GRADE Table 02. Safety of hepatitis E vaccine in immunocompetent individuals

Population : Immunocompetent individuals (>16 years)
Intervention : Hepatitis E vaccination (Hecolin®)
Comparison : Non-hepatitis E vaccination
Outcome : Serious adverse events following immunization

In immunocompetent individuals, what is the incidence of serious adverse events following immunization (versus control) with any dose of hepatitis E vaccine?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT 3/ observational[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious[3]	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			Evidence supports a moderate degree of confidence in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.
	Conclusion			Evidence supports a moderate degree of confidence in the estimate of the effect that incidence of serious adverse events following hepatitis E vaccination is low. Judged on the phase I, II and III trials and the reactogenicity subset of the latter study, the rates of solicited adverse events were not concerning. Nevertheless the safety follow-up surveillance was largely passive, only healthy individuals aged 16-65 years were included and the pregnancy safety data were limited.

[1] Based on encouraging safety assessments in the observational phase I trial (Wu et al. 2012(2)), a phase IIa/IIb randomized controlled trial (Zhang et al. 2009 (4)) with a total of 457 (16-55years) (20 µg at 0,1,6 months or at 0,6 months, Hepatitis B vaccine as control) and 155 subjects (16-19years) (10, 20, 30, 40 µg at 0,1,6 months) indicated no serious adverse events (SAE) following immunization above grade 3 (SFDA Guideline). No significant difference in grade 3 local or systemic reactions between the vaccine group and the control. One large phase III trial (Zhu et al. 2010 (5)) with 112 604 healthy individuals (30 µg at 0,1,6 months) showed no significant difference of adverse events between vaccine and control group within the total cohort. Within a reactogenicity subset including 1645 subjects, solicited local adverse events within 72h after each dose were higher (<0.0001) in the vaccine group (13.5%) than in the placebo group (7.1%). Systemic adverse events were similar for both groups (20.3%vs.19.8%). These findings are reflected within the entire cohort. Safety was confirmed in two observational study subsets: A pregnancy subset- retrospective analysis of the phase III trial (Wu et al. 2012(1)) found no significant difference of SAE in women or their infants when receiving vaccine or placebo. Same applies to an analysis of a subset within the phase III trial of individuals with pre-existing chronic hepatitis B (Wu et al. 2013 (3)).

[2] Allocation concealment not clearly stated (Zhang et al. 2009 and Zhu et al. 2010)

[3] Only healthy individuals aged 16- 55 were included, no data available on immunization of children and immunocompromised. No downgrading as the determined age group in which the vaccine should be used may vary among settings. Limited data on 12 cases of ALT increase excluded from analysis on safety by the DSMB, no downgrading regarding this issue (5).

Reference List[1-5]

1. Wu T, Zhu FC, Huang SJ, et al. Safety of the hepatitis E vaccine for pregnant women: a preliminary analysis. Hepatology 2012;55(6):2038.

2. Wu T, Li SW, Zhang J, et al. Hepatitis E vaccine development: a 14 year odyssey. Hum Vaccin Immunother 2012;8(6):823-827.

3. Wu T, Huang SJ, Zhu FC, et al. Immunogenicity and safety of hepatitis E vaccine in healthy hepatitis B surface antigen positive adults. Hum Vaccin Immunother 2013;9:2474-2479.

4. Zhang J, Liu CB, Li RC, et al. Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine. Vaccine 2009;27:1869-1874.

5. Zhu FC, Zhang J, Zhang XF, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet 2010;376:895-902.