Vaccine 33 (2015) 3129–3134

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety, tolerability, and immunogenicity of zoster vaccine in subjects on chronic/maintenance corticosteroids☆

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ARTICLE INFO

Article history:
Received 20 October 2014
Received in revised form 24 April 2015
Accepted 27 April 2015
Available online 8 May 2015

Keywords:
Herpes zoster
Zoster vaccine
Safety
Tolerability
Immunogenicity

ABSTRACT

Background: This randomized, placebo-controlled study assessed the safety, tolerability, and immunogenicity of live virus zoster vaccine (ZV) in individuals receiving chronic/maintenance systemic corticosteroid therapy (daily dose equivalent of 5–20 mg prednisone) for ≥2 weeks prior to vaccination and ≥6 weeks postvaccination.

Methods: Subjects were followed for adverse experiences (AEs), exposure to varicella or herpes zoster (HZ), or development of varicella/varicella-like or HZ/HZ-like rashes for 42 days postvaccination (primary safety follow-up period) and for serious AEs (SAEs) through Day 182 postvaccination (secondary follow-up period). Varicella-zoster virus (VZV) antibody titers by glycoprotein enzyme-linked immunosorbent assay (gpELISA) were measured at baseline and at Week 6 postvaccination.

Results: The proportions of subjects reporting systemic AEs and SAEs were similar in both groups. A higher percentage of subjects reported injection-site AEs in the ZV group (21.5%) than in the placebo group (12.1%). One SAE of ophthalmic HZ (onset Day 16 postvaccination) was reported in the ZV group and deemed vaccine-related by the study investigator; however, PCR testing confirmed the presence of wild-type (not vaccine strain) VZV.

Geometric mean titer (GMT) at 6 weeks postvaccination was higher for ZV recipients than placebo recipients, with estimated geometric mean fold rises (GMFR) of 2.3 (CI: 2.0, 2.7) and 1.1 (CI: 1.0, 1.2) respectfully.

Conclusions: In adults ≥60 years old on chronic/maintenance corticosteroids, ZV was generally well tolerated and immunogenic. The VZV-specific gpELISA antibody GMT at 6 weeks postvaccination and the GMFR from baseline to 6 weeks postvaccination were higher in the ZV group than in the placebo group.

Abbreviations: AE, adverse experience; AEMS, Adverse Experience Monitoring Study; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control; CI, confidence interval; CMI, cell-mediated immunity; COPD, chronic obstructive pulmonary disease; GMFR, geometric mean fold rise; GMT, geometric mean titer; gpELISA, glycoprotein enzyme-linked immunosorbent assay; HZ, herpes zoster; PCR, polymerase chain reaction; SAE, serious adverse experience; SEC, Safety Evaluation Committee; SPS, Shingles Prevention Study; VRC, Vaccination Report Card; VZV, varicella-zoster virus; ZV, zoster vaccine.

☆ Data from this manuscript were presented in poster format at the ACR/ARHP Scientific Meeting, Chicago, IL, 2011.

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http://dx.doi.org/10.1016/j.vaccine.2015.04.090
0264-410X/

1. Introduction

Herpes zoster (HZ) is caused by a reactivation of the varicella-zoster virus (VZV), which has remained latent in the cranial nerve and sensory ganglia since primary VZV infection [1–3]. Clinically, HZ is characterized by a painful, unilateral, dermatomal, vesicular rash, and may be complicated by post-herpetic neuralgia in 10%–50% of cases [3,4]. Zoster vaccine (ZV: ZOSTAVAX®; zoster vaccine live, Merck & Co., Inc.), a live attenuated VZV vaccine, is licensed for prevention of HZ and its complications in adults ≥50 years of age.

All prior studies in the clinical development of live virus ZV have excluded individuals receiving systemic corticosteroid therapy at doses greater than required for physiologic replacement (≥5 mg of daily prednisone or equivalent for ≥2 weeks). However, subjects who are receiving higher doses and longer durations of systemic corticosteroids for treatment of chronic inflammatory conditions may benefit from vaccination with ZV, since the immunosuppressant effects of chronic systemic corticosteroid therapy may increase the risk of developing HZ. Although receiving a live attenuated vaccine such as ZV poses a potential safety risk in this patient population that is greater than in the general population, exposure to vaccine virus in a controlled clinical setting is expected to be preferable to developing HZ. Therefore, vaccination, if well tolerated, is desirable for this population.

This study (NCT00546819) was designed to evaluate the safety, tolerability, and immunogenicity of ZV in individuals receiving chronic/maintenance systemic corticosteroid therapy (daily dose equivalent of 5–20 mg prednisone) for ≥2 weeks prior to vaccination, and ≥6 weeks postvaccination. Subjects were not eligible to participate in the study if they were receiving other concomitant immunosuppressive therapies.

2. Methods

2.1. Study population

Varicella-zoster virus (VZV)-experienced adults ≥60 years of age who were receiving chronic/maintenance systemic corticosteroid therapy (daily dose of 5–20 mg of prednisone or equivalent) for at least 2 weeks prior to vaccination and 6 weeks or more following study vaccination were eligible for the study. Subjects were excluded if they had a prior history of HZ; previous vaccination with any VZV-containing vaccine; immune dysfunction (other than the condition requiring corticosteroid use); received immunosuppressive medications (including corticosteroids at a daily dose of >20 mg of prednisone or equivalent) within 8 weeks prior to vaccination or expected for 6 weeks postvaccination; received blood products within 5 months prior to vaccination through 6 weeks postvaccination; had hypersensitivity or anaphylactic reactions to gelatin or neomycin; currently were using any form of non-topical antiviral therapy; or received any live vaccine within 4 weeks prevaccination, any inactivated vaccine within 7 days prevaccination, or either during the study period. The protocol was conducted in accordance with principles of Good Clinical Practice, approved by the Ethical Review Committee of each participating country/site, and written informed consent was obtained from each subject prior to study entry.

2.2. Vaccine

The lyophilized ZV (lots WL00010964, WL00027069, WL00030806, WL00031970, and WL00032884) and placebo (lots WL00018605 and WL00026615) were supplied in 0.7 mL single-dose vials and stored at −15 °C or colder. The placebo contained the same stabilizers as the ZV but no live virus or virus components. ZV and placebo were reconstituted with sterile diluent immediately prior to administration. All subjects received a single 0.65 mL subcutaneous injection of either ZV or placebo in the deltoid area.

2.3. Study design

This was a randomized, double-blind, placebo-controlled, multicenter (45 sites) study conducted in North America and Europe between October 2007 and August 2010. Subjects completed 182 days of safety follow-up following a single dose of ZV or placebo on Day 1. A total of 309 subjects were randomized and 306 were vaccinated. Randomization occurred in a 2:1 ratio according to a computer-generated, site-balanced allocation schedule to receive either ZV or placebo. Enrollment was stratified by daily prevaccination corticosteroid dose (5–10 mg and >10–20 mg of prednisone or equivalent). Subjects were further stratified by age (60–69, 70–79, and ≥80 years of age).

Blood samples were drawn at Day 1 (prevaccination) and Week 6 postvaccination, and tested for VZV antibody titer by glycoprotein enzyme-linked immunosorbent assay (gpELISA) [5]. Lesion samples were to be collected from all HZ-like and VZV-like rashes that developed during the study, and evaluated by VZV polymerase chain reaction (PCR) assay for the presence of vaccine strain VZV DNA [6].

2.4. Study objectives

The primary objective was to determine whether ZV has an acceptable safety profile when administered to subjects who were receiving chronic/maintenance corticosteroid therapy. The secondary objective was to determine whether ZV was immunogenic when administered to this population. This was an estimation study with no hypothesis testing.

2.5. Safety surveillance

Safety was monitored by the sponsor's protocol team and a separate Safety Evaluation Committee (SEC) in a blinded manner. Membership in the SEC included personnel from sponsor and independent clinical experts in the field of infectious diseases and/or vaccinology. At the request of the SEC, the treatment group for specific adverse experiences could be unblinded and provided to the SEC by sponsor personnel not otherwise associated with the study.

During the primary safety follow-up period (Day 1 to Day 42) subjects were followed for injection-site and systemic adverse experiences (AEs), including VZV-like rash. Safety and tolerability were assessed with a Vaccination Report Card (VRC), which specifically prompted for injection-site AEs of erythema, swelling, and pain or tenderness. The subject recorded the maximum size (in inches) of erythema and swelling, and the maximum severity of pain or tenderness (based on a scale of none, mild, moderate, and severe) for all other injection-site reactions. The site investigator evaluated each AE as to seriousness, action taken, maximum intensity, duration, and relationship to vaccine. All VRCs were reviewed to ensure that all varicella, varicella-like, HZ, or HZ-like rashes and serious AEs were recorded.

During the secondary safety follow-up period (Day 1 to Day 182), all serious adverse events, regardless of causality, were collected. Subjects were instructed to report any serious AEs immediately to study site personnel. At 2, 3, 4, 5 and 6 months postvaccination, subjects were called by the study staff, using a prespecified telephone script, to determine if the subject had a previously unreported serious AE and to collect any relevant information.