

Safety and Immunogenicity of Adenovirus Type 5 (Ad5) HIV-1 gag Vaccines

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Abstract

Background: Studies in animals have demonstrated that immunization with recombinant adenovirus vectors is an efficient way to elicit HIV-specific cell mediated immune (CMI) responses. Two prototype recombinant Ad5 vaccines expressing a human codon optimized consensus clade B HIV-1 gag gene were tested in clinical trials.

Methods: The first vaccine, Ad5 HIV-1 gag, was tested in a multi-center, placebo controlled, randomized double blind trial in 160 healthy volunteers 18-50 years of age at low risk of HIV infection using a 3 dose regimen (Day 1, Week 4, Week 26) escalating doses from 10⁸ to 10¹¹ viral particles/dose (vp/dose). After the study had been initiated, genetic instability in the vector was noted in later passages; therefore the vector was modified to improve stability. The resulting vector, MRKAd5 HIV-1 gag, was tested in a multi-center, placebo controlled, randomized double blind trial in 92 healthy volunteers 18-50 years of age at low risk of HIV infection using escalating doses from 10⁸ to 10¹¹ vp/dose. In both studies subjects were followed for safety and immunogenicity.

Results: Both vaccines were generally safe and well tolerated. CMI responses, as measured by ELISpot, were elicited at all dose levels studied, though the vaccines were less immunogenic in subjects with high titers (>200) of pre-existing neutralizing antibodies to Ad5. The dose-response relationship to immunogenicity was similar for each vaccine; therefore the data from both vaccines are combined in the table below.

Pooled Ad5 and MRKAd5 gag Vaccine ELISpot Summaries at Wk 8 by Baseline Ad5 Titer

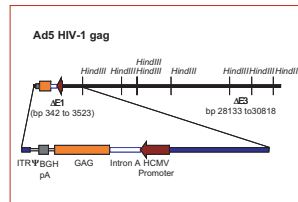
Dose Level (vp/d)	Baseline Ad5 Titer	
	≤200	>200
10 ⁸	% Resp.	60%
	G. Mean (Resp.)	276
	N	15
10 ⁹	% Resp.	69%
	G. Mean (Resp.)	213
	N	32
10 ¹⁰	% Resp.	69%
	G. Mean (Resp.)	263
	N	36
10 ¹¹	% Resp.	75%
	G. Mean (Resp.)	286
	N	44
Pooled	% Resp.	70%
	G. Mean (Resp.)	259
	N	127

ELISpot responder: ≥ 55 SFCs/10⁶ PBMCs and ≥ 4-fold over media control

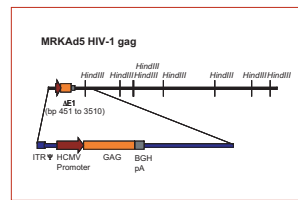
Conclusions: In these 2 studies, both adenovirus type 5 vectors were generally safe and well tolerated and were immunogenic in humans. Pre-existing immunity to Ad5 dampens immunogenicity.

Monovalent gag Vaccines

- Similarities in the vectors
 - Deletion of E1 gene
 - Disables viral replication
 - Diminishes adenovirus gene expression
 - E1 provided in trans by production in PER.C6 cells
 - Gag transgene is identical
 - Near consensus Clade B isolate (CAM-1)
 - Human codon-optimized to enhance antigen production



- Differences in the vectors
 - Ad5 HIV-1 gag was genetically unstable after multiple passages, MRKAd5 HIV-1 gag is stable to passages beyond that expected for large-scale manufacture
 - Ad5 HIV-1 gag also has deletion of E3, MRKAd5 HIV-1 gag is E3+
 - Ad5 HIV-1 gag has CMV Intron A, MRKAd5 HIV-1 gag does not
 - Orientation of the transgene
 - 5' packaging region was modified in MRKAd5 HIV-1 gag to make it more like wild-type adenovirus



Study Design

- Both studies were randomized, double-blind, placebo-controlled, dose escalating studies
- Protocol 007
 - Ad5 HIV-1 gag vaccine
 - N=160
 - 3 injections: Day 1, Week 4, Week 26
 - Dose levels: 1x10⁸, 1x10⁹, 1x10¹⁰, 1x10¹¹vp/dose
- Protocol 012
 - MRKAd5 HIV-1 gag vaccine
 - N=92
 - 3 injections: Day 1, Week 4, Week 26
 - Dose levels: 1x10⁸, 1x10⁹, 1x10¹⁰vp/dose

Protocols 007 and 012 Demographics

	Placebo (N=49) n (%)	1x10 ⁸ (N=24) n (%)	1x10 ⁹ (N=49) n (%)	1x10 ¹⁰ (N=65) n (%)	1x10 ¹¹ (N=65) n (%)
Gender					
Male	21 (43%)	11 (46%)	28 (57%)	35 (54%)	31 (48%)
Female	28 (57%)	13 (54%)	21 (43%)	30 (46%)	34 (52%)
Age (years)					
Mean	34.3	35.5	35.6	32.3	33.7
SD	10.1	8.9	10.0	8.8	9.5
Median	35.0	37.0	36.0	31.0	33.0
Range	18 TO 51	20 TO 50	19 TO 50	18 TO 49	19 TO 50
Male	21 TO 50	27 TO 50	19 TO 50	18 TO 48	19 TO 50
Female	18 TO 51	20 TO 48	19 TO 50	20 TO 49	20 TO 47
Race/Ethnicity					
Asian/Pacific	0 (0%)	1 (4%)	0 (0%)	1 (2%)	2 (3%)
Black	6 (12%)	4 (17%)	5 (10%)	5 (8%)	4 (6%)
Caucasian	43 (88%)	19 (79%)	42 (86%)	54 (83%)	56 (86%)
Hispanic	0 (0%)	0 (0%)	2 (4%)	5 (8%)	1 (2%)
Indian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Native American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)

Disposition of Enrolled Subjects

- 252 Subjects Enrolled
- 232 Subjects Continuing at Week 30
 - 230 subjects completed vaccination series and continued study follow-up
 - 2 subjects did not complete vaccination series due to clinical adverse event (back pain and throat and chest tightness/difficulty breathing) but continued study follow-up
- 18 Subjects Discontinued Prior to Completion of Vaccination Series
 - 1 due to clinical adverse event (depression with suicidal ideation)
 - 6 lost to follow-up
 - 4 moved
 - 4 withdrew consent
 - 3 due to other reason
- 2 Additional Subjects Discontinued Prior to Week 30
 - 1 withdrawal consent
 - 1 due to protocol deviation

Safety and Immunogenicity Results

Ad5 and MRKAd5 gag Vaccines

- Both vaccines were generally well tolerated
 - Injection site reactions were common
 - Frequency increased with dose
 - Generally mild to moderate intensity
 - No subject discontinued due to injection site AE
 - Systemic AEs
 - Most common were headache, fever, chills, myalgias
 - More common after the first injection
 - Frequency increased with dose
 - More common in subjects with low pre-existing immunity to Ad5
 - Two vaccine related serious AEs (chills and fatigue)
- See poster # 503 for more detailed safety analyses

Summary of Common AEs After 1st Vaccination by Dose Level

AE	1x10 ⁸	1x10 ⁹	1x10 ¹⁰	1x10 ¹¹
Injection site			<▲>	<▲>
Chills			<▲	<▲
Fatigue			<▲	<▲
Myalgia			<▲>	<▲>
Pyrexia			<▲	<▲
Pain		<▲	<▲	<▲
Back pain			▲	▲
Nasal congestion				▲>
Dizziness		▲		<
Nasopharyngitis			▲	
Pharyngolaryngeal pain				▲>
Body temperature increased				<
Sinus headache		▲		

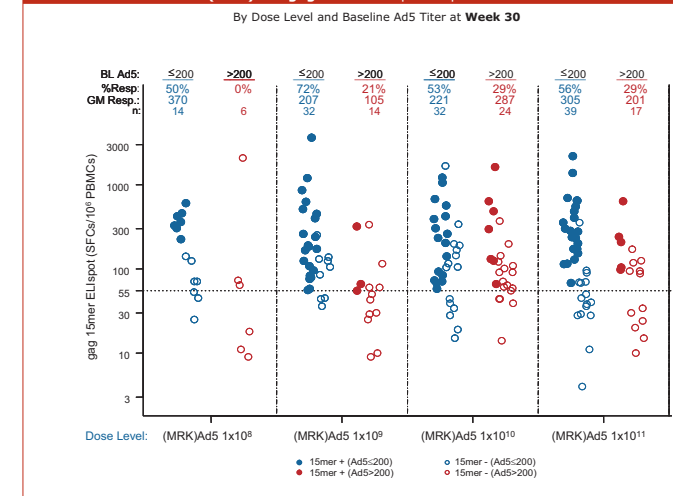
- ▲ significantly higher AE rate in the vaccine group than placebo after Double False Discovery Rate multiplicity adjustment (for subjects in all strata)
- ▲ nominal p-value below 0.05 for testing higher AE rate in the vaccine group (for subjects in all strata)
- < for the stratum Ad5 titer ≤200; > for the stratum Ad5 titer >200

Protocol 007 and 012: (MRK)Ad5 gag Vaccine 15mer ELISpot Summaries by Baseline Ad5 Titer

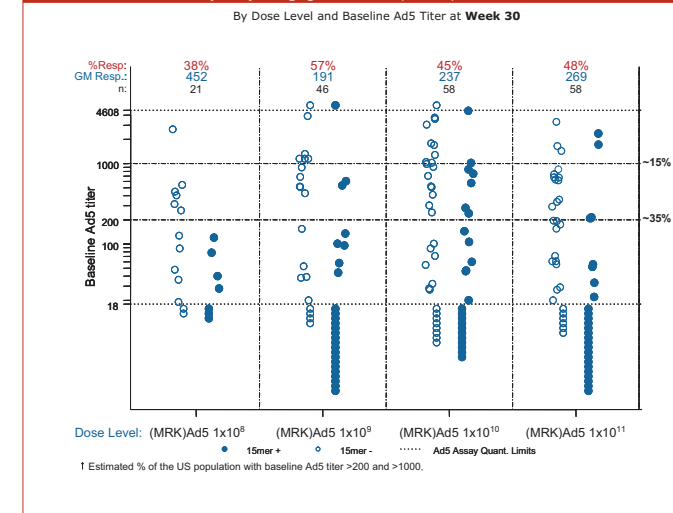
Dose (vp/d)	Ad5 Titer ≤ 200			Ad5 Titer > 200			All Subjects		
	Wk 4	Wk 8	Wk 30	Wk 4	Wk 8	Wk 30	Wk 4	Wk 8	Wk 30
10 ⁸	% Resp.	53%	60%	50%	0%	0%	39%	43%	38%
	G. Mean (Resp.)	282	276	370			272	307	452
	N	15	15	14	7	7	6	23	21
10 ⁹	% Resp.	34%	69%	72%	20%	20%	21%	30%	57%
	G. Mean (Resp.)	217	213	207	197	187	105	213	209
	N	32	32	32	15	15	14	47	46
10 ¹⁰	% Resp.	47%	69%	53%	36%	33%	29%	44%	45%
	G. Mean (Resp.)	259	263	221	248	309	287	263	284
	N	36	36	32	25	24	24	63	58
10 ¹¹	% Resp.	69%	75%	56%	24%	53%	29%	55%	70%
	G. Mean (Resp.)	295	286	305	160	168	201	275	243
	N	45	44	39	17	17	17	64	58

Dosing regimen: Wks 0, 4 (priming series) + Wk 26 (booster)
ELISpot Responder: ≥55 SFC/10⁶ PBMCs and ≥4-fold over media control
False positive rate of ELISpot assay < 1% (Mogg et. al, 2002)
N for "All Subjects" includes subjects with missing Ad5 titer results

Protocols 007 and 012: (MRK)Ad5 gag 15mer ELISpot Responses



Protocols 007 and 012: (MRK)Ad5 gag 15mer ELISpot Responses



Summary/Conclusions

- Both monovalent vaccines were generally well tolerated at all doses
- AEs were dose related
 - Most common at 1x10¹¹vp/dose
 - Most common following 1st dose
 - Systemic AEs were less common following subsequent doses
 - AEs were more common in subjects with low baseline Ad5 neutralizing titers
- Gag-specific ELISpot responses were observed at all doses
 - At doses ≥1x10⁹vp/dose >50% of subjects developed a positive ELISpot response
 - Proportion of responders was higher in subjects with baseline Ad5 titers ≤200
- The monovalent vaccines resulted in gag-specific ELISpot responses similar to those reported with the trivalent vaccine (Abstract # G-109)

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