Signal

Yellow Fever Vaccine and Herpes Zoster

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Summary

This report contains 29 well documented cases of herpes zoster occurring a median of 6 days after 17D Yellow fever vaccination which were retrieved from VigiBase, a computerized pharmacovigilance system that collects reports from national pharmacovigilance centers in the 125 countries in the WHO Program for International Drug Monitoring UMC in Uppsala. The 17D YFV is a highly immunogenic and effective vaccine leading to viral replication and subsequent induction of protective immunity which may interfere with VZV viral latency and immune surveillance and thus favor the appearance of herpes zoster. Current labelling does not include reference of the risk of herpes zoster, which, although a causal relationship cannot be established with certainty should be mentioned.

Signal

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Restricted

Introduction

Yellow fever (YF) is a mosquito-borne viral disease caused by Yellow fever virus (YFV) a flavivirus with a single serotype that is antigenically conserved whose clinical presentation varies from mild febrile illness to very severe disease with hemorrhagic fever. It is a tropical and travel related disease and particularly present in Africa and South America, causing up to 200'000 symptomatic cases and 30'000 deaths per year[1]. To date, there is no specific therapy and the most important means of prevention is the live attenuated 17D YF vaccine (YFV), which is recommended for travelers and general population of endemic zones. The study of its safety profile has started long time ago, as its use began in the 1930s, but until recently, the too small number of reported adverse events to yellow fever vaccine could not allow a complete assessment of its side effects. In 2001 WHO recommended to reinforce surveillance through detecting any YF adverse event[2], which allowed to individuate a possible correlation between YFV and adverse reactions.

Methods

VigiBase, a computerized pharmacovigilance system that collects reports from national pharmacovigilance centers in the 125 countries in the WHO Program for International Drug Monitoring, was the original data source. All reports for YFV and herpes zoster (HZ) were identified for this investigation.

Current information about zoster-like reactions to YFV was searched also in pharmaceuticals labels and in international specific medical or drug databases.

Reports in VigiBase

A total of 33 Individual Case Safety Reports (ICSRs) with the combination yellow fever vaccine and shingles or herpes zoster, associated with all licensed 17D vaccines, have been reported between August 2000 and July 2018. They were retrieved from VigiBase, the WHO global database of ICSRs, on April 2019 and were reviewed case by case.

Four duplicate reports were identified, therefore only 29 cases were considered. 5 reports (17.24%) included symptoms of systemic inflammation (fever, asthenia, flu-like illness, etc.). Case series distribution of gender, age, seriousness and concomitant vaccines is set out in Table 1.

The origin of the cases were from North America (6 from the USA, 2 from Canada), European countries (7 from Germany, 6 cases were found in France, 2 in Switzerland, 2 in UK, one single case in the Netherlands, In Denmark and in Spain) and one event was reported in South Africa.

24 reports included the patients age at onset of the symptoms, which ranged from 14 to 79 years. Events in females occurred and were then described in 10 reports, 18 in male, while the gender was not specified in one report.

Table 1.

Variable	**General population** N=29
Patient female gender (%)	10 (34.5%)
Age at onset (y)	48.79 ± 18.15 (range 14 - 79)
Age ≤ 49 years	13 of 24 (44.8%)
Time to HZ onset (days)	4 [6] (range 0 - 90)
Number of cases reported as serious (%)	9 (31%)
Administration of concomitant vaccines	18 (62.1%)
• concomitant live vaccine (live attenuated thyphoid vaccine)	1 (3.4%)
• concomitant non-live vaccines	17 (58.6%)
• concomitant polysaccharide vaccines	5 (17.2%)

Table 1. Data are mean±SD, median (IQR) or n (%)

The time to onset of herpes zoster manifestations ranged from 12 hours to 90 days with a median time to onset of 6 days. In 3 reports there was no information regarding the time to onset, while in 2 cases this was over 3 weeks (45 and 90 days respectively)

Concomitant vaccines were administered in 18 cases. In 2 ICSRs other concomitant medications were reported. In one case the patient was under PPI, statin and amlodipine; in the other the vaccinee was using a statin regularly.

9 out of 29 cases were considered serious (31%), 2 of them because of prolonged hospitalization, one because of disabling consequences, in the other 6 reports the cause was not further described.

Probability of causality was judged directly by reporters in 9 cases: 6 episodes were defined as unlikely, 2 as possible and 1 as unclassifiable. In one case, the field was left empty, but we could establish, thanks to the case narrative and sender's comments, that it was a case of HZ recurrence after one month of the last episode.

Average age at herpes zoster onset was 48.79 in a range from 14 to 79, with 54.2% of patients younger than 50 years old. Also, among serious cases, half were younger than 50 years old.

Literature and labelling

Few similar cases have been previously described in the international literature. One perineal and one thoracic HZ occurred in two immunocompetent individuals 2-3 weeks after YF vaccination and were reported in 2001 at the 7th conference of the International Society of Travel Medicine in Innsbruck, Austria. One other case was reported in Spain in 2001, 3 days after YFV, occurring in a healthy 64-year-old woman[3].

The product label of Sanofi Pasteur Inc., published among the other sites in Dailymed, VaccineShoppe and in the USFDA web pages, cites, under "post-marketing experience", different neurological complications like Guillain-Barré syndrome, acute disseminated encephalomyelitis, YEL-AVD and bulbar palsy. The European Medicine Agency and the Australian Therapeutic Goods Administration add convulsion and focal neurological deficits.

Both UKeMC and Codifa, an italian pharmaceutical information tool, illustrate, among the others, paresthesia as possible peripheral nervous adverse reaction, but don't quote any herpes zoster.

Among other drug information sources, Micromedex Drugdex mentions dermatologic effects like injection site edema/severe rash or urticaria, hepatic complications, hypersensitivity reactions, myalgia, fever, or influenza-like illness, headache, multiple organ failure, yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and different neurological effects: acute disseminated encephalomyelitis, Guillain-Barre syndrome, meningoencephalitis, post yellow fever vaccination encephalitis, progressive bulbar palsy, seizures and acute transverse myelitis. Micromedex Martindale adds that YFV may be possible porphyrinogenic.

No mention is done to possible zoster or zoster-like reactions in the Swiss label, UpToDate, Gideon Guide to Vaccines and Globulin Preparations 2019 nor in CDC vaccine information statement.

Discussion and conclusion

We describe a case series of 29 adult patients who developed HZ after YFV. The question arises is whether this might be due simply to chance or due to a causal relation between injection of 17D YF vaccine virus and subsequent reactivation of VZV in the form of herpes zoster.

The time to onset was a median of 6 days after receiving the vaccine. It has been shown that the protective effect of 17D YFV is mediated by the induction of humoral immunity and stimulation of CD4+ T cells[4]. This is concomitant with the decline of viremia that peaks at day 5 after vaccination and at least 3 days after serum chemokines (IL-8/CXCL-8, MCP-1/CCL-2, MIG/CXCL-9 and IP-10/CXCL-10) and pro-inflammatory cytokines (gamma-IFN and TNF) rise significantly above pre-vaccination serum levels[5]. In another study on the kinetics of the innate immune response in the peripheral blood following 17DD yellow fever (17DD-YF) first-time vaccination the researchers observed an increased frequency of monocytes and NK cell subpopulations besides an up-regulation of granulocytes activation status (CD28+/CD23+ and CD28+/HLA- DR+, respectively). Up-regulation of Fc gamma-R and IL-10-R expression emerge as putative events underlying the mixed

pattern of phenotypic features triggered by the 17D yellow fever (17DD-YF) vaccination. Mixed pattern of chemokine receptors expression is compatible with the interpretation that a parallel establishment of activation/modulation of microenvironment is triggered by the 17D-YF vaccine[6]. The systemic nature of this reaction may interfere with immune control of VZV and may lead to herpes zoster.

No case report contained other known risk factors that are associated with VZV reactivation such as immunosuppressive treatments or comorbidities favoring VZV reactivation[7] apart from one case receiving statin treatment which due to their immunomodulating properties may increase the risk of varicella zoster virus reactivation[8].

While it is reported, in the available literature, that up to 68% of herpes zoster cases occur in individuals aged 50 years and older[9], the 24 reports where age group was stated show a slightly younger average age and the majority (54.2%) belonged to the category ≤ 49 years. This may be another argument in favor of a causal relationship between 17D YFV vaccination and herpes zoster but may also simply be due that the age distribution of YFV vaccinees is different from that of the general population.

The reported cases thus provide circumstantial evidence for a possible causative effect of the 17D-YF vaccine on VZV reactivation probably due to the systemic immune activation provided by the live vaccine which should be reported in the vaccine label.

References

1. «District guidelines for yellow fever surveillance». [In linea]. Available at: https://apps.who.int/iris/handle/10665/64384. [Consultato: 04-ago-2019].

2. M. S. Cetron et al., «Yellow fever vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002», MMWR Recomm. Rep. Morb. Mortal. Wkly. Rep. Recomm. Rep., vol. 51, n. RR-17, pagg. 1–11; quiz CE1-4, nov. 2002.

3. J.-M. Bayas, R. González-Alvarez, e C. Guinovart, «Herpes zoster after yellow fever vaccination», J. Travel Med., vol. 14, n. 1, pagg. 65–66, feb. 2007.

4. A. M. Watson, L. K. M. Lam, W. B. Klimstra, e K. D. Ryman, «The 17D-204 Vaccine Strain- Induced Protection against Virulent Yellow Fever Virus Is Mediated by Humoral Immunity and CD4+ but not CD8+ T Cells», PLoS Pathog., vol. 12, n. 7, pag. e1005786, 2016.

5. A. C. Campi-Azevedo et al., «Subdoses of 17DD yellow fever vaccine elicit equivalent virological/immunological kinetics timeline», BMC Infect. Dis., vol. 14, n. 1, pag. 391, lug. 2014.

6. M. A. Martins et al., «Innate immunity phenotypic features point toward simultaneous raise of activation and modulation events following 17DD live attenuated yellow fever first-time vaccination», Vaccine, vol. 26, n. 9, pagg. 1173–1184, feb. 2008.

7. K. Kawai e B. P. Yawn, «Risk Factors for Herpes Zoster: A Systematic Review and Meta- analysis», Mayo Clin. Proc., vol. 92, n. 12, pagg. 1806–1821, dic. 2017.

8. L. Fan, Y. Wang, X. Liu, e X. Guan, «Association between statin use and herpes zoster: systematic review and meta-analysis», BMJ Open, vol. 9, n. 2, pag. e022897, feb. 2019.

9. B. P. Yawn, P. Saddier, P. C. Wollan, J. L. St Sauver, M. J. Kurland, e L. S. Sy, «A population- based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction», Mayo Clin. Proc., vol. 82, n. 11, pagg. 1341–1349, nov. 2007.

SANOFI PASTEUR

July 15, 2020

Reference: Invitation to Comment on Draft WHO Signal on Yellow Fever Vaccines and Herpes Zoster

Thank you for the opportunity to comment on the WHO UMC draft signal text with a patient safety concern on Yellow Fever Vaccine (YFV) and Herpes Zoster (HZ).

Background

Sanofi Pasteur is the market authorization holder (MAH) of two live attenuated yellow fever 17D-204 vaccines: Stamaril® and YF-VAX®.

Sanofi Pasteur has not previously identified a safety signal for HZ following any of its YFVs.

In response to this invitation to comment, Sanofi Pasteur performed a literature search, a query of its Global Pharmacovigilance (GPV) database and an observed to expected analysis.

Results

From 01 January 1993 (date of initial GPV database set-up) to 31 May 2020, MAH retrieved 41 cases: 31 after Stamaril (around 569.4 million doses distributed worldwide), 7 after YF-VAX (15.37 million doses distributed worldwide) and 3 after YFV from an unknown manufacturer (MFR UNK). Following individual medical review, 25 cases were excluded from the analysis: 17 cases with primary varicella-zoster virus; 1 case with relapse of herpes NOS[a]; 3 cases identified as triplicates and 4 cases with time to onset > 2 months.

For the 16 remaining cases, 12 involved Stamaril, 3 YF-VAX and 1 YFV MFR UNK. Three cases came from North America, 11 from Europe and 2 from other countries. The characteristics (country, age, gender, latency, seriousness, concomitant drug use) of these 16 cases were similar to the 27 cases from VigiBase.

The HZ cases occurred from 2 to 18 days post-vaccination (62.5% occurring within the first week) with a median time-to-onset of 7 days. The time-to-onset is concurrent with the transient, low-titer viremia that usually occurs within 3-7 days after YF vaccination and persist for 1- 3 days.

Among the 16 cases, 6 (37.5%) were reported in older patients (>50-yo). Two male elders (75-yo) reported additional conditions identified as risk factors for HZ reactivation that confounded the causality assessment, including diabetes, recent history of HZ and probable fever-induced reactivation. A 56-yo woman had a medical history of celiac disease and a recent cold sore. A 64-yo woman, who received simultaneous vaccinations, was diagnosed with right brachial HZ 4 days after administration of Stamaril. The effect of simultaneous vaccinations

a Not other specified

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cannot be assessed despite the rash appeared on Stamaril injection side. This case was also retrieved in the literature search.[1] The other two cases in older adults were insufficiently documented.

Ten cases were reported in younger patients (<50-yo). Three of them were immunocompetent adults: a 43-yo man developed shingles 6 days after a Stamaril dose and was also exposed to emotional stressors. A 47-yo woman with previous HZ experienced perineal zoster 2 weeks after simultaneous vaccinations, including Stamaril. A 24-yo man experienced thoracic zoster 3 weeks after a Stamaril dose. The latency appears too long based on potential effects of YF viremia on cellular immunity, making the role of the vaccine unlikely. For the 7 remaining cases, the time-to-onset ranged from 2 to 10 days, making the role of the vaccine possible. However, information on the medical histories were missing to assess these patients.

The resulting reporting rate of HZ in MAH's PV database is 0.03 cases per million doses distributed. HZ remains as a very rarely reported AE temporarily linked to YF vaccination. Findings of an observed to expected analysis with conservative estimates, provided evidence against an increased risk of HZ following YFV for a 14-day risk window. A similar result was obtained with a 21-day risk window. Risk window of HZ reactivation between 1 to 14 days and 1 to 21 days after YFV administration was determined for the purpose of this analysis based on potential effects of YF viremia kinetics on cellular immunity.

A literature review was conducted for articles reporting YFV and HZ. One article was retrieved pertaining YFV and brachial HZ commented above. One abstract reported HZ 2- and 3-weeks after YFV in immunocompetent subjects[2]. Rare AEs temporally related to 17D YFVs have been reported, including HZ. They likely represent chance associations in time.[3]

Two articles resulted when the search was extended to ALL vaccines: one described HZ reactivation after each course of multiple routine vaccines in a 13-yo girl with relapsing acute lymphoblastic leukemia who received an HPT[b] in the UK[4]. The other discussed HZ after influenza vaccine, hepatitis A vaccine and simultaneous administration of rabies and Japanese encephalitis vaccines.[5]

Discussion

More than 90% of HZ cases occur in immunocompetent individuals; however, immunosuppression increases the risk by 20- to 100-fold.[6] A higher proportion of younger patients <50-yo was observed in VigiBase and MAH's GPV database, compared with 32% of cases occurring in those <50-yo in the general population.[7] Interestingly, HZ was more often reported in men (69%) than in women (31%) following YFV, contrasting with the finding that the incidence rate of HZ is higher in women than men in the general population[8]. The age and sex distribution of the spontaneously reported HZ cases may reflect the characteristics of the target group of vaccination with Stamaril and YF-VAX, i.e., travelers and people living in endemic areas.

[b] HPT: Hemopoietic progenitors transplant

Several risk factors have been linked to HZ, mainly related to a decrease in T-cell immunity, but some are related to family history, ethnicity, physical trauma, stress or mental disorders. However, vaccination[c] has not been described as a risk factor although anecdotical HZ cases temporarily linked to vaccines are retrieved from the literature but causal association to vaccination have not been addressed through epidemiological research. Vaccine-induced immunomodulation has been observed, but the exact mechanism remains elusive.[9]

Conclusion

Despite the temporal association and a mechanistic proposal, a comprehensive review of the available data in the MAH's GPV database is not suggestive of a causal relationship between vaccination with Sanofi Pasteur's YFVs and HZ. The association might be valid for any other vaccine concomitantly administered for this very rare case reports. As a result, Sanofi Pasteur considers that there is no need to include HZ in the labelling. Notwithstanding these findings, occurrence of HZ will continue to be monitored through routine pharmacovigilance activities.

References

1 Bayas J, Gonzalez-Alvarez R, Guinovart C. Herpes Zoster after Yellow Fever vaccination. Journal of Travel Medicine 2007;14(1):65-66

2 Djoussou F , Malvy D , Hernandez-Martinez JP , et al . Zoster as side effect to the 17D yellow fever vaccine: two cases. Abstract presented at the 7th Conference of the International Society of Travel Medicine; May 27–31, 2001; Innsbruck, Austria

3 Plotkin's Vaccines. 7th Ed. Ed. Elsevier, 2017

4 Patel S, Ortin M. Varicella-Zoster Reactivation in a Patient Receiving Routine Revaccinations After an Allogeneic Hemopoietic Progenitors Transplant. Journal of Pediatric Hematology/Oncology 2005;27(2):106-108

5 Walter R, Hartmann K, Fleisch F, et al. Reactivation of herpesvirus infections after vaccinations? Lancet 1999;353:810

6 O'Connor K, Paauw D. Herpes zoster. Med Clin N Am 2013;97:503-22.

7 Yawn BP and Gilden D. The global epidemiology of herpes zoster. Neurology 2013;81(10): 928-930

8 Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. *BMC Infect Dis.* 2015;15:502.

9 Walter R, Hartmann K, Fleisch F, Reinhart W et Kunh M. Reactivation of herpesvirus infections after vaccinations? Lancet 1999;353:810

c Other than VZV vaccination

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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