therapeutics letter
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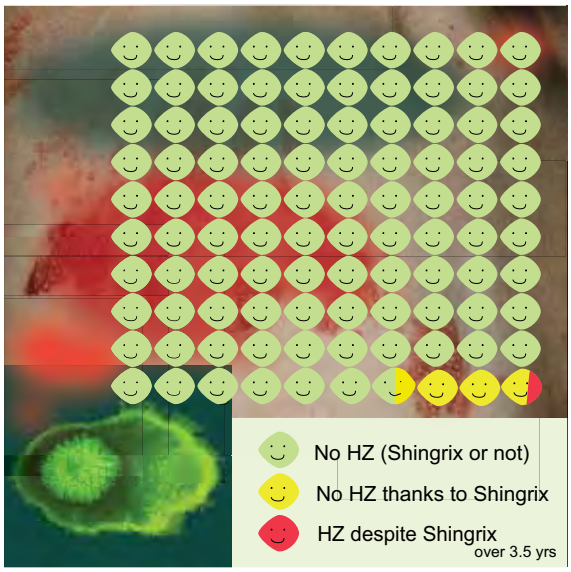
THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Shingrix: A New Vaccine for Shingles

Herpes zoster (HZ) or "shingles" occurs when the varicella zoster virus (VZV), lying latent in the sensory ganglia, becomes reactivated. An HZ outbreak typically presents as a vesicular skin eruption most characteristically forming a painful girdle around one side of the thorax. The rash and pain usually resolve over a few weeks. However, about 10% of patients with shingles develop some degree of persistent HZ-related pain (post-herpetic neuralgia or PHN).[1] Health Canada approved a two-dose adjuvanted herpes zoster subunit vaccine (Shingrix) in October 2017.



Zostavax, a live attenuated vaccine, was approved 10 years ago. Both vaccines are for the prevention of HZ in people ≥ 50, but neither is approved for prevention of PHN.

Shingrix clinical evidence

Indication	Prevention of herpes zoster (HZ) or "shingles" in people age 50 or older

Findings from main clinical studies	• ZOE-50[10], 2015: n = 15,411 immunocompetent, follow-up 3.2 years
	• ZOE-70[9], 2016: n = 13,900 immunocompetent, follow-up 3.7 years
	• Chlibek 2013[11], n = 410 immunocompetent, follow-up 12 months
	• Pooled analysis (using total vaccinated cohort) over about 3.5 years:
	  • Incidence of HZ:[9-11] Shingrix: 0.28% vs placebo 3.54%, ARR 3.26%, NNV = 31; age-based subgroups:
	  • Age 50-59: ARR 2.97%
	  • Age 60-69: ARR 4.10%
	  • Age ≥70: ARR 3.16%
	  • Incidence of PHN:[9,10] Shingrix: 0.06% vs placebo 0.34%, ARR 0.28%, NNV = 358
	  • Incidence of solicited or unsolicited adverse effects in 7 days post-vaccination:[9,10] Shingrix: 83.94% vs placebo 37.39%, ARI 46.55%, NNH = 2
	  • Grade 3 systemic reaction (preventing normal activity):
	  • ZOE-50[10]: ARI 8.96%, NNH = 11; ZOE-70[9]: ARI 3.97%, NNH = 25

Special populations	• Elderly patients included: mean age in ZOE-70[9] = 76 years; approx. 22% ≥ 80 years
	• Pregnancy/Nursing: no data
	• Immunocompromised: limited data; satisfactory immune response and safety profile in:
	  • HIV population: 1 RCT (n = 123)[14]
	  • Renal transplant population: 1 RCT (n = 265)[5]
	  • Hematopoietic stem cell transplant recipients: 2 RCTs (n = 187[6] and n = 121[15])
	• Those with history of HZ: limited data; 1 non-randomized study (n = 96)[16] showed similar immune response and safety to those without previous HZ
	• Those with previous vaccination against HZ with live vaccine: limited data; 1 non-randomized study (n = 430)[17] showed similar immune response and adverse effects rate to a matched, non-vaccinated population

Duration of HZ protection	Unknown beyond 4 years
Cost	Approximately $300 per two-shot series in BC

ARR = absolute risk reduction, ARI = absolute risk increase, NNV = number needed to vaccinate, NNH = number needed to harm

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Background

More than 90% of Canadian adults have had chicken pox (VZV) infection.[2] A major risk factor for developing HZ is increased age, with an incidence of 6 to 8 per thousand people per year at age 60, and 8 to 12 per thousand people per year at age 80.[3] About 5% of people with HZ experience recurrence.[4] Population-based data in British Columbia reports that the overall HZ incidence increased from 3.2 per thousand in 1997 to 4.5 per thousand in 2012, but the increase in incidence may reflect an increase in reporting.[4]

Methods

We used Cochrane systematic review methods for the literature search, data collection and analysis, and risk of bias assessment. We included randomized controlled trials (RCTs) of Shingrix versus active vaccine, no vaccine or placebo. We sought out and included related unpublished data from registries[5,6] and clinical study reports[7,8].

Results

Five RCTs (with about 32,000 participants) met our inclusion criteria.[9-13] No trials directly compared Shingrix to Zostavax. Three trials included a placebo comparator and were meta-analyzed.[9-11] In our pooled analysis, HZ occurred in 0.28% of patients who received the HZ vaccine versus 3.54% for placebo over about 3.5 years. This translates to a Number Needed to Vaccinate (NNV) of about 31 to prevent 1 case of HZ over 3.5 years. The incidence of post-herpetic neuralgia (PHN) declined in RCTs in proportion to the reduction of HZ, but the absolute reduction is much smaller, NNV = 358.[9,10] Not all PHN is severe or lasts for years. Of every 10 patients vaccinated, 8 or 9 had an adverse effect, most commonly injection-site pain, myalgia or fatigue lasting up to a few days. There was no difference in serious adverse events in around 4 years of follow-up, or withdrawals due to adverse events.

Two additional studies did not report on clinical efficacy outcomes of interest and reported insufficient information on safety.[12,13]

Our full systematic review is available on our website.[1]

Risk of bias of included studies

All included studies were funded by the manufacturer. Other limitations include the use of data carried from last point of patient contact for patient withdrawals, selective reporting of some patient analyses and substantial inconsistency in the magnitude of vaccine effect when pooling study data. Overall, we graded the certainty of evidence as moderate.[1]

Conclusions

- Compared to placebo the Shingrix vaccine reduced the incidence of herpes zoster by 3.26 % (NNV = 31) over 3.5 years in all age groups and reduced the incidence of post-herpetic neuralgia by 0.28% (NNV ≈ 350).
- Compared to placebo Shingrix increased grade 3 systemic reactions (which prevented normal daily activities for about 1-3 days) by 4 to 9% (NNH 11 to 25).
- The effectiveness (i.e. maintained protection) and safety of Shingrix are still unknown beyond about four years.
- Discuss the balance of baseline herpes zoster risk, harms, benefits and costs when considering this vaccine.

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The draft of this Therapeutics Letter was submitted for review to 130 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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