vaccines

MDPI

Supplementary Information

Mucosal Vaccination Strategies Against *Clostridioides difficile* Infection

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Supplementary Table S1 . *C. difficile* vaccine candidates in clinical trials.

Name (Manufacturer)	Strategy	Status	Findings	References
PF-06425090 (Pfizer)	Toxoid; genetically and chemically detoxified TcdA and TcdB	Phase III	*In vitro*	
			• Produced mutant TcdA and TcdB using an expression vector in a non-sporulating *C. difficile* strain that does not carry either *tcdA* or *tcdB* • Mutant TcdA (D285A/D287A) and TcdB (D286A/D288A) lacked glucosyltransferase and autoproteolytic processing activities • Toxin mutants were found to have greatly reduced toxicity to IMR-90 fibroblasts • Formalin inactivation removed residual toxicity of mutant TcdA and TcdB	NCT01706367 [1]
			In vivo	
			• Inactivated, mutant TcdB and TcdA were immunogenic in hamsters • Vaccine offered 60% protection from death compared to 0% in unvaccinated hamsters	NCT01706367 [1]
			Human trials	
			• In 50-85 year olds, vaccine was immunogenic and safe • Vaccine was less immunogenic with aluminum hydroxide adjuvant • No dose response observed	NCT01706367 [2]
			• Vaccine was safe and immunogenic in 65–85 year olds • Optimized vaccine dose amount and time interval between the three doses	NCT02561195 [3]
			• Vaccine candidate offered complete protection from severe CDI as well as reduced CDI episode length • Only 31-49% efficacy at preventing primary CDI, which did not meet study goals	NCT03090191
VLA84 (Valneva)	recombinant chimeric TcdB and TcdA binding domains	Phase II	*In vitro*	
			• Vaccine-induced antibodies neutralized toxin activity in T84 cells	[4]
			• Vaccination of mice, hamsters, and monkeys with fusion protein induced antibodies that could neutralize toxins in a Vero cell model • Dose-dependent response observed between antibody neutralization capability and use of vaccine adjuvant, aluminum hydroxide	[5]
			In vivo	
			• Vaccine provided mice with complete protection from death from TcdA challenge • Vaccine protection from death by TcdB challenge in mice was strong • In hamsters, vaccine offered complete protection from non-lethal dose of *C. difficile* even without adjuvant, but adjuvant was required for complete protection from lethal *C. difficile* dose	[5]
			Human trials	
			• VLA84 was safe and immunogenic in adults • IgG antibodies responses lasted at least 6 months	[4]

Continued.

Supplementary Table S1 Cont.

Name (Manufacturer)	Strategy	Status	Findings	
Cdiffense (Sanofi/Pasteur)	Formalin-inactivated TcdA and TcdB	Phase III halted	*In vitro*	
			• Anti-TcdA and anti-TcdB antibodies triggered by the vaccine could neutralize the toxic effect on IMR-90 fibroblasts	[6]
			Human trials	
			• Parenteral administration of TcdA toxoid triggered significant, protective levels of anti-TcdA antibodies in healthy individuals	[7]
			• Vaccine was safe an immunogenic in patients with recurrent CDI • Prevented recurrence of CDI, albeit sample size was small (3 patients)	[6]
			• Candidate was immunogenic and safe in a cohort of healthy individuals • Adjuvant use increased immunogenicity, but the effect was not significant	[8]
			• Vaccine was immunogenic and safe in patients 18-55 years	NCT00772954
			• Vaccine was immunogenic and safe in patients 18-55 years old (NCT001278030 and >65 years old (NCT00214461)	NCT00127803 NCT00214461 [9]
			• Optimized vaccine dose amount and time interval between the three doses • Determined that vaccine was more immunogenic in people aged 40–75 years with aluminum hydroxide adjuvant	NCT01230957 [10]
			• Phase III testing found that the vaccine candidate did not provide protection from CDI	NCT00772343 [11]

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