patients who will develop PHN.

Conflict of interest statement

All authors were members of the study scientific committee for which they received grants. JG, TH, OL, CM, CR, OR, and CS are members of Avancées Vaccinales, a French vaccine expert group supported by an unrestricted grant from Sanofi Pasteur MSD that, in general, advises on and advocates vaccination. The use of the DN4 and NPSI questionnaires is subject to fees for their developers, including DB.

Acknowledgment

Supported in part by Sanofi Pasteur MSD, Lyon, France.

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