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A critical appraisal of 'Shingrix', a novel Herpes Zoster Subunit (HZ/Su or GSK1437173A) vaccine for Varicella Zoster Virus.

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Abstract

HZ/Su, branded as 'Shingrix', is one of the newest vaccines to be submitted for multi-national regulatory approval. It is targeted to prevent shingles, predominantly affecting the elderly, but a global concern with ageing populations and significant associated morbidity and mortality. A vaccine for shingles has been available for over a decade, however it is contraindicated in specific subgroups of people, and there are added concerns regarding long-term immunogenicity. HZ/Su is the first subunit vaccine developed to protect against shingles. This paper provides a critical appraisal of current evidence regarding HZ/Su.

Introduction

Endemic worldwide, varicella zoster virus (VZV) is a highly neurotropic and T-cell tropic alphaherpes virus. Primary infection leads to the common clinical condition, varicella or 'chickenpox'. Subsequently, VZV remains dormant in sensory dorsal root ganglia, with the potential for reactivation in one or more sensory neurones leading to herpes zoster (HZ) or 'shingles', and complications such as postherpetic neuralgia (PHN) (1). The incidence of HZ in the United States and Europe increases with advanced age is estimated at 3 to 10 cases per 1000 person-years (2). For unclear reasons this incidence has steadily increased with time (3). A vaccine for varicella has been available since 2002, and production and licensing of a live-attenuated vaccine for HZ occurred in 2006 (4). Notably, there are contra-indications to live-attenuated vaccines, such as VZV naive or immunosuppressed patients in whom vaccination may cause disease. We critical appraise published data on a novel subunit vaccine for VZV, HZ/Su or GSK1437173A (GSK).

- Virology

VZV is an enveloped, spherical to pleomorphic double-stranded DNA virus with a monopartite genome approximately 125 kilobases, illustrated in Figure 1 and 2. The genome encodes at least 71 open reading frames (ORFs) and related promoter sequence. Approximately two thirds of the ORFs are necessary for replication, and this includes 40 genes common among all herpes viruses (5). Glycoprotein E (gE) is a large unique N terminus (amino acids 1–187) essential for replication and T-cell entry. This is the most abundant and immunogenic glycoprotein, and the target utilised in the HZ/Su vaccine. Figure 3 summarises the natural history of the virus, and the basic cell mechanism of viral replication.

- Immunology

During primary infection, the initial immune response to VZV involves the innate immune system, with the release of antiviral cytokines and the activation of NK cells (1). This is suggested to control viral replication in the mucosa, as well as triggering adaptive immunity. Memory immunity to VZV involves persistence of VZV IgG and VZV-specific CD4 and CD8 cells, however it is cell-mediated immunity that correlates best with the severity of primary infection (6). The cell-mediated response is crucial for preventing reactivation of latent VZV residing in ganglionic cells. This immunity naturally wanes over time, and this is thought to be the reason HZ chiefly afflicts the elderly.

Delineating this further, a strong VZV-specific CD4 response at the onset of HZ is associated with improved clinical outcomes. Within a cohort of patients who developed HZ in the Shingles Prevention Study (SPS) increased expression of IFN-γ in peripheral blood mononuclear cells (PMBCs) after stimulation with VZV antigen was associated with reduced morbidity and a lower incidence of PHN (8). The frequency of VZV-specific memory T cells present predicted development of HZ and severity. Subjects who did not develop HZ during follow up tended to have higher baseline frequencies of VZV-specific T cells when compared to subjects who subsequently developed HZ. Both administration of the attenuated zoster vaccine or an episode of HZ resulted in an increase in VZV-specific T cells in subjects (9). Interestingly levels of anti-VZV antibodies did not correlate with protection against HZ, matching previous observations (10). It is essential therefore that an effective vaccine to prevent HZ elicits a sustained cellular immune response against VZV.

- Nature of the disease

The reactivation of latent VZV residing in the dorsal root ganglion, see Figure 3, has been demonstrated to involve a decline in cell-mediated immunity (11). Risk factors include older age, cell-mediated immune dysfunction, diabetes, female gender, genetic susceptibility,

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mechanical trauma, recent psychological stress and white race (12). The clinical presentation involves three phases: 1) Prodrome, 2) Infectious rash and 3) Resolution. The prodrome of acute neuralgia may precede the rash by 2-100 days (1). The rash typically involves a single dermatome, with an erythematous macular rash followed by vesicular lesions that ulcerate, scars and heals. Data suggests that complications occur in 12% (13). Persisting pain, or pain which appears more than 90 days after symptom onset is termed postherpetic neuralgia and increases with age. Aside from the severe pain that may be associated with HZ, there are potentially devastating complications: secondary bacterial infection and sepsis, meningoencephalitis, visual and hearing impairment. It is suggested that up to 4% of persons who develop shingles attend secondary care.

- Treatment

Antiviral treatment with intravenous or oral Aciclovir, Valaciclovir or Famciclovir administered within 72 hours of symptoms onset, reduce the severity and duration of HZ (14). There are no licensed antivirals to reduce or prevent the onset of PHN, and management depends on supportive care such as analgesia.

- Epidemiology and Public Health aspects:

The estimated lifetime risk of HZ is 25-30%, and the subsequent risk of developing PHN is approximately 20% (3). In contrast to varicella, there is no seasonal distribution, and cases occur more frequently with increasing age (15). Exogenous exposure to VZV boosts the immune system and prevents reactivation. Undeniably, current epidemiological data has been focused in Europe, U.S.A. and Australia and it is in these settings that experience has been gained with the existing live-attenuated HZ vaccine, Zostavax.

Key issues

- Primary VZV infection causes varicella, and reactivation causes shingles/Herpes Zoster.

- Cell-mediated immunity prevents VZV reactivation, and is primed by repeated exogenous exposure to VZV. However, this immunity wanes with increasing age, leading to HZ in the elderly.

- HZ is common, with 3-5 cases/person-year worldwide. Complications include sepsis due to secondary bacterial impairment, severe and persistent pain, visual and hearing impairment.

- Persistent pain at least 90 days after the rash has healed, postherpetic neuralgia (PHN), is the commonest complication. This occurs in up to 1 in 5 patients, resulting in considerable morbidity. The incidence and severity of PHN increases with age.

- Antivirals may shorten symptom duration and severity. However, they must be administered within 72 hours of symptom onset, and there is insufficient evidence to demonstrate a benefit in preventing postherpetic neuralgia.

- Immunisation to prevent HZ has existed for over a decade in the form of a live-attenuated vaccine, Zostavax. It is the only licensed HZ vaccine, now licensed in 50 countries.

- The efficacy of Zostavax to reduce the burden of illness of HZ falls from 61.1% at year four to 37.3% at eleven years post vaccination.

- Zostavax is contraindicated in immunosuppressed patients, in whom vaccination may lead to disease.

- "HZ/Su" or GSK1437173A varicella zoster vaccine (Shringrix™) is a novel subunit vaccine based on glycoprotein E with AS01 as an adjuvant.

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Zostavax, the existing shingles (HZ) vaccine

The live-attenuated Oka strain was developed in Japan in the 1970s as a vaccine for the prevention of varicella (16). This was derived from VZV isolated from a 3-year-old boy with varicella, and passaged in human embryonic fibroblasts, guinea pig fibroblasts, and then in human diploid fibroblasts. Two decades later the same vaccine at a significantly higher concentration was successfully trialled for the prevention of HZ (17). This was based on Hope-Simpson's theory that an episode of HZ would boost VZV-specific cell-mediated immunity and prevent another episode of HZ (18).

The live-attenuated HZ vaccine was first licensed on the 19th May 2006. It is produced by Zostavax Merck/ Sanofi Pasteur for adults over 50 years of age, and costs $100-200 for a single dose.

A recent Cochrane review included 10 randomised controlled trials of Zostavax. 4 studies were deemed to have a low risk for bias but overall, the vaccine reduced the incidence and complications of HZ (19). Vaccine efficacy however decreased with time and protection against the burden of illness from HZ reduced from 61.1% at year four, to 50.1% at year seven and 37.3% at year eleven. Efficacy in prevention of PHN similarly decreased from 66.5% at year four to 35.4% at year eleven (20,21). Notably, the external validity of the study was low due to the homogeneity of the population.

52 countries have now licensed Zostavax, and there has been variable introduction in immunisation policies and uptake. In the UK, the vaccine was deemed cost-effective for 70 year olds. The decision was based on the milder symptoms and lower risk of complications in people aged under 70 years, and the limited efficacy above 80 years.

Issues with Zostavax include preclusion of the vaccine to categories of immunosuppressed patients, the limited efficacy demonstrated beyond 5 years or in those patients over 80

years. There are concerns that Zostavax uptake has been low, and suggestions that there is lower confidence in a live-attenuated vaccine. It is for these reasons that an alternative may be necessary.

Design and development of product

The "HZ/su" or GSK1437173A varicella zoster vaccine (Shringrix™) is an investigational subunit vaccine manufactured by GSK containing 50 μg of recombinant VZV glycoprotein E (gE) formulated with $AS01_B$ adjuvant.

Glycoprotein E is a 90-98 kDa protein encoded by ORF68 and is the most abundant membrane found on VZV-infected cell membranes and present in high concentrations within the skin during episodes of HZ (22). gE is thought to be essential in facilitating VZV neurotropism and virulence represents a major target in the development of host immunity (5). Early studies demonstrated that primary infection results in development of anti-gE antibodies (23) and CD4 responses specific to gE (24) in human subjects. Monoclonal antibodies raised against gE neutralised infectious virions in vitro with the presence of complement (25). A recombinant, truncated gE molecule lacking the transmembrane anchor and carboxyterminal domains was immunogenic in mice and capable of stimulating production of neutralising antibodies (26). A subsequent gE fusion protein was also capable of stimulating specific humoral and T-cell responses in guinea pigs (27) supporting it as a potential candidate for subunit vaccine development.

AS01 Adjuvant

AS01 (GSK, Rixensart, Belgium and Antigenics Inc, USA) is a proprietary adjuvant system containing MPL (3-O-desacyl-4'-monophosphoryl lipid A), the saponin derived QS21 combined with dioleoylphosphatidycholine (a phospholipid) and cholesterol. MPL is derived from the Salmonella Minnesota lipopolysaccharide and stimulates antigen presenting cells

expressing Toll-Like receptor 4 through activation of the innate immunity. QS21 is a molecule extracted from the South American tree Quillaja saponaria Molina fraction 21 and stimulates innate pathways in monocytes through an unclear mechanism (28). The liposomal formulation is thought to offset the intrinsic haemolytic activity of QS21 (29), but may also enhance antigen presentation when compared with its emulsion formulation AS02 (30)

The synergy between MPL and QS21 resulted in stimulation both classical and monocyte-derived dendritic cells and enhances antigen presentation to T cells. Although within preclinical studies AS01 enhances IFN driven responses, clinical experience has shown that AS01 predominantly induces production of antigen-specific antibodies and specific CD4 cells. AS01 has been used in candidate vaccines in hepatitis B, HIV and malaria with no safety concerns or increased risks of immune-mediated diseases (31). An increased risk of meningitis without clear aetiology was reported in the Phase 3 trial in children who received RTS,S/AS01 compared to control but the significance of this was unclear (32).

Combination gE / AS01 in animal models

Humoral and cellular mediated immune responses induced by recombinant gE formulated with $AS01_B$ adjuvant ('B' refers to the dilutions - 50 µg each of MPL and QS21) was investigated through a VZV-primed C57BL/6 mouse model (33). Mice immunised twice with gE formulated with $AS01_B$ resulted in significantly higher total frequencies of activated CD4 cells and gE-specific CD4 cells producing IFN-γ and IL-2 when compared to formulation with alum or saline. The geometric mean concentrations of anti-gE antibody at day 30 were higher in mice vaccinated with gE/ $AS01_B$. In direct comparison of $AS01_B$ with the oil emulsion-based adjuvant AS02 no significant differences in gE-specific CD4 cells were observed at day 30, although a higher frequency of IFN-γ was observed with $ASO1_B$.

Clinical studies on HZ/Su

Phase I/II trials in humans and safety, and immunogenicity in young subjects

The safety and immunogenicity of the recombinant gE/AS01 candidate vaccine (HZ/Su) was examined in a phase I/II open-label, randomised study with 155 enrolled subjects (34). Through a staggered recruitment design 20 young adults (aged 18-30 years) and 135 older adults (aged 50-70 years) were randomised to receive two doses of: HZ/Su (50 μg recombinant VZV gE with $AS01_B$), or HZ/Su and OKA, (a live attenuated Oka strain VZV vaccine containing approximately 10^4 PFU per dose injected subcutaneously) or OKA alone on months 0 and 2.

Higher numbers of younger and older subjects who received a regimen containing HZ/Su experienced local symptoms when compared to the OKA only group - Up to 11% experienced pain at injection site at grade 3 severity (i.e. preventing normal daily activities) and 20% had > 50 mm of local redness. General reactions such as myalgia and fatigue were also more common in those receiving HZ/Su. No vaccine related serious adverse events (SAEs) or deaths were reported on follow up to month 42.

Humoral immunogenicity measured through geometric mean concentrations (GMC) of serum anti-gE and anti-VZV antibody was higher in subjects immunised with HZ/Su or HZ/Su with OKA compared OKA alone. Antibody levels were highest after the first dose in young adults but after the second dose in the older group and anti-gE specific responses were greater than anti-VZV. At month 42 in those vaccinated with HZ/Su alone there was a decline of both anti-VZV and anti-gE GMCs although this remained higher when compared to baseline.

Cellular immunity was measured through intracellular cytokine staining and T cells considered positive if they expressed at least 2 cytokines induction with VZV lysate or gE. T

cell responses were highest after 2 doses of HZ/Su or HZ/Su with OKA compared to 2 doses of OKA alone. The frequency of VZV-specific CD4 cells secreting at least 2 cytokines decreased to levels comparable baseline at month 30. Stimulation of CD8+ cells was not detected in any of the groups.

The authors conclude that HZ/Su was generally tolerated and safe. Although appearing more immunogenic when compared with OKA alone they note that this may not translate into clinical efficacy given that the risks and immunological correlates of protection for HZ are still unclear (21).

Phase I/II trials in older subjects> 50 years (Chilibek), safety and 3 different formulations (Chilibek)

Two phase II, randomised multicentre studies conducted in parallel between 2007 and 2011 and funded by GSK Biologicals investigated the impact of vaccine and adjuvant formulation on the safety and immunogenicity of the HZ/Su vaccine in older adults.

In the vaccine formulation study (35) 714 patients aged ≥ 60 were recruited to receive two doses of trial vaccine 2 months apart. Subjects were randomised to receive two doses of 25 μg or 50 μg or 100 μg of gE combined with $AS01_B$ two months apart, or saline in month 0 followed by one dose of 100 μg gE/ $AS01_B$, or two doses of unadjuvanted 100 μg gE two months apart. In the adjuvant study (36) 410 adults ≥ 50 years were randomised to receive two doses of 50 μg gE/ $AS01_B$, or 50 μg gE/ $AS01_E$ (a lower dose adjuvant containing 25 μg MPL and 25 μg QS21), or 50 μg gE unadjuvanted or saline two months apart.

Similar to the previous study, injection site pain, fatigue, myalgia and headache were the most common reported symptoms and this was attributed to the adjuvant. Subjects in both studies who received a vaccine containing AS01 had a higher incidence of local and general reactions with the majority experiencing pain at injection site. Within the vaccine

formulation study < 6.1% of subjects reported a grade 3 local or general reaction; this incidence was higher in subjects aged 60-69 years compared to those over 70. In adjuvant study up to 87% of subjects receiving gE adjuvant experienced local or general symptoms, of which 9.3% were classed as a grade 3 reaction. In contrast 5.3% in saline only group and 2.7% in the gE/saline group experienced grade 3 reactions. Overall the majority of symptoms resolved within 3 days. In addition, solicited reactions were more frequent when the higher dose adjuvant (AS01$_B$) was used when compared to lower dose (AS01$_E$).

At follow up through to 14 months no SAEs or deaths attributable to vaccination occurred in either study. 2 subjects withdrew due to treatment related AEs in the adjuvant formulation study. The authors comment that formulation with AS01 specifically was more immunogenic and induced more adverse reactions in its recipients. However, this did not lead to lower uptake of a second dose of the vaccine, and they conclude AS01 was overall well tolerated under trial conditions.

Subjects who received 2 doses of gE/AS01 had higher anti-gE and anti-VZV titres at month 3 compared to other groups, and those who received either 50 or 100 μg of gE with AS01$_B$ had higher GMCs than subjects who received 25 μg. These responses persist through to month 36 and remained higher than pre-vaccination levels. A higher dose adjuvant with AS01$_B$ also elicited a stronger humoral response. Notably, based on the anti-VZV antibody criteria used, 38.7% and 17.5% were non-responders with AS01$_B$ and AS01$_E$ respectively. The significance of this was unclear.

Cellular immune responses were measured through intracellular cytokine staining of stimulated T cells and after adjustment frequencies were higher at month 3 for the 50 and 100 μg gE/ AS01$_B$ groups compared two doses of 25 μg gE/ AS01$_B$ or one dose of 100 μg gE/AS01 or two doses of 100 μg gE/Saline groups. In the adjuvant study, cellular responses

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were significantly higher in $AS01_B$ group compared to $AS01_E$. Non-responder rates approximately <12% for gE-specific cellular immunity but 50% according to VZV cellular immunity. In both studies subjects ≥70 years old who received gE and AS01 showed similar levels of cellular immunity responses and immunogenicity at month 3 when compared to the other age groups. At 6 years follow up of 119 (out of 166) subjects who received 50 μg/$AS01_B$ the gE-specific immunity remained 3.8 times higher than pre-vaccination levels (37).

Phase III RCTs in 50s and 70s

A multicentre phase 3 randomised placebo controlled trial ZOE-50 (ClinicalTrials.gov number NCT01165177, funded by GSK Biologicals) was performed between 2010 and 2011 (38). 16,160 participants ≥ 50 years who were not immunosuppressed were randomised in a 1:1 ratio to receive either HZ/Su vaccine (consisting of 50 μg gE with $AS01_B$) or placebo (0.9% saline) at months 0 and 2. The investigators and participants were blinded to the intervention administered.

A confirmed case of herpes zoster was defined as unilateral rash with sensory symptoms confirmed by a positive real-time polymerase chain reaction (PCR) result targeting VZV ORF62. Investigators were to examine suspected cases within 48 hours and obtain photographs of the lesions. If the PCR assay was negative for the internal positive control or if samples were unavailable, then diagnosis was established through unanimous agreement amongst 5 members of a committee through case review.

14,759 (95.8%) of participants were included in the final analysis including exclusion of 749 subjects due to Good Clinical Practice deviations. Most were recruited from Europe and 71.8% were white and 61.2% were female. The mean age of all participants was 62.3 years old.

As with previous studies up to 84.4% participants in the HZ/Su group reported symptoms. 17.2% of participants receiving HZ/Su reported grade 3 reactions lasting a median duration of 1 day, including 9.5% reporting local site reactions and 11.4% systemic symptoms. This compared with 3.2% of participants who received placebo reporting grade 3 reactions. In the first 30 days after vaccination 1 HZ/Su and 3 placebo recipients had a SAE related to vaccination. The occurrence and nature of potential immune-mediated diseases was not significantly different in the HZ/Su and placebo group (1.0 and 1.3% respectively throughout the study period). With a mean follow up of 3.5 years the incidences of SAEs and deaths were similar in both the HZ/Su and placebo group.

408 participants reported suspected HZ of which 244 (59.8%) of these cases were confirmed. 33 cases were inconclusive and not included in final evaluation. After exclusion of participants who did not receive 2 doses of vaccine 216 confirmed cases of HZ were analysed – with 6 occurring in HZ/Su group and 210 in placebo group with a mean follow-up duration of 3.2 years. The overall rate of herpes zoster was 0.3 per 1,000 person-years in the HZ/Su cohort and 9.1 per 1,000 person-years in the placebo cohort. The rate of HZ in the placebo cohort is comparable to population estimates (2).

Notably the HZ rate in the HZ/Su group was similar across different age groups and the derived vaccine efficacy was approximately 97.2% at 3.2 years (95% confidence interval 93.7 to 99.0%; p <0.001) with no significant difference across all age groups.

A separate phase 3 randomised, placebo controlled multicentre trial ZOE-70 (ClinicalTrials.gov NCT01165229, funded by GSK Biologicals) was performed in parallel with ZOE-50 between 2010 and 2011 to examine the efficacy and safety of the HZ/Su vaccine in adults older than 70 years old in reducing the incidence of HZ and PHN (39). 14,816 participants were recruited to receive either HZ/Su or placebo in a 1:1 ratio. The protocols

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for the assessment potential clinical cases of HZ were similar to ZOE-50 and assessment of PHN cases carried out through daily questionnaires for 28 days and follow up for at least 90 days after onset of rash.

13,163 (94.7%) participants with a mean age of 75.6 years were included in the final analysis cohort. 22.1% of the cohort were 80 years or older. Around 74.1% of participants who received HZ/Su experienced local reactions, 8.5% of which were of grade 3 severity. The authors observe that adverse reactions occurred less frequently in participants who were older than 80 years old compared to the 70 to 79-year-old group. The overall rate of grade 3 adverse reactions in HZ/Su recipients in turn appear to be lower than that of the younger ZOE-50 cohort which received HZ/Su. With a mean follow up of 4 years the incidence of SAEs including deaths and immune mediated diseases were similar in the HZ/Su and placebo groups.

246 cases of HZ occurred in the final modified vaccinated cohort – 23 in HZ/Su and 223 in placebo patients after a mean duration of 3.7 years. The incidence rate for HZ was 0.9 cases/1000 person-years in the HZ/Su group and 9.2 cases/1,000 person-years in the placebo group. Vaccine efficacy in ZOE-70 was 89.8% (84.2 to 93.7, p <0.001) and 87.9% (95% CI 73.3 to 95.4) four years after vaccination. This did not differ significantly between the 70-79 and ≥ 80-year-old cohort.

The calculation of vaccine efficacy against PHN included pooling of participants form the ZOE-50 trial. All patients who developed PHN were over 70 years of age. During a mean follow up of 3.8 years the incidence of PHN in the HZ/Su group was 0.1 cases/1000 person-years and 0.9 cases/1000 person-years in the placebo group deriving a vaccine efficacy against PHN of 88.8% for participants 70 years or older. The incidence of PHN in HZ/Su

cohort who developed HZ was not significantly different to that in participants who received placebo.

Phase I/II trials in adults with HIV infection

Patients with HIV have a higher risk of developing HZ. This risk is attenuated but does not return to age-matched population rates after commencement of anti-retroviral therapy (ART) and remains approximately 3-5 times higher (40). Although live attenuated vaccines are thought to be safe in patients with HIV with a CD4 count of greater than 200 mm^3 its efficacy is not clear (BHIVA guidelines 2015 use of vaccines in HIV-positive).

The safety and immunogenicity of the HZ/Su vaccine in a cohort of adults infected with human immunodeficiency virus (HIV) was supported through a randomised placebo controlled study (41). Three cohorts of subjects infected with HIV were recruited: 94 subjects established on ART for at least a year and had a CD4 count of ≥ 200 cells/mm^3, 14 subjects on ART with a CD4 count of 50-199 cells/mm^3, and 15 adults ART-naïve with a CD4 count of ≥ 500. Each group was randomised to receive 3 doses of HZ/Su or 3 doses of saline at months 0, 2, and 6.

123 subjects were enrolled and the majority (91.1%) completed follow up to month 18. Local and systemic adverse events were more common in the HZ/Su group but were short-lived (median duration 1-3 days). Up to 16.4% of subjects receiving HZ/Su and 8.3% receiving saline experienced a grade 3 local or general reaction. Overall administration of HZ/Su had no impact on CD4 cell count, HIV viral load or haematological/biochemical parameters through month 18 of follow up.

The overall magnitude of gE-specific cellular immunity and anti-gE antibody response was higher in the HZ/Su group compared to the saline. This was demonstrated in the combined cohort consisting of ART/high CD4 count and the ART naïve/high CD4 count cohort. The gE-

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specific cellular immunity did not increment dramatically after the third dose the HZ/Su

vaccine and the authors conclude that a 2-dose schedule is likely to be appropriate for HIV

infected adults.

The authors comment that although the exact immunological correlates of clinical

protection are not defined in HIV infection the HZ/Su vaccine was safe, and immunogenic in

subjects with relatively high CD4 count. Because of the low numbers recruited in the

ART/low CD4 group there was insufficient statistical power to assess the effects of

vaccination within this cohort for which an efficacious subunit vaccine would be of most

benefit.

Phase 1/2 study in autologous haematopoietic stem cell transplant (HCT) recipients.

Patients with haematopoietic stem cell transplants have rates of 15-30% of HZ during first

year after transplantation (42) and furthermore this is associated with more severe

complications such as disseminated infection.

121 adult subjects who underwent autologous HCT within the previous 50-70 days between

2009 and 2012 in the United States were randomised to receive: 3 doses of gE/ $AS01_B$, or3

doses of gE/ $AS01_E$ or 1 dose of saline with 2 doses of gE/ $AS01_B$, or 3 doses of saline on

months 0, 1 and 3 (43).

Subjects who received gE/AS01 vaccines experienced a higher rate of symptoms with up to

17.2% experiencing local reactions rated as grade 3. $AS01_B$ tended to be more reactogenic

than the lower dose $AS01_E$. One SAE was considered related to vaccination was reported up

to month 15 but no deaths or immune mediated inflammatory disorders attributable to

vaccination.

At month 4 the overall gE-specific and VZV-specific CD4 cell frequency was higher in all

gE/AS01 groups compared to saline. There was no significant difference in the CD4 response

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between the 3 dose $AS01_B$ and the 3 dose $AS01_E$. A similar relationship was also observed in terms of anti-gE antibody titres. Similar to previous studies the increase in immunogenicity after the 3rd dose of gE/AS01 was modest.

Notably anti-gE GMCs with $AS01_B$ / $AS01_E$ did not increase in subjects with NHL B cell lymphoma. This was likely caused by B cell depletion through rituximab administration as part of underlying treatment. Given immune reconstitution and engraftment is brought by HCT and risk of HZ is greatest within 2 years of transplant even a modest short term protection may be beneficial and should be explored in further clinical studies.

GSK approval

In October 2016 GSK submitted a Biologics License Application to the United States Food and Drug Administration for approval of HZ/Su the prevention of herpes zoster and its complications in persons aged 50 years or over. In November 2016 applications were submitted to the European Medicines Agency and Health Canada.

Conclusions

An existing single dose of a live attenuated vaccine to prevent HZ is currently licensed in 52 counties. However, there are understandable concerns about the efficacy of the vaccine, and the fact that it is contraindicated in a sub-section of the population. The results of the novel sub-unit vaccine, HZ/Su, have been eagerly awaited.

HZ/Su has demonstrated immunogenicity in preclinical studies and efficacy in preventing HZ in clinical trials. The vaccine efficacy to prevent development of HZ at 4 years follow up was 97% overall in subjects older than 50 years of age, and around 90% in participants older than 70 years old. More importantly the response appears preserved with age. In the ZOE-50 and 70 studies the incidence of HZ within the vaccinated cohort remained similar between the age 60-69 and group ≥ 70-year-old group (0.7 and 0.9 cases per 1,000 person-

years respectively). In the SPS incidence of HZ in the vaccinated group increased from 3.90 cases per 1,000 person-years in the 60 to 69-year-old group to 7.18 per 1000 person-years in the ≥70-year-old group. Direct comparison of the two studies can be difficult given different primary end points were employed.

The main burden of HZ remains PHN. Mainly through reduction in the incidence of HZ HZ/Su appears to be able to protect against PHN. The exact relationship between HZ and risk for PHN remains unclear. The authors note that the efficacy of HZ/Su in prevention of PHN does not extend beyond development of HZ. However, the low numbers of HZ onset in the vaccine groups make it difficult to draw conclusions.

HZ/Su is reactogenic and local or general reactions are almost universal (up to 95% for example experience across all studies). The incidence of grade 3 reactions which prevent activities of daily living in addition around 10% may have a disproportionate impact on the willingness for patients outside trial conditions to take up the vaccine. In particular, the target population tends to be frail and older. SAEs and deaths were not increased between trial and placebo groups with follow up at 4 years in the overall pooled studies with no increase in the incidence of immune mediated diseases.

Overall vaccine efficacy for HZ/Su for participants over 50 years of age appeared to decrease with time (from 96.6% at year 1 to 87.9% at year 4), however the authors conclude that the difference was not statistically significant and this will need to be followed up with longer term studies.

Studies in immunocompromised patients unable to receive live attenuated vaccines have been encouraging, with immunogenicity and acceptability demonstrated in patients after HSCT and in HIV infection - although measurements of VZV immunity across the different HZ/Su trials have not been standardised. Within the HIV trial the few numbers of patients in

the low CD4 group completing the study meant analysis was not possible but the vaccine appeared safe.

Future directions

It has been predicted that the incidence of HZ will rise with the increasing ageing of the population. There were concerns that this would be particularly marked for several years after the introduction VZV vaccine in numerous countries. Interestingly, current epidemiological evidence suggests that the incidence of HZ in countries adopting the VZV vaccine has actually fallen (44). It is possible that wider uptake of the VZV vaccine will have a considerable reduce the burden of HZ, and the need for a vaccine.

In terms of the current evidence, the trials have been conducted in areas where the majority of participants were VZV IgG positive. The impact of the vaccine on recipients who are VZV IgG negative, or have previously received the VZV/chickenpox vaccine will need to be evaluated. Given the reactogenicity of HZ/Su studies addressing its management may be important for acceptability outside clinical trial conditions. Although the introduction of routine childhood chickenpox vaccination is thought not to have contributed to the increasing incidence of shingles (44) the changing epidemiology of shingles and the impact of introducing a potentially expensive new vaccine need to be carefully examined.

Clinical trials examining vaccine safety of HZ/Su in renal transplant recipients and vaccine efficacy in HSCT recipients are ongoing (ClinicalTrials.gov NCT02058589 and NCT01610414 respectively). In addition, a direct head-to-head comparison study between Zostavax and HZ/Su in the elderly is underway (ClinicalTrials.gov NCT02114333). The outcomes of these studies may influence future vaccination policy on shingles in different subpopulations.

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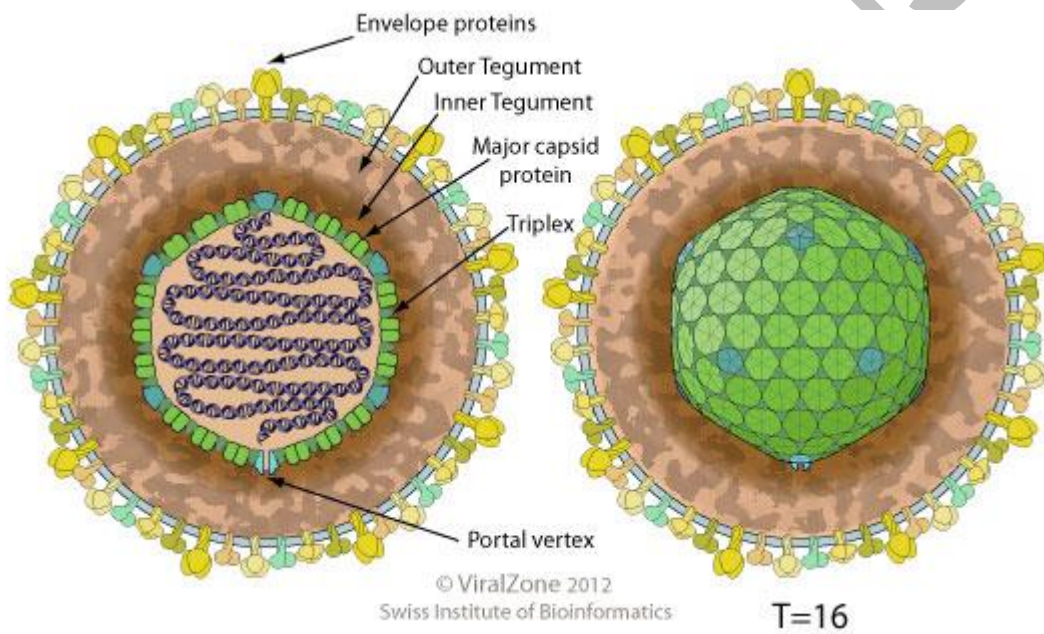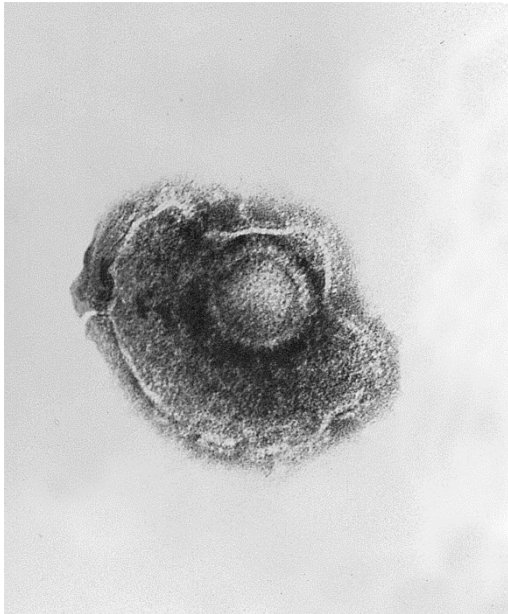
Figure 1&2: 1) Transmission electron microscopic (TEM) image of a VZV particle (CDC/ Dr Erskine Palmer and

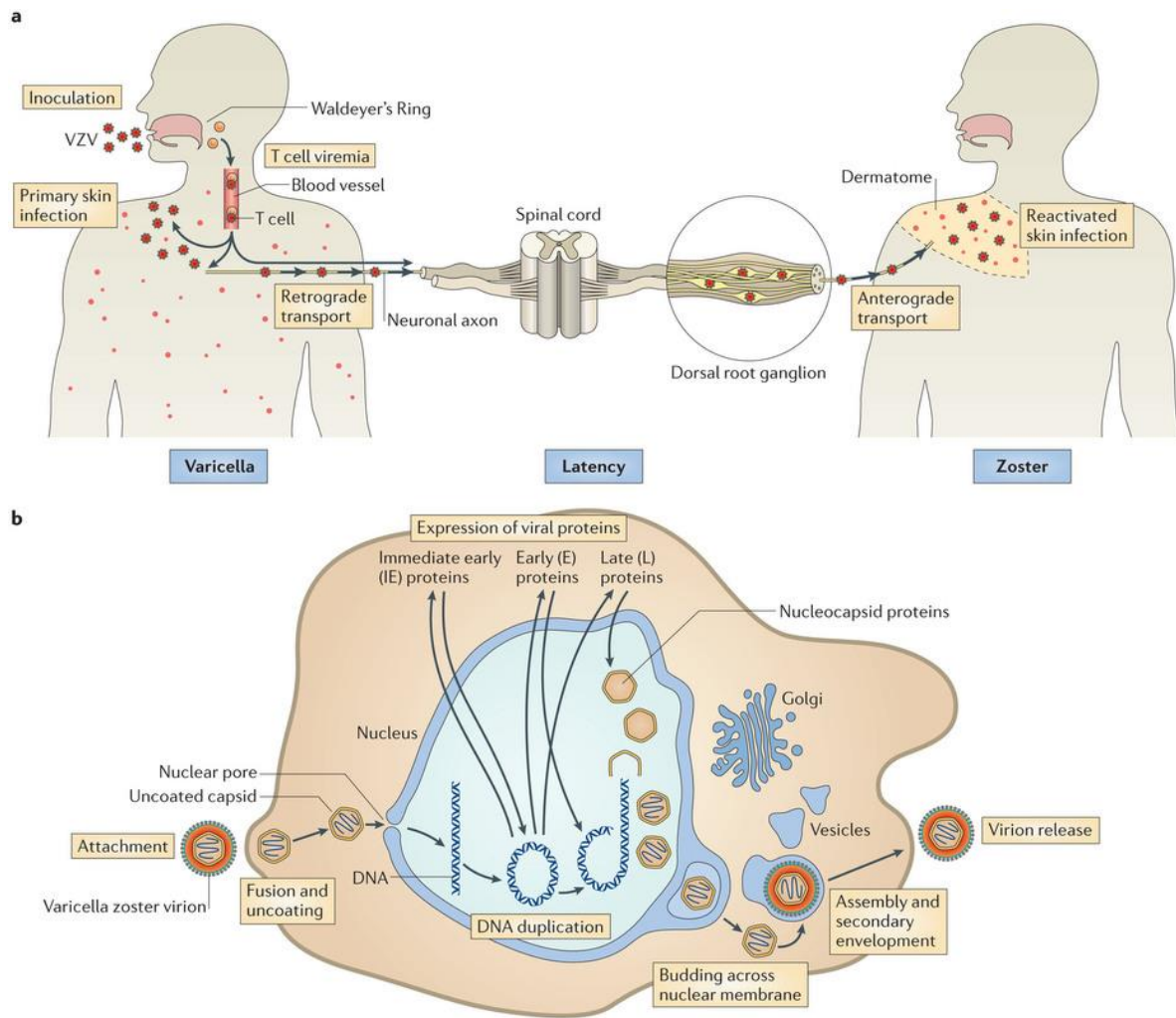B.G. Partin). 2) Structure of VZV virus (Viralzone, SIB Swiss Institute of Bioinformatics).

Figure 3: The natural history of VZV infection. (Zerboni *et al*, 2014)