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Crimean-Congo Hemorrhagic Fever Virus for Clinicians—Diagnosis, Clinical Management, and Therapeutics

Appendix 1

Appendix 1 Table. CCHF Vaccine Candidate Pre-Clinical Immunogenicity and Protection Results

CCHF antigen target	Vaccine type	No. doses; route	CCHFV IgG	CCHFV neutralizing antibodies	CCHFV T-cell response†	Protection against‡		Ref.
						Symptomatic disease	Lethal disease, % survival	
Gc only	DNA fused to lysosome-associated membrane protein 1	3; IM	Yes	Yes	Yes	NA	NA	Hu et al. (*1*)
	Protein subunit anchored to gram positive enhancer matrix	3; SC	Yes	Yes	Yes	NA	NA	Wang et al. (*2*)
	Protein subunit anchored to gram positive enhancer matrix with ISA201VG and PolyI:C adjuvant	3; SC	Yes	Yes	Yes	NA	NA	Wang et al. (*2*)
	Protein subunit with Sigma adjuvant system	2; IP	Yes	Yes	NA	No	0	Kortekaas et al. (*3*)
Gn only	DNA fused to lysosome-associated membrane protein 1	3; IM	Yes	Yes	Yes	NA	NA	Hu et al. (*1*)
	Protein subunit anchored to gram positive enhancer matrix	3; SC	Yes	No	Yes	NA	NA	Wang et al. (*2*)
	Protein subunit anchored to	3; SC	Yes	No	Yes	NA	NA	Wang et al. (*2*)

CCHF antigen target	Vaccine type	No. doses; route	CCHFV IgG	CCHFV neutralizing antibodies	CCHFV T-cell response†	Protection against‡		Ref.
						Symptomatic disease	Lethal disease, % survival	
	gram positive enhancer matrix with ISA201VG and PolyI:C adjuvant							
	Protein subunit with Sigma adjuvant system	2; IP	Yes	Yes	NA	No	NA	Kortekaas et al. (*3*)
Gc and Gn	Protein subunit produced in mosaic tobacco plants	5; oral	Yes§	NA	NA	NA	NA	Ghiasi et al. (*4*)
	Nucleoside-modified mRNA lipid nanoparticles	2; ID	Yes	Yes	Yes	Yes	100	Appelberg et al. (*5*)
	Ubiquitin-linked DNA	3; IM with electroporation	No	No	Yes	No	NA¶	Hawman et al. (*6*)
G-NAb (glycoprotein epitope spanning amino acids 1443–1566 on the M genome segment)	Protein subunit anchored to gram positive enhancer matrix	3; SC	Yes	No	Yes	NA	NA	Wang et al. (*2*)
	Protein subunit anchored to gram positive enhancer matrix with ISA201VG and PolyI:C adjuvant	3; SC	Yes	No	Yes	NA	NA	Wang et al. (*2*)
GP38 only	DNA	3; IM with electroporation	Yes	NA	NA	Partial	20	Suschak et al. (*7*)
M genome segment proteins except for GP38 and mucin-like domain	DNA	3; IM with electroporation	Yes	NA	NA	No	0	Suschak et al. (*7*)
All M genome segment proteins (all glycoprotein components and nonstructural proteins)	Alphavirus-based replicon RNA	2; IM	Possible (IgG antibodies in only 25% of vaccinated animals)	No	Yes	No	37.5	Leventhal et al. (*8*)
	DNA	3; transcutaneous via gene gun	Yes	~50%	NA	NA	NA	Spik et al. (*9*)

CCHF antigen target	Vaccine type	No. doses; route	CCHFV IgG	CCHFV neutralizing antibodies	CCHFV T-cell response†	Protection against‡		Ref.
						Symptomatic disease	Lethal disease, % survival	
	DNA	3; IM with electroporation	Yes	Yes	NA	Partial	>60	Garrison et al. (*10*)
	DNA	3; IM with electroporation	Yes	NA	Yes	No	80–100	Suschak et al. (*7*)
	Modified vaccinia Ankara vector	2; IM	Yes	NA	Yes	Yes	100	Buttigieg et al. (*11*) Dowall et al. (*12*)
	Vesicular stomatitis virus vector (replication incompetent)	2; IP	NA	NA	NA	No	0	Rodriguez et al. (*13*)
	Vesicular stomatitis virus vector (replication competent)	1; IP	Yes	Yes	NA	No	100	Rodriguez et al. (*13*)
	Vesicular stomatitis virus vector (replication competent)	2; IP	Yes	Yes	NA	Yes	100	Rodriguez et al. (*13*)
Nucleoprotein	Alphavirus-based replicon RNA	1; IM	Yes	NA	Yes (low levels)	Partial	100	Leventhal et al. (*8*)
	Alphavirus-based replicon RNA	2; IM	Yes	No	Yes (low levels)	Yes	100	Leventhal et al. (*8*)
	Bovine herpesvirus type 4 vector	2; IP	Yes	No	Yes	No	100	Farzani et al. (*14*)
	DNA fused to lysosome-associated membrane protein 1	3; IM	Yes	Yes	Yes	NA	NA	Hu et al. (*1*)
	DNA-based Sindbis virus replicon	3; IM	Yes	NA	Yes	NA	NA	Tipih et al. (*15*)
	DNA-based Sindbis virus replicon adjuvanted with PolyI:C	3; IM	Yes	NA	Yes	NA	NA	Tipih et al. (*15*)
	DNA adjuvanted with CD24	2; IM	Yes	No	Yes	Partial	100	Farzani et al. (*16*)
	DNA	2; IM	Yes	No	Yes	Partial	100	Farzani et al. (*16*)
	DNA	2; IM	Yes	No	Yes	No	75	Farzani et al. (*14*)
	Human adenovirus 5 vector	2; IP	Yes	No	Yes	No	100	Farzani et al. (*14*)

CCHF antigen target	Vaccine type	No. doses; route	CCHFV IgG	CCHFV neutralizing antibodies	CCHFV T-cell response†	Protection against‡		Ref.
						Symptomatic disease	Lethal disease, % survival	
	Nucleoside-modified mRNA lipid nanoparticles	2; ID	Yes	No	Yes	Yes	100	Appelberg et al. (*5*)
	Modified vaccinia Ankara vector	2; IM	Yes	NA	Yes	No	0	Dowall et al. (*12*)
	Transcriptionally competent viral like particle	3; IM with electroporation	Yes	No	Yes	Yes	NA¶	Hawman et al. (*17*)
	Transcriptionally competent viral like particle	3; IP	Yes	Yes	NA	No	40	Hinkula et al. (*18*)
	Ubiquitin-linked DNA	2; IM with electroporation	Yes	No	Yes	No	NA¶	Hawman et al. (*6*)
	Ubiquitin-linked DNA	3; IM with electroporation	Yes	No	No	No	NA¶	Hawman et al. (*6*)
Nucleoprotein and all M genome segment proteins	Alphavirus-based replicon RNA	1; IM	Yes	NA	Yes	Yes	100	Leventhal et al. (*8*)
	Alphavirus-based replicon RNA	2; IM	Yes	No	Yes	Yes	100	Leventhal et al. (*8*)
Nucleoprotein, Gc, and Gn	Nucleoside-modified mRNA lipid nanoparticles	2; ID	Yes	Yes	Yes	Yes	100	Appelberg et al. (*5*)
	Ubiquitin-linked DNA	3; ID with electroporation	Yes	Yes	NA	Yes	100	Hinkula et al. (*18*)
All CCHF viral proteins	Viral replicon particle containing L and S genome segments#	1; SC	Yes	NA	NA	Yes	100	Scholte et al. (*19*)
			Yes	NA	NA	Yes	100	Spengler et al. (*20*)
			NA	NA	NA	Vaccinated ≥7 d before viral challenge: Yes. Vaccinated 3 d before viral challenge: Partial. Vaccinated 1 d before or after viral challenge: No	Vaccinated ≥3 d before viral challenge,100. Vaccinated 1 d before or after viral challenge, 0	Spengler et al. (*21*)
	Inactivated whole virus	3; IP	Yes	Yes	Yes	Partial	80–100	Berber et al. (*22*)

CCHF antigen target	Vaccine type	No. doses; route	CCHFV IgG	CCHFV neutralizing antibodies	CCHFV T-cell response†	Protection against‡		Ref.
						Symptomatic disease	Lethal disease, % survival	
	adjuvanted with alum derived from cell culture							Canakoglu et al. (*23*) Pavel et al. (*24*)

*CCHFV, Crimean-Congo hemorrhagic fever virus; ID, intradermal; IM, intramuscular; IP, intraperitoneal; SC, subcutaneous; NA, Not assessed.
†Direct measurement of CCHFV, CCHFV antigen-stimulated T-cell, or splenocyte responses only. Studies measuring serum cytokine levels post-vaccination were excluded.
‡For studies that assessed vaccine dosing ranges, the protection against symptomatic disease or lethal disease is presented only for the highest dose used.
§IgA antibodies were also detectable in serum and fecal pellets from vaccinated mice.
¶Unable to assess survival benefit due to non-lethal disease in the unvaccinated animal comparator study arm.
#The M genome segment is not contained in the viral replicon particle, however proteins from the M genome segment are provided *in trans* during the creation of the viral replicon particle leading to the incorporation of M genome segment proteins on the surface of the viral replicon particle.

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