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GTL001, A Therapeutic Vaccine for Women Infected with Human Papillomavirus 16 or 18 and Normal Cervical Cytology: Results of a Phase I Clinical Trial

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Abstract

Purpose: Women infected with human papillomavirus (HPV) with normal cytology to mild abnormalities currently have no treatment options other than watchful waiting or surgery if high-grade cervical lesions or cancer develop. A therapeutic vaccine would offer the possibility of preventing high-grade lesions in HPV-infected women. GTL001 is a therapeutic vaccine composed of recombinant HPV16 and HPV18 E7 proteins fused to catalytically inactive *Bordetella pertussis* CyaA. This study examined the tolerability and immunogenicity of GTL001 in women infected with HPV16 or HPV18 with normal cytology.

Experimental Design: This was a phase I trial (EudraCT No. 2010-018629-21). In an open-label part, subjects received two intradermal vaccinations 6 weeks apart of 100 or 600 μg GTL001 + topical 5% imiquimod cream at the injection site. In a double-blind part, subjects were randomized 2:1:1 to two vaccinations 6 weeks apart of 600 μg GTL001 + imiquimod, 600 μg GTL001 + placebo cream, or placebo + imiquimod.

Results: Forty-seven women were included. No dropouts, treatment-related serious adverse events, or dose-limiting toxicities occurred. Local reactions were transient and mostly mild or moderate. HPV16/18 viral load decreased the most in the 600 μg GTL001 + imiquimod group. In *post hoc* analyses, the 600 μg GTL001 + imiquimod group had the highest rates of initial and sustained HPV16/18 clearance. Imiquimod increased antigen-specific T-cell response rates but not rates of solicited reactions. All subjects seroconverted to CyaA.

Conclusions: For women infected with HPV16 or HPV18 with normal cervical cytology, GTL001 was immunogenic and had acceptable safety profile. *Clin Cancer Res; 22(13); 3238–48. ©2016 AACR.*

Introduction

The development of diagnostic tests for human papillomavirus (HPV) has created a new opportunity to identify women at risk for cervical intraepithelial neoplasia (CIN) and cervical cancer before lesions appear (1). Although prophylactic HPV vaccines are available for preventing cervical cancer in women not yet infected with HPV, they are not effective once a woman is infected, so these women have no treatment options other than watchful waiting for clearance or, in the event that a high-grade lesion or cancer appear, surgery with possible adjunct chemotherapy (2). Surgical excision is very successful for high-grade lesions and cervical cancer, but alternatives are needed because surgery can lead to infertility, pregnancy problems, incontinence, and sexual dysfunction (2–5).

A therapeutic vaccine would offer the possibility of treating HPV-infected women before local immunosuppression and viral escape mechanisms develop and high-grade lesions appear (2, 6). To control existing infections and malignancies, a therapeutic vaccine should induce T-cell–mediated immunity against HPV-infected cells. Most therapeutic vaccines in development target the HPV E7 protein and, in some cases, also the E6 protein, which are required for cellular transformation and maintenance of a neoplastic phenotype and are expressed by all cervical cancers and precursor lesions (7–9). A variety of approaches have been tested, including a chimeric virus–like particle, a dendritic cell vaccine, fusion proteins, peptides, an attenuated virus, and recombinant viruses (10–12). Several have shown promise in treating vulvar and high-grade CIN, and some induce cellular immunity against HPV, but these vaccines have only been tested in women who already have high-grade lesions. For example, recent studies showed that two therapeutic DNA vaccines, one targeting HPV16 and HPV18 E6 and E7 (13) and the other targeting HPV16 E7 (14), can induce regression of CIN2/3.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Women infected with oncogenic human papillomavirus (HPV) who still have normal cervical cytology or mild abnormalities have no treatment options other than watchful waiting or, if high-grade lesions or cancer develop, surgery with possible adjunct chemotherapy. The development of highly sensitive HPV genotyping tests has opened the possibility of treating HPV-infected women before high-grade lesions appear. GTL001 is a candidate therapeutic vaccine consisting of HPV16 and HPV18 E7 both fused to CyaA from *Bordetella pertussis*. This phase I trial showed that GTL001, adjuvanted with topical 5% imiquimod cream, has an acceptable safety profile and is immunogenic in women infected with HPV16 or HPV18 who had normal cervical cytology. In addition, the study provided initial evidence that GTL001 adjuvanted with imiquimod cream can promote clearance of HPV16 and HPV18. The ability of GTL001 to prevent high-grade lesions in HPV-infected women is being investigated in a phase II clinical trial.

GTL001 is a candidate therapeutic vaccine that targets HPV16 and HPV18, which are associated with the highest risk of developing CIN3 and cervical cancer (15). It is designed to induce a T-cell immune response to HPV16 and HPV18 and prevent the development of high-grade lesions in infected women who still have normal cervical cytology or mild abnormalities. GTL001 contains recombinant HPV16 and HPV18 E7 proteins each fused to a catalytically inactive *Bordetella pertussis* adenylate cyclase (CyaA) as a vaccine vector (16, 17). CyaA specifically interacts with the CD11b/CD18 integrin, so that the E7 antigens are delivered to $CD11b^+$ antigen-presenting cells. In the antigen-presenting cells, the E7 proteins are processed and presented as $CD4^+$ and $CD8^+$ T-cell epitopes to T lymphocytes (16). Vaccination of mice with a recombinant CyaA bearing the HPV16 E7 antigen has been shown to induce an anti-HPV E7-specific T-cell response and to eliminate established HPV16 E7-expressing tumors (17–19).

Here, we report the results of a phase I study examining the safety, tolerability, and immunogenicity of GTL001 in women infected with HPV16 or HPV18 who have normal cervical cytology.

Materials and Methods

Study design

This phase I trial (EudraCT No. 2010-018629-21) was performed at the Vaccine and Infectious Disease Institute (VAX-INFECTIO, University of Antwerp, Antwerp, Belgium) between June 18, 2010, and December 31, 2012. The primary objective was to examine the safety and the local and general tolerability from week 0 to 10 of GTL001 solution and GTL001 powder in women infected by HPV 16, HPV 18, or both who have normal cytology. Secondary objectives were to examine the safety, local and general tolerability, and the cellular and humoral immunogenicity of GTL001 solution and GTL001 powder from week 10 to 26. The study included three open-label cohorts and one randomized, placebo-controlled, double-blind cohort (Fig. 1).

Safety and tolerability endpoints included the incidence of treatment-emergent adverse events (TEAEs) up to week 10 and during the follow-up phase (week 10–26); treatment-emergent changes in vital signs, clinical laboratory tests, and physical examinations; incidence and severity of solicited local reactions (pain, tenderness, erythema, swelling, induration, ulceration, scabs, and itching) and systemic reactions (arthralgia, myalgia, headache, fatigue, nausea, fever, rigors) during the 7 (cohorts 1–3) or 14 (cohort 4) days after the first vaccination and during the 7 (cohorts 1–3) or 10 (cohort 4) days after the second vaccination; and changes in cervical cytology and cervical HPV virology at weeks 10, 26, and during the post-week 26 follow-up. Immunogenicity endpoints were assessed up to 26 weeks and included treatment-emergent changes in T-cell responses to HPV16 and HPV18 E7 antigen stimulation by IFNγ enzyme-linked immunosorbent spot (ELISpot) assay and treatment-emergent changes in anti-HPV16 E7, anti-HPV18 E7, and anti-CyaA serum antibody titers as measured by ELISA.

Ethics

The study was approved by the Comité Voor Medische Ethiek (Universitair Ziekenhuis Antwerpen) and complied with Belgian laws, Good Clinical Practice, and the Declaration of Helsinki. All subjects participating in the study provided written informed consent.

Subjects

Healthy, nonpregnant, nonlactating women 18 to 45 years of age were considered for enrolment if they were infected with HPV16, HPV18, or both according to two different genotyping tests (see heading "Virology") and had consecutive normal cervical cytology examinations separated by 6 weeks to 12 months and a normal gynecologic examination. They could not have had a history of cervical cancer or untreated high-grade histologic lesion (CIN grade 2 or 3) or any other disease or condition that, in the opinion of the investigator, could have affected the outcome of the trial. Full selection criteria are provided in the Supplementary Methods.

Vaccines and topical creams

GTL001 consists of equal amounts of two recombinant E7-CyaA fusion proteins expressed in and purified from *Escherichia coli*. The HPV16 E7–CyaA fusion protein included amino acids 1–29 of HPV16 E7 inserted between amino acids 319–320 of CyaA and amino acids 43–98 of HPV16 E7 inserted between amino acids 224–235 of CyaA. The HPV18 E7–CyaA fusion protein included amino acid 1–31 of HPV18 E7 inserted between amino acids 319–320 of CyaA and amino acids 43–105 of HPV18 E7 inserted between amino acids 224–235 of CyaA. Thus, the E7 sequences in should not bind retinoblastoma protein.

The solution formulation of GTL001 (lot no. G091/PRO001/FC001) was provided in sterile, single-use vials and was diluted prior to use to give 100 μg (low dose) or 600 μg (high dose) GTL001 in 1 mL of PBS with 1.32 mol/L urea. The powder formulation of GTL001 (lot no. G152/C16C18/FC001) was provided in single-use vials and was reconstituted prior to use with sterile water to 3 mg/mL (0.6 mg in 0.2 mL) of GTL001 in PBS with 1.32 mol/L urea and 33 g/L trehalose. The placebo injection was PBS + 1.32 mol/L urea. All injections were intradermal in the upper thigh. Placebo and the solution formulation of GTL001

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were administered as five 0.2-mL injections, and the powder formulation of GTL001 was administered as a single 0.2-mL injection.

Topical 5% imiquimod cream (Aldara™) was from 3M Health Care Limited. Placebo cream (Excipial Hydrolotion Neutre) was from Laboratoires SPIRIG SAS. Imiquimod and placebo creams (50 mg/injection site) were applied 15 minutes and 24 hours after each injection at each injection site.

Study conduct

The first two cohorts comprised an open-label portion of the trial (Fig. 1). In the first cohort, five subjects were treated with the low-dose (100 μg) GTL001 solution at weeks 0 and 6 adjuvanted with topical application imiquimod cream. Following approval by a safety review committee, five subjects were treated with the high-dose (600 μg) GTL001 solution and imiquimod cream in a second cohort, also at weeks 0 and 6.

After review of all available safety data, the third cohort enrolled 28 subjects. The subjects were randomized 2:1:1 to receive, at weeks 0 and 6, 600 μg GTL001 solution + imiquimod cream, 600 μg GTL001 solution + placebo cream, or placebo + imiquimod cream. Subjects in this cohort were randomized using an unstratified computer-generated list containing a three-digit randomization number and the corresponding treatment group allocation. The randomized treatment assignments were communicated to an unblinded site pharmacist who prepared the injections and creams, and investigators, clinical and laboratory staff, study monitors, and subjects were blinded to treatment assignment.

In the fourth cohort, nine subjects were treated open label with a single 0.2-mL intradermal injection of 600 μg GTL001 powder + imiquimod cream at weeks 0 and 6.

Blood samples were collected at baseline (before the first vaccination) and at weeks 2, 6, 8, 10, and 26. Gynecologic examinations including cervical brush scrapings were performed at the screening visit (0–3 weeks before the first vaccination) and at weeks 10 and 26. Additional cervical brush scrapings were taken before the last date of follow-up included in this analysis (December 31, 2012). Cervical cells were collected into BD-SurePath (BD Diagnostics – Tripath) using a Cervex-Brush Combi (Rovers Medical Devices B.V.).

TEAEs were recorded by investigators throughout the study and were coded using MedDRA version 14 (MedDRA MSSO). Local reactions and TEAEs were graded by clinicians at postvaccination visits and solicited reactions were graded by subjects in daily diaries according to Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (ref. 20; see Supplementary Methods for details). Investigators assessed the relatedness of events to the treatment.

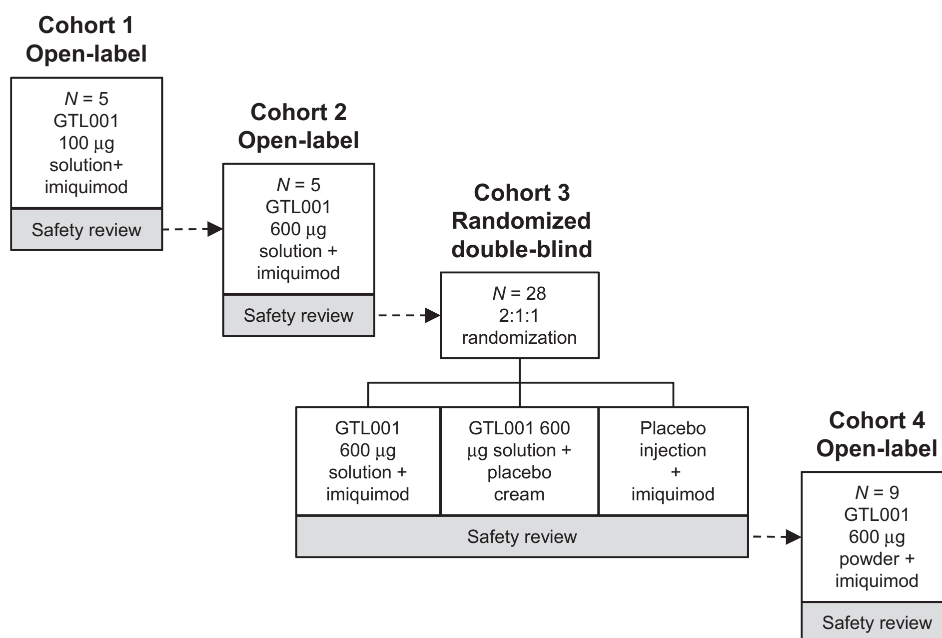

Figure 1.

Study design. The study included three open-label cohorts with an escalating dose design and one randomized, placebo-controlled, double-blind cohort. The first two cohorts composed of an open-label escalating dose portion of the trial. In the first cohort, five subjects were treated with the low-dose (100 μg) GTL001 solution as five 0.2-mL injections at weeks 0 and 6 adjuvanted with topical application imiquimod cream at each injection site. Following approval by a safety review committee, a second cohort of five subjects was treated with the high-dose (600 μg) GTL001 solution and imiquimod cream, also as five 0.2-mL intradermal injections at weeks 0 and 6. Following approval by the safety review committee, a third cohort of 28 subjects was randomized 2:1:1 to receive five 0.2-mL intradermal injections at weeks 0 and 6 of 600 μg GTL001 solution + imiquimod cream, 600 μg GTL001 solution + placebo cream, or a placebo injection + imiquimod cream. In the fourth and final cohort, nine subjects were treated open label with a single 0.2-mL intradermal injection of 600 μg GTL001 powder + imiquimod cream at weeks 0 and 6. In addition to the safety reviews before cohorts 2 and 3, the safety review committee made decisions about whether to proceed with second vaccinations and with subsequent cohorts.

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Cervical cytology and HPV virology

Cytology was assessed in thin-layer cell preparations of cervical cells collected from brush scrapings. Thin-layer cell preparations with staining for cytologic analysis were generated with the BD PrepStain slide processor using 200 μL of cervical cell–enriched fraction. Thin-layer cytology slides were read without knowledge of HPV results. Cytologic results were classified according to the 2001 version of the Bethesda System (21). Epithelial abnormalities in the Bethesda system include: atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells of undetermined significance—cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma, and atypical glandular cells (AGC).

To assess HPV virology, cells were collected from remaining cervical brush samples by density sedimentation at 3,000 × *g* on a BD PrepMate system (BD Diagnostics - Tripath). DNA was isolated from the cell pellet remainder as described by Micalessi and colleagues (22) using a JANUS Automated Solution Handling System (Perkin-Elmer). TaqMan-based multiplex qPCR (Life Technologies), a clinically validated type-specific qPCR test (23) that is accredited for use in Belgium by the Belgian Accreditation Organization, was performed to detect HPV genotypes including HPV16 and HPV18, with β-globin as a control. HPV16/18 positivity was defined as ≥1 HPV copy/10,000 cells. Full details of nucleic acid preparation and PCR methods are described in the Supplementary Methods. HPV virology was reported as viral load change from baseline. In addition, in a *post hoc* analysis, HPV16/18 clearance and sustained clearance were described until the last date of follow-up included in this analysis (December 31, 2012). HPV16/18 clearance was defined as the nondetection of both HPV16 and HPV18 by qPCR at a given time point, and sustained HPV16/18 clearance was defined as the maintenance of an initial clearance of HPV16 and HPV18 until the end of the follow-up period.

Ex vivo IFNγ ELISpot

Peripheral blood mononuclear cells (PBMC) were isolated from heparinized blood samples and stored in liquid nitrogen. PBMC were thawed, diluted in CTL test medium (Cellular Technology Limited) + 1% L-glutamine, and added (4×10^5/well) to 96-well ELISPOT plates (Millipore) coated with anti-IFNγ mAb (Thermo Fisher Scientific). Cells were stimulated in triplicate with 15-mer peptides (Bachem; 50 or 100 μg/mL) overlapping by 11 amino acids covering the full HPV16 or HPV18 E7 sequences (as six pools of peptides). All assays also included medium alone as a negative control and 5 μg/mL phytohemagglutinin (Sigma Aldrich) as a positive control. After 20 hours at 37°C, cells secreting IFNγ were detected by biotin-labeled anti-IFNγ (Thermo Fisher Scientific) followed by streptavidin-horseradish peroxidase (Becton Dickinson) and color development with 3-amino-9-ethyl carbazole (Sigma Aldrich; Sigma). The number of spots was measured with an Immunospot Analyzer and Immunospot software (Cellular Technology Limited).

For each subject, peptide pool, and time point, the specific ELISpot response was calculated as [(mean antigen-stimulated spot-forming cells [SFC] − SD of antigen-stimulated SFC) − (mean SFC for medium + 2 × SD of SFC for medium)]. A specific response was considered to be positive if it was >20 SFC per 4×10^5 PBMC and the mean antigen-specific SFC was >3 × mean SFC for medium alone. For each peptide pool, a subject was considered a responder if (i) they had a positive specific response to any peptide pool at any postvaccination time point before week 26 and did not have a specific response at baseline; or (ii) they had a specific positive response to any peptide pool at any postvaccination time point before week 26 ≥ 2 × specific response at baseline (if they had a specific positive response at baseline).

ELISA

Anti-HPV16 E7, anti-HPV18 E7, and anti-CyaA serum antibodies were measured by ELISA. Recombinant CyaA (i.e., empty vector) was produced in *E. coli* and purified from inclusion bodies by a two-step procedure that included DEAE-sepharose and phenyl-sepharose chromatography (GE Healthcare; ref. 24). HPV16 E7-HIS (SCIL) and HPV18 E7-HIS (GTP) were produced as described by Mirecka and colleagues (25). These two His-tag-proteins were expressed in *E. coli* and purified on a metal chelate affinity chromatography column preloaded with Ni^{2+} (GE Healthcare). MaxiSorp 96-well plates (Nunc-Thermo Fisher Scientific) were coated overnight at 4°C with 5 μg/mL recombinant HPV16 E7-HIS and HPV18 E7-HIS or 0.625 μg/mL CyaA in 50 mmol/L carbonate–bicarbonate buffer pH 9.6. The plates were then blocked 2 hours at room temperature in PBST-BSA and then incubated for 1 hour at room temperature with the sera to be tested diluted in PBST-BSA. For anti-CyaA ELISA, sera were prepared as a series of seven two-fold dilutions starting at 1:500. For anti-HPV16 and anti-HPV18 E7 ELISAs, sera were diluted 1:160 in quadruplicate. After washing with PBST, specific antigen–antibody complexes were detected by a peroxidase-conjugated anti-human immunoglobulin (Sigma-Aldrich) followed by color development with tetramethylbenzidine. The absorbance at 405 nm was measured with a microtiter plate reader (Molecular Devices). For the anti-CyaA ELISA, the cutoff was defined using a panel of sera of nonvaccinated subjects as previously described (26, 27). Antibody titers were calculated using SoftMax Pro (Molecular Devices) by comparison with a standard of pooled anti-CyaA–positive serum in which the concentration was arbitrarily set as 10,000 ELISA units/mL. Seroconversion to CyaA was defined as a >4-fold increase in titer compared with the prevaccination value. For the anti-HPV16 and anti-HPV18 E7 ELISAs, serologic status (responder/nonresponder) was determined using an internal negative control on each plate combined with the defined cut-off factor for each assay.

Statistical analysis

Calculations were made using Excel 2010 (Microsoft) or SAS version 9.2 (SAS Institute). No formal statistical comparisons were planned. The end of follow-up for this analysis was December 31, 2012. Safety and tolerability endpoints were analyzed in the safety population, defined as all subjects who received any study treatment. Immunogenicity endpoints were assessed in the intent-to-treat population, defined as all subjects in the randomized cohort and those in the open-label cohorts who received any amount of study treatment and who had at least one post-baseline immunologic evaluation.

Results

Subjects

Forty-seven healthy women positive for HPV16 or HPV18 but with normal cervical cytology were enrolled in the study

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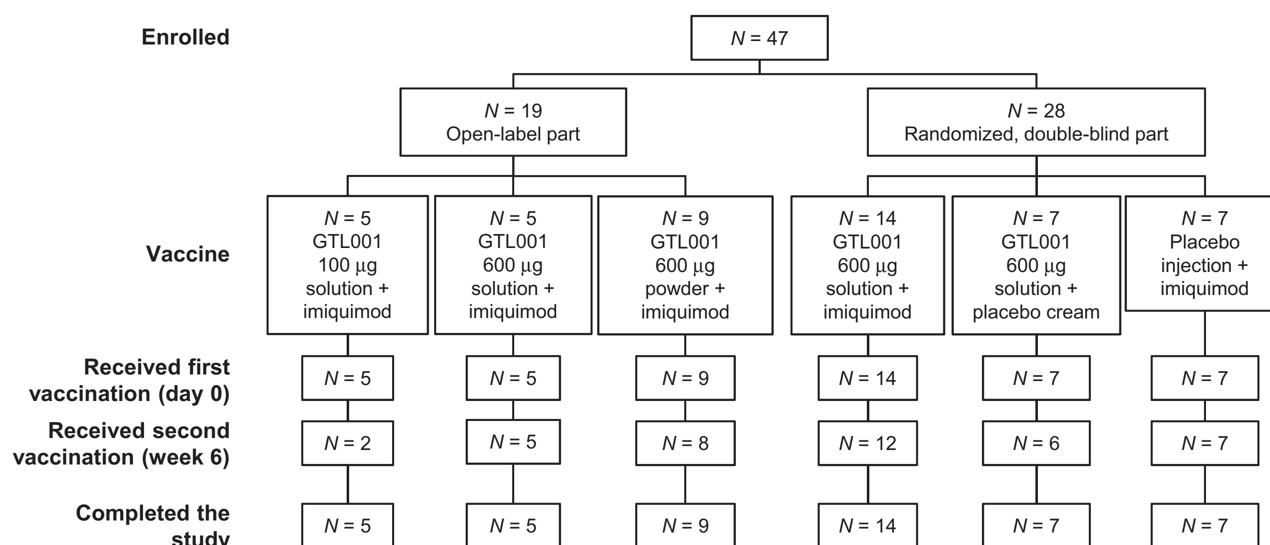

Figure 2.

Subject disposition. Nineteen healthy women positive for HPV16 and/or HPV18 and with normal cervical cytology were enrolled in the open-label part and 28 were enrolled in the randomized double-blind part. All subjects completed the study, although seven received only a single vaccination.

between June 18, 2010, and November 29, 2011 (Fig. 2). The end of follow-up for this analysis was December 31, 2012 [mean follow-up time = 16.7 months (range 5.7–29.3)]. All subjects completed the study, although in seven cases, after consulting with the safety review committee, the investigator decided to not give a second vaccination because of concerns that a severe local reaction would occur and in light of the product's unproven efficacy.

Baseline demographic characteristics were similar in all treatment groups (Table 1). HPV16 was detected in 76.6% ($n = 36$) and HPV18 in 23.4% ($n = 11$). Coinfection with HPV subtypes other than HPV16 and HPV18 was detected in 21.3% ($n = 10$). All

Table 1. Baseline characteristics

Characteristic	Cohort 1 Open-label GTL001 100 µg solution + imiquimod N = 5	Cohort 2 Open-label GTL001 solution 600 µg + imiquimod N = 5	Cohort 3 Randomized, double-blinded GTL001 solution 600 µg + imiquimod N = 14	Cohort 3 Randomized, double-blinded GTL001 solution 600 µg + placebo N = 7	Cohort 3 Randomized, double-blinded Placebo injection + imiquimod N = 7	Cohort 4 Open-label GTL001 600 µg powder + imiquimod N = 9
Mean age ± SD (y)	29.0 ± 8.9	29.8 ± 3.1	33.1 ± 6.5	33.3 ± 10.2	32.7 ± 8.7	33.2 ± 7.6
Race						
Caucasian	5 (100.0)	4 (80.0)	14 (100.0)	7 (100.0)	7 (100.0)	9 (100.0)
Other	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HPV type, *n* (%)						
HPV16	5 (100.0)	4 (80.0)	11 (78.6)	5 (71.4)	5 (71.4)	6 (66.7)
HPV18	0 (0.0)	1 (20.0)	3 (21.4)	2 (28.6)	2 (28.6)	3 (33.3)
Co-infection with other HPV types, *n* (%)	1 (20.0)	1 (20.0)	5 (35.7)	0 (0.0)	1 (14.3)	2 (22.2)
Mean duration of infection (mo)[a]						
HPV16	19.8	6.5	14.6	12.2	15.4	13.7
HPV18	—	3.5	15.3	10.0	3.5	25.7
Cytology at baseline[b], *n* (%)						
Negative (NILM)	5 (100.0)	5 (100.0)	14 (100.0)	7 (100.0)	7 (100.0)	9 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Previous cytology[b] (past 5 years), *n* (%)						
Negative (NILM)	2 (40.0)	3 (60.0)	7 (50.0)	2 (28.6)	4 (57.1)	4 (44.4)
ASC-US	3 (60.0)	0 (0.0)	5 (35.7)	1 (14.3)	0 (0.0)	1 (11.1)
LSIL	0 (0.0)	2 (40.0)	2 (14.3)	2 (28.6)	2 (28.6)	3 (33.3)
HSIL	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	0 (0.0)

NOTE: Values are for the safety population.

[a]Number of months between the earliest recorded relevant positive result and the first study visit with no intervening negative results.

[b]Graded according to the Bethesda system (21). Categories include: atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells of undetermined significance—cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma, and atypical glandular cells (AGC).

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subjects were negative for intraepithelial neoplasia or malignancy at screening, although approximately half (23/47; 49%) had one or more reports of abnormal cytology in the 5 years before the study.

Safety and tolerability

Solicited reactions. All subjects reported solicited reactions, most of which were grade 1 or 2 (mild to moderate; Table 2). Seventeen subjects, all treated with GTL001, reported grade 3 (severe) solicited reactions. These grade 3 events were not dose or adjuvant dependent. Most of these were at the injection-site [pain ($n = 9$), tenderness ($n = 9$), erythema ($n = 6$), swelling ($n = 4$), itching ($n = 2$), and induration ($n = 2$)], although a few grade 3 systemic reactions were reported [fatigue ($n = 3$), myalgia ($n = 1$)]. Seven of the subjects experiencing grade 3 reactions were treated with medication (over-the-counter oral analgesics). In most cases, grade 3 reactions decreased in intensity within 1 to 2 days (data not shown).

Injection-site reactions were reported by all of the subjects treated with GTL001 but few (0–28.6%) treated with placebo. Scabs at the injection site, all grade 1, were reported only by subjects treated with GTL001 solution 600 μg + imiquimod (4/19; 21.1%), and none of the subjects reported ulceration.

After the first vaccination with GTL001, subjects reported two peaks of solicited injection-site reactions, most of which were of mild-to-moderate intensity. The initial reactions peaked on the same day or on the day after vaccination and then diminished or even disappeared, after which they reappeared with greater intensity on the second to fifth day after the vaccination and lasted 2 to 3 days (data not shown). In contrast, following the second vaccination, a single peak of injection-site reactions appeared immediately, and none of the subjects experienced recall of injection-site reactions at the first vaccination site.

Headache, myalgia, and fatigue were the most common systemic reactions in all groups. For several of the solicited systemic reactions, proportions were higher with GTL001 than placebo (52.5% vs. 14.3% for myalgia, 67.5% vs. 57.1% for headache, 72.5% vs. 57.1% for fatigue, 7.5% vs. 0.0% for fever, and 30.0% vs. 14.3% for rigors).

Within the randomized, double-blind cohort (cohort 3), proportions reporting solicited reactions were similar for subjects treated with GTL001 600 μg + placebo cream and GTL001 600 μg + imiquimod, whereas few subjects treated with the placebo injection + imiquimod reported solicited reactions. Solicited reactions appeared to be similar for subjects treated with GTL001 100 μg solution, GTL001 600 μg solution, and GTL001 600 μg powder. However, grade 3 injection-site pain, erythema, and induration were more common with the powder formulation.

TEAEs. All subjects treated with GTL001 had TEAEs considered by the investigator to be treatment related. Other than erythema, pain/tenderness, induration, and swelling at the injection site, which were also reported by subjects as solicited reactions, the most common temporary treatment-related TEAEs were injection-site discoloration (100% for GTL001, 28.6% for placebo), injection-site dryness (50.0% for GTL001, 0.0% for placebo), and lymphadenopathy ipsilateral to the injection sites (27.5% for GTL001, 0.0% for placebo; Supplementary Table S1). One subject treated with GTL001 600 μg powder + imiquimod had grade 3 lymphadenopathy that resolved after treatment with ibuprofen and fusidine cream; all other cases were grade 1 or 2. None of the subjects withdrew from the study due to an adverse event. A single subject experienced SAEs (syncope and a fall with concussion) that were considered unrelated to treatment.

Cervical HPV virology. In most groups treated with GTL001 600 μg + imiquimod, mean viral loads decreased over time (Table 3). In the *post hoc* analysis, we found that the number of subjects who cleared (i.e., had no detectable) HPV16 and HPV18 increased over time in all groups, although the largest increases were in subjects treated with GTL001 600 μg + imiquimod.

In addition, in this *post hoc* analysis, we examined sustained HPV16/18 clearance in subjects ($n = 21$) who had virology data after an initial clearance. Within the randomized cohort (cohort 3), sustained HPV16/18 clearance was more frequent (5/6) in subjects treated with GTL001 solution 600 μg + imiquimod than in subjects treated with placebo + imiquimod (1/3) or GTL001 solution 600 μg + placebo cream (0/2). In the open-label portion of the study, sustained clearance was observed in most subjects (2/3 treated with GTL001 solution 100 μg + imiquimod, 2/3 treated open-label with GTL001 solution 600 μg + imiquimod, and 3/4 treated with GTL001 powder 600 μg + imiquimod). Overall, sustained clearance of HPV16 and HPV 18 was observed in seven of nine subjects treated with GTL001 600 μg solution + imiquimod.

Cervical cytology. During the study, 13 subjects developed cytologic abnormalities excluding ASC-US, including 8 of 40 (20.0%) subjects treated with GTL001 and 5 of 7 (71.4%) treated with placebo (Supplementary Table S2). Two of these subjects, both treated with GTL001 600 μg solution + imiquimod, had high-grade lesions, both of whom underwent conization. Clear differences in cytology between treatment groups were not observed.

Immunogenicity

Cellular immunogenicity. Cellular immunogenicity was assessed by ELISpot (Supplementary Figs. S1–S6). In the randomized portion of the study (cohort 3), 53.8% (7/13) of subjects treated with GTL001 solution 600 μg + imiquimod were considered responders, whereas only 16.7% (1/6) of those treated with placebo + imiquimod and 16.7% (1/6) of those treated with GTL001 solution 600 μg + placebo cream were considered responders (Table 4 and Supplementary Table S3). In the open-label portion of the study, 80.0% (4/5) of subject treated with GTL001 solution 600 μg + imiquimod, 62.5% (5/8) treated with GTL001 powder 600 μg + imiquimod, and 40.0% (2/5) treated with GTL001 solution 100 μg + imiquimod were considered responders.

Humoral immunogenicity. GTL001 did not induce seroconversion to HPV16 or HPV18 E7 antigens (Table 4). In contrast, all subjects vaccinated with GTL001 and none vaccinated with the placebo seroconverted to CyaA.

Discussion

GTL001, a therapeutic HPV vaccine containing recombinant E7 of HPV16 and HPV18, each fused to catalytically inactive

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Table 2. Proportions of subjects reporting solicited reactions after any vaccination

Reaction	Cohort 1 Open-label GTL001 100 µg solution + imiquimod N = 5	Cohort 2 Open-label GTL001 solution 600 µg + imiquimod N = 5	Cohort 3 Randomized, double-blinded GTL001 solution 600 µg + imiquimod N = 14	Cohort 3 Randomized, double-blinded GTL001 solution 600 µg + placebo N = 7	Cohort 3 Randomized, double-blinded Placebo injection + imiquimod N = 7	Cohort 4 Open-label GTL001 600 µg powder + imiquimod N = 9
Injection site						
Pain						
Grade 1	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (14.3)	0 (0.0)
Grade 2	4 (80.0)	5 (100.0)	9 (64.3)	6 (85.7)	0 (0.0)	4 (44.4)
Grade 3	1 (20.0)	0 (0.0)	3 (21.4)	1 (14.3)	0 (0.0)	4 (44.4)
Tenderness						
Grade 1	0 (0.0)	0 (0.0)	1 (7.1)	2 (28.6)	2 (28.6)	1 (11.1)
Grade 2	4 (80.0)	5 (100.0)	9 (64.3)	3 (42.9)	0 (0.0)	6 (66.7)
Grade 3	1 (20.0)	0 (0.0)	4 (28.6)	2 (28.6)	0 (0.0)	2 (22.2)
Erythema						
Grade 1	0 (0.0)	1 (20.0)	2 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)
Grade 2	4 (80.0)	4 (80.0)	10 (71.4)	6 (85.7)	0 (0.0)	5 (55.6)
Grade 3	0 (0.0)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)	4 (44.4)
Swelling						
Grade 1	2 (40.0)	2 (40.0)	4 (28.6)	4 (57.1)	0 (0.0)	2 (22.2)
Grade 2	1 (20.0)	2 (40.0)	6 (42.9)	3 (42.9)	0 (0.0)	6 (66.7)
Grade 3	1 (20.0)	1 (20.0)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Induration						
Grade 1	1 (20.0)	3 (60.0)	3 (21.4)	4 (57.1)	0 (0.0)	2 (22.2)
Grade 2	2 (40.0)	2 (40.0)	8 (57.1)	2 (28.6)	0 (0.0)	5 (55.6)
Grade 3	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	1 (11.1)
Ulceration						
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Scabs						
Grade 1	0 (0.0)	2 (40.0)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Itching						
Grade 1	3 (60.0)	4 (80.0)	9 (64.3)	2 (28.6)	1 (14.3)	8 (88.9)
Grade 2	2 (40.0)	1 (20.0)	4 (28.6)	4 (57.1)	0 (0.0)	1 (11.1)
Grade 3	0 (0.0)	0 (0.0)	1 (7.1)	1 (14.3)	0 (0.0)	0 (0.0)
Systemic						
Arthralgia						
Grade 1	0 (0.0)	2 (40.0)	0 (0.0)	1 (14.3)	1 (14.3)	4 (44.4)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia						
Grade 1	2 (40.0)	3 (60.0)	4 (28.6)	1 (14.3)	1 (14.3)	1 (11.1)
Grade 2	0 (0.0)	1 (20.0)	2 (14.3)	3 (42.9)	0 (0.0)	3 (33.3)
Grade 3	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache						
Grade 1	1 (20.0)	1 (20.0)	8 (57.1)	2 (28.6)	3 (42.9)	4 (44.4)
Grade 2	2 (40.0)	1 (20.0)	3 (21.4)	3 (42.9)	1 (14.3)	2 (22.2)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue						
Grade 1	4 (80.0)	2 (40.0)	7 (50.0)	4 (57.1)	4 (57.1)	2 (22.2)
Grade 2	0 (0.0)	1 (20.0)	3 (21.4)	1 (14.3)	0 (0.0)	2 (22.2)
Grade 3	1 (20.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	0 (0.0)
Nausea						
Grade 1	2 (40.0)	1 (20.0)	5 (35.7)	1 (14.3)	2 (28.6)	3 (33.3)
Grade 2	0 (0.0)	0 (0.0)	1 (7.1)	2 (28.6)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever						
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)
Grade 2	1 (20.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rigors						
Grade 1	0 (0.0)	0 (0.0)	3 (21.4)	3 (42.9)	0 (0.0)	2 (22.2)
Grade 2	1 (20.0)	0 (0.0)	1 (7.1)	1 (14.3)	1 (14.3)	1 (11.1)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: Values are for the safety population and are the number of subjects with the percentage in brackets.

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Table 3. Cervical HPV virology

Category	Time	Value	Cohort 1 Open-label GTL001 100 μg solution + imiquimod	Cohort 2 Open-label GTL001 solution 600 μg + imiquimod	Cohort 3 Randomized, double-blinded: GTL001 solution 600 μg + imiquimod	Cohort 3 Randomized, double-blinded: GTL001 solution 600 μg + placebo	Cohort 3 Randomized, double-blinded: Placebo injection + imiquimod	Cohort 4 Open-label GTL001 600 μg powder + imiquimod
Change in HPV16 viral load from baseline	—	No. positive at baseline	5	4	11	5	5	6
	Week 10	Mean ± SD	108.2 ± 167.1	−370.5 ± 998.3	−775.7 ± 2808.6	11.7 ± 31.1	855 ± 2406.1	−562.3 ± 1252.1
		Min, max	−11, 374	−1850, 340	−9217, 669	−7, 67	−612, 5139	−3114, 10
	Week 26	Mean ± SD	647.4 ± 1148.2	−784.7 ± 1568.2	−41.9 ± 2886.2	−1.7 ± 4.6	2042.6 ± 4984.1	−322.5 ± 872.4
		Min, max	−5, 2675	−3137, 2	−6401, 6499	−6, 6	−637, 10946	−2091, 234
	Last obs	Mean ± SD	1710 ± 4190.4	−824.7 ± 1636.9	−959.0 ± 2956.5	32.8 ± 77.1	185.4 ± 677.8	−355.2 ± 789.6
		Min, max	−925, 9159	−3280, −3	−9411, 143	−6, 171	−259, 1364	−1764, 88
	Time to last obs	Median (mo)	22.9	24.3	15.8	17.6	17.0	11.3
Change in HPV18 viral load from baseline		No. positive at baseline	0	1	3	2	2	3
	Week 10	Mean ± SD	—	−20.0	−91.1 ± 154.1	−2.3 ± 3.1	20.0 ± 52.3	76.0 ± 188.7
		Min, max	—	—	−269, 0	−4, 0	−17, 57	−62, 291
	Week 26	Mean ± SD	—	−20.0	−91.1 ± 154.1	−2.1 ± 2.7	−6.0 ± 42.4	−70.3 ± 72.1
		Min, max		—	−269, 0	−4, 0	−36, 24	−145, −1
	Last obs	Mean ± SD	—	−20.0	−90.8 ± 154.4	−2.6 ± 3.5	−63.0 ± 38.2	−70.7 ± 72.1
		Min, max		—	−269, 1	−5, 0	−90, −36	−145, −1
	Median time to last obs (mo)	Median (mo)	—	18.7	14.8	10.4	20.8	11.1
HPV16/18 clearance[a]	Baseline	*n/N* (%)	0/5 (100.0)	0/5 (0.0)	0/14 (100.0)	0/7 (0.0)	0/7 (0.0)	0/9 (0.0)
	Week 10	*n/N* (%)	1/5 (20.0)	1/5 (20.0)	4/14 (28.6)	1/7 (14.3)	0/7 (0.0)	3/9 (33.3)
	Week 26	*n/N* (%)	1/5 (20.0)	2/5 (40.0)	4/14 (28.6)	1/7 (14.3)	3/7 (42.9)	4/9 (44.4)
	Last obs	*n/N* (%)	2/5 (40.0)	5/5 (100.0)	9/14 (64.3)	2/7 (28.6)	3/7 (42.9)	5/9 (55.5)
Sustained HPV16/18 clearance[b]	—	*n/N* (%)	2/3 (66.7)	2/3 (66.7)	5/6 (83.3)	0/2 (0.0)	1/3 (33.3)	3/4 (75.0)

NOTE: HPV16 and HPV18 were detected by qPCR. Values are for the safety population.

Abbreviation: obs, observation.

[a]*Post hoc* analysis in which clearance was defined as an HPV-negative qPCR result at the indicated time point.

[b]*Post hoc* analysis in which sustained clearance was defined as an HPV-negative qPCR result followed by maintenance of HPV-negative results until the last date of follow-up included in this analysis (December 31, 2012).

B. pertussis CyaA as a vaccine vector, is intended for women infected with HPV16 or HPV18 before they develop high-grade lesions. This phase I study examined the tolerability and immunogenicity of GTL001 in HPV-infected women with normal cervical cytology. The study was conducted in 47 subjects, evaluated two GTL001 formulations, and included both open-label dose-escalation and placebo-controlled randomized, double-blinded parts.

The study showed that intradermal vaccination with GTL001 has an acceptable safety profile. Local reactions were mostly mild to moderate. After the first vaccination, subjects reported an initial peak of local reactions (erythema, swelling, and pain) after 1 to 2 days, followed by a secondary peak approximately 2 to 5 days postinjection. This second peak of local reactions was probably due to delayed-type (type IV) hypersensitivity reactions (28, 29), most likely resulting from vaccine-induced HPV16/18-specific T cells homing to the vaccination sites, as reported by Welters and colleagues (30). After the second vaccination, a single immediate peak of local reactions was observed. This could be due to rapid homing of vaccine-specific T cells to the vaccination site.

Systemic reactions more common with GTL001 than placebo included myalgia, fatigue, and lymphadenopathy. All reactions were transient, and the only interventions needed were oral over-the-counter analgesics and fusidine cream for a few cases.

A T-cell–mediated immune response against HPV antigens is important in controlling progression to CIN by sustaining viral clearance (31). The systemic and local reactions induced by GTL001 were consistent with the pharmacologic effects of a vaccine inducing a T-cell response. In addition, GTL001 appeared to induce an imiquimod-enhanced E7-specific T-cell response. Although effector T-cell responses in the blood are weak, require *ex vivo* sensitization to be detected and have been considered to not reflect the T-cell response at the site of infection in the cervix or reliably identify persons whose lesions will regress (9), a recent study showed that peripheral ELISpot responses generated by a therapeutic synthetic DNA vaccine statistically correlated with high-grade lesion regression (13). Whether this is the case with GTL001 will be investigated in future clinical trials.

Consistent with preclinical studies (17), GTL001 induced a humoral response to CyaA in all subjects but did not induce anti-E7 antibodies. The inability of GTL001 to induce a humoral response against E7 is probably because the E7 antigen was split before insertion into CyaA, disrupting its natural sequence and conformation.

The first three cohorts assessed vaccination with the solution formulation of GTL001 at five sites on the upper thigh. In the fourth and final cohort, we assessed a powder formulation of GTL001 that is 5-fold more concentrated and that allowed for vaccination at a single site. Immunogenicity and tolerability of a single injection of the powder formulation and five injections of the solution formulation were generally similar, although grade 3 injection-site pain and erythema tended to be more common with the powder formulation.

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The randomized portion of the study examined the effect of GTL001 adjuvanted with topical 5% imiquimod cream. Imiquimod is a nucleoside analogue of the imidazoquinoline family that activates toll-like receptor 7 and to a lesser extent toll-like receptor 8 and is active against a variety of malignancies, including HPV-associated tumors, when applied at the tumor site (2, 32). Activation of toll-like receptors by imiquimod stimulates the production of pro-inflammatory cytokines, chemokines, and other mediators, which in turn, activate antigen-presenting cells and other aspects of the innate immune system. Imiquimod-activated and matured antigen-presenting cells allow the induction of a strong $CD8^+$ T-cell immune response (32). In this study, we applied 5% imiquimod cream 15 minutes and 24 hours after vaccination because we previously showed that this timing and dose of imiquimod increases the frequency of HPV16 E7 and HPV18 E7-specific T-cell responses in mice (19) and because other studies have shown that multiple applications of imiquimod are needed for optimal effects (33). In this study, we found that topical imiquimod cream enhanced the cellular immune response but did not have a noticeable effect on reactogenicity.

To confirm the safety of GTL001, we measured HPV viral loads in cervical samples. Decreases in viral loads from baseline were highest in subjects treated with GTL001 600 μg + imiquimod. In a *post hoc* analysis, we assessed HPV clearance, defined after consultation with the European Medicines Agency, as the nondetection of both HPV16 and HPV18 at a given time point. According to this stringent definition, we confirmed that HPV16/18 clearance rates were highest in the subjects treated with GTL001 600 μg + imiquimod. We also found that sustained clearance, assessed in subjects with virology data after an initial clearance, was highest in subjects treated with GTL001 600 μg + imiquimod. In the randomized portion of our trial, sustained clearance occurred in 5 of 6 (83%) patients treated with the highest dose of GTL001 (600 μg) versus 1 of 3 (33%) treated with placebo. Clearance rates in other clinical trials have ranged from 23% to 37% for the active treatment versus 0% to 14% for placebo (34–36). A more recent randomized trial showed higher rates of clearance (approximately 80%) with both the DNA vaccine VGX-3100 and the placebo (approximately 50%), although this may have been due to the calculations being limited to patients with histopathologic regression (13). It is important to note, however, that clearance at a single time point is not the same as sustained clearance and, furthermore, that assays, experimental conditions, and thresholds differ, so that the sustained clearance rates determined in this study cannot be compared directly with the clearance rates reported elsewhere.

Although our virology results indicated that GTL001 + imiquimod might enhance HPV clearance, the results may be due to or masked by spontaneous clearance, which can occur within 1 year in as many as half of HPV16- and HPV18-infected women (37). Furthermore, this phase I trial was not designed to detect significant differences in viral clearance, and we cannot exclude the possibility of transient HPV carriage following a recent sexual exposure. Thus, although these results are interesting, larger studies will be needed to make conclusions about efficacy.

We also examined cervical cytology as part of the safety assessments. Two women treated with GTL001 + imiquimod had high-grade lesions and underwent cervical conization. Although all subjects had to have normal cytology on consecutive visits, these women might have had hidden high-grade (CIN grade 2+) lesions at enrolment, which would not have been detected because colposcopy was not performed. As with HPV virology, cervical cytology, however, was not assessed as an efficacy endpoint in this study, and the study was not designed to detect significant differences in cytologic outcomes.

A variety of candidate therapeutic vaccines have been tested, including a chimeric virus–like particle, a dendritic cell vaccine, fusion proteins, peptides, an attenuated virus, and recombinant viruses (10–12). Several have shown some promise in treating vulvar and high-grade CIN, and some induce cellular immunity against HPV, but these vaccines have only been tested in women who already have high-grade lesions. For example, recent studies showed that two therapeutic DNA vaccines, one targeting HPV16 and HPV18 E6 and E7 (13) and the other targeting HPV16 E7 (14), can induce regression of CIN2/3. GTL001 is the first therapeutic vaccine tested in women infected

Table 4. Cellular and humoral immune responses

Measure	Cohort 1 Open-label GTL001 100 μg solution + imiquimod $N = 5$	Cohort 2 Open-label GTL001 solution 600 μg + imiquimod $N = 5$	Cohort 3 Randomized, double-blinded GTL001 solution 600 μg + imiquimod $N = 14$	Cohort 3 Randomized, double-blinded GTL001 solution 600 μg + placebo $N = 7$	Cohort 3 Randomized, double-blinded Placebo injection + imiquimod $N = 7$	Cohort 4 Open-label GTL001 600 μg powder + imiquimod $N = 9$
T-cell response, *n/N* (%)[a]	2/5 (40.0)	4/5 (80.0)	7/13 (53.8)	1/6 (16.7)	1/6 (16.7)	5/8 (62.5)
Seroconversion, *n* (%)[b]						
Anti-HPV16 E7 antibody	1/5 (20.0)	1/5 (20.0)	1/14 (7.1)	0/7 (0.0)	1/7 (14.3)	0/9 (0.0)
Anti-HPV18 E7 antibody	0/5 (0.0)	1/5 (20.0)	0/14 (0.0)	1/7 (14.3)	1/7 (14.3)	0/9 (0.0)
Anti-CyaA antibody	5/5 (100.0)	5/5 (100.0)	14/14 (100.0)	7/7 (100.0)	0/7 (0.0)	9/9 (100.0)

NOTE: Values are for the intent-to-treat population.

[a]The T-cell response to overlapping 15-mer peptides covering HPV16 or HPV18 E7 was assessed by IFNγ ELISpot in PBMC collected at weeks 2, 6, 10, and 26. For each subject, peptide pool, and time point, the specific ELISpot response was calculated as [(mean antigen-stimulated spot-forming cells [SFC] − SD of antigen-stimulated SFC) − (mean SFC for medium + 2 × SD of SFC for medium)]. A specific response was considered to be positive if it was >20 SFC per 4×10^5 PBMC and the mean antigen-specific SFC was >3 × mean SFC for medium alone. For each peptide pool, a subject was considered a responder if (i) they had a positive specific response to any peptide pool at any post-vaccination time point before week 26 and did not have a specific response at baseline; or (ii) they had a specific positive response to any peptide pool at any post-vaccination time point before week 26 $\geq 2 \times$ specific response at baseline (if they had a specific positive response at baseline).

[b]Serum antibodies to CyaA, HPV16 E7, and HPV18 E7 were assessed by ELISA at weeks 2, 6, 10, and 26. Seroconversion was defined as (i) no detectable antibody at baseline and detectable antibody at any post-baseline time point; or (ii) if detectable antibody was present at baseline, a four-fold increase in antibody titer at any post-baseline time point.

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with HPV16 or HPV18 who have normal cervical cytology. This phase I study indicated that, in this population, GTL001 adjuvanted with topical imiquimod cream has an acceptable safety profile and that it can induce an antigen-specific cellular immune response. On the basis of these promising results, we are now conducting a phase II clinical trial on vaccination with the powder formulation of GTL001 in women infected with HPV16 or HPV18 who have normal cervical cytology or mild abnormalities (ASC-US/LSIL).

Disclosure of Potential Conflicts of Interest

P. Van Damme reports receiving speakers bureau honoraria from Genticel. M. Bouillette-Marussig and B. Timmerman hold ownership interest (including patents) in Genticel SA. M.-C. Bissery holds ownership interest (not including patents) in Genticel. C.E. Depuydt is an employee of AML-Sonic Healthcare; and is a consultant/advisory board member for BD, Cepheid, and Genticel. T. Hercend holds ownership interest in, and is a consultant/advisory board member for Genticel. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The study funder, Genticel, participated in study design, data analysis, data interpretation, and writing of the report.

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