Research Article

MUC1 Vaccine for Individuals with Advanced Adenoma of the Colon: A Cancer Immunoprevention Feasibility Study

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Abstract

Cancer vaccines based on human tumor-associated antigens (TAA) have been tested in patients with advanced or recurrent cancer, in combination with or following standard therapy. Their immunogenicity and therapeutic efficacy has been difficult to properly evaluate in that setting characterized by multiple highly suppressive effects of the tumor and the standard therapy on the patient’s immune system. In animal models of human cancer, vaccines administered in the prophylactic setting are most immunogenic and effectively prevent cancer development and progression. We report results of a clinical study that show that in patients without cancer but with a history of premalignant lesions (advanced colonic adenomas, precursors to colon cancer), a vaccine based on the TAA MUC1 was highly immunogenic in 17 of 39 (43.6%) of vaccinated individuals, eliciting high levels of anti-MUC1 immunoglobulin G (IgG) and long-lasting immune memory. Lack of response in 22 of 39 individuals was correlated with high levels of circulating myeloid-derived suppressor cells (MDSC) prevaccination. Vaccine-elicited MUC1-specific immune response and immune memory were not associated with significant toxicity. Our study shows that vaccines based on human TAAs are immunogenic and safe and capable of eliciting long-term memory that is important for cancer prevention. We also show that in the premalignant setting, immunosuppressive environment (e.g., high levels of MDSC) might already exist in some individuals, suggesting an even earlier premalignant stage or preselection of nonimmunosuppressed patients for prophylactic vaccination. Cancer Prev Res; 6(1); 18–26. ©2012 AACR.

Introduction

Colorectal cancer is under strong immune surveillance. The presence of tumor-specific antibodies (1, 2) or infiltrating T cells in primary tumors can prolong time to disease recurrence and extend survival (3, 4). Immunosurveillance begins early in the neoplastic process as tumor-specific antibodies and T cells are found in subjects with premalignant adenomas (5, 6). A successful prophylactic colon cancer vaccine would boost or improve natural immune surveillance leading to elimination of premalignant lesions before their progression to malignant disease (7, 8).

Many candidate tumor-associated antigens (TAA) have been identified for vaccines against cancer (9–11), including several for colon cancer (5, 12, 13). MUC1 glycoprotein is one such antigen (14, 15). In contrast to low-level luminal or apical expression of the heavily glycosylated MUC1 on normal colonic epithelial cells, neoplastic cells express high levels of the hypoglycosylated form of MUC1 that lacks luminal polarity. This abnormal expression induces humoral and cellular immune responses (16–20). Abnormal expression of MUC1 is also found on premalignant colorectal adenomas where it promotes malignant transformation by interacting with β-catenin, ras, and other tumor-promoting signaling pathways (21–24).

Ever since the first characterization of MUC1 as a tumor antigen (16) and successful cloning of the muc1 gene (25), MUC1 has been a promising candidate for vaccine-based interventions against human adenocarcinomas. Many different MUC1 vaccines such as MUC1 peptides with adjuvants, MUC1 loaded dendritic cells, or MUC1 DNA expressed in viral vectors have been tested in phase I/II trials in patients with cancer who had failed standard therapy (26–33). These therapeutic vaccines were well tolerated, but only mildly immunogenic. In contrast, many of these same vaccines tested in the prophylactic setting in animal models (34–37) were highly immunogenic and resulted in immune protection against either transplantable or spontaneous MUC1⁺ tumors. To date, with the exception of the study

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we are reporting here, no cancer vaccine based on a TAA has been tested in the prophylactic setting in humans.

In patients with cancer, it has been difficult to determine if the low vaccine immunogenicity is due to the wrong antigen choice (e.g., some TAA may be mostly self-molecules and thus subject to self-tolerance), bad vaccine design (e.g., weak or ineffective adjuvant), the immunosuppressive tumor microenvironment, the immunosuppressive effect of previous therapy, patient circumstances such as advanced age, or a combination of some or all of the above.

We evaluated the immunogenicity of a MUC1 peptide vaccine in the absence of cancer by assessing the elicited immune response in the premalignant setting in individuals with a history of an advanced adenoma of the colon. Patients with advanced adenomas are at higher risk for subsequent colorectal cancer (38) and are recommended to undergo more frequent surveillance colonoscopy (39, 40). Because these patients do not have invasive cancer nor have they undergone immunosuppressive chemotherapy, the response to a vaccine could be assessed in the absence of these and other confounding factors that are present in patients with cancer.

The vaccine was immunogenic in 43.6% of subjects and capable of inducing long-term memory responses. A large number of responders provided the opportunity for comparison with nonresponders (56.4%) for host-specific factors that control vaccine response. Nonresponders had a significantly higher percentage of circulating myeloid-derived suppressor cells (MDSC) before vaccination.

Materials and Methods

Subjects

All subjects provided informed consent and the study was monitored by Data Safety Monitoring Board of the Clinical Translational Science Institute of the University of Pittsburgh (Pittsburgh, PA). The primary eligibility criteria included: (i) age 40–70 years; (ii) a history of an advanced colorectal adenoma(s) defined as: (a) 1 cm or more in size, or (b) with villous or tubulovillous histology, or (c) with high-grade dysplasia; (iii) normal (within specified parameters) hemoglobin, liver, and renal testing; and (iv) antinuclear antibodies (ANA) 1:160 or less. Subjects were excluded if they had a history of a heritable cancer syndrome, autoimmune disease, or a malignancy within 5 years before the enrollment, excluding nonmelanoma skin cancer. Subjects with use of corticosteroids within 12 weeks before enrollment or current or planned use of immunomodulators were excluded.

Peripheral blood mononuclear cells (PBMC) from healthy, age-matched, nonsmoking donors were collected under a separate protocol via recruitment at community organizations and events.

Vaccine preparation and administration

A certified clinical grade 100-amino acid synthetic MUC1 peptide with the molecular structure of H$_2$N-(GVTSDPRTPGSTAPPAlH)$_2$-CONH$_2$, was synthesized at the University of Pittsburgh Peptide Synthesis Facility. The adjuvant, Toll-like receptor (TLR) 3 agonist, poly-ICLC (Hiltonol), was supplied by Oncovir Inc. in single-dose vials of 1 mL solution containing 2 mg poly-IC, 1.5 mg poly-i-lysine, and 5 mg sodium carboxymethylcellulose in 0.9% sodium chloride, adjusted to pH 7.6 to 7.8 with sodium hydroxide. The vaccine consisted of 100 µg of the MUC1 100 mer peptide dissolved in 50 µL of sterile saline, admixed with 500 µg of Hiltonol in 250 µL, for a total injection volume of 300 µL. Vaccine was administered subcutaneously in the same upper thigh on each occasion. The vaccine received an Investigational New Drug (IND) approval from the U.S. Food and Drug Administration (FDA). The trial was registered at ClinicalTrials.gov with NCT-007773097.

Vaccine protocol

This was a phase I/II open label study to evaluate the immunogenicity [anti-MUC1 immunoglobulin G (IgG)] of the 100 mer MUC1 peptide with the adjuvant polyinosinic-polycytidylic acid stabilized with poly-i-lysine and carboxymethylcellulose (poly-ICLC; Hiltonol), a TLR 3 agonist (41). Vaccine was administered at week 0, 2, and 10. To assess memory response, a booster dose was given at week 52. Subjects underwent blood draws immediately before each vaccination at week 2, 10, and 52, and postvaccination at week 12, 28, and 54.

Anti-MUC1 IgG response was the main measure of vaccine immunogenicity because elicitation of IgG antibody requires activation not only of MUC1-specific B cells, but also of MUC1-specific helper T cells that promote anti-MUC1 antibody isotype switching from IgM to IgG. The preset criterion for considering subjects as responders to the vaccine was a ratio of anti-MUC1 IgG levels at week 12 to prevaccination levels at week 0 ≥2. This criterion was based on results previously obtained with the same or a similar vaccine in cancer subjects (27). Lacking examples from trials in patients with cancer in whom vaccine-elicited memory responses could not be evaluated, the criterion for a positive memory response was arbitrarily set at a ratio of IgG levels at week 54 (2 weeks postbooster administration) to prebooster levels at week 52 of ≥2.

Monitoring for adverse events

The National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE3.0) were used to monitor toxicity. Laboratory monitoring including complete blood count, blood urea nitrogen, creatinine, and liver function tests was conducted at baseline, before each vaccine dose, and at week 28 and 54. A repeat ANA test was conducted at week 52 before booster vaccination. Physical examination was conducted at baseline and at week 52. Phone calls to subjects were made at week 6, 16, and 40.

Immunologic assays

Immediately after collection, heparinized blood was centrifuged over a density gradient (Ficoll) to separate the
plasma and PBMC. Plasma was collected, aliquoted, and stored at −20°C. PBMC were washed several times, aliquoted, slowly frozen to −80°C in PBS with 20% dimethyl sulfoxide and stored in the vapor phase of liquid nitrogen.

Anti-MUC1 IgG was measured by ELISA as previously published (32). Immulon 4 (Thermo-Fisher Scientific) microtiter plates were coated overnight at 4°C with 1 µg of synthetic MUC1 100 mer peptide (vaccine antigen) dissolved in 0.9% Dulbecco’s PBS. Corresponding control plates received PBS but no antigen. The plates were washed 3 times with and incubated with 2.5% bovine serum albumin (BSA) in PBS (PBS-BSA) to fully coat the microtiter plate wells with protein and block nonspecific binding. PBS-BSA was removed and plasma diluted in PBS-BSA was added to the wells. After 1-hour incubation at room temperature, the plates were washed 5 times with PBS with 0.1% Tween-20 (Sigma-Aldrich), and alkaline phosphatase–conjugated anti-human IgG secondary antibody (Sigma-Aldrich) in PBS-BSA was added. Following a 1-hour incubation, the plates were washed 5 times and the substrate, p-nitrophenyl phosphate (Sigma-Aldrich), was added to each well. The reaction was terminated after 1 hour by adding 0.5 mol/L NaOH. The results were read at optical density (OD) 405 nm on a spectrophotometer. The OD values from the control wells containing no antigen were subtracted from the OD values in test wells coated with peptide. Every sample was assayed multiple times at multiple dilutions, in at least triplicate wells.

For detecting MDSC, PBMC were thawed and stained with allobiocyanin (APC)-labeled mouse anti-human CD11b antibody (clone: ICRF44, BD Biosciences), phycoerythrin (PE)–labeled mouse anti-human HLA-DR antibody (clone: WM53, BD Biosciences), and fluorescein isothiocyanate (FITC)–labeled mouse anti-human CD33 antibody (clone: 236A/E7, BD Biosciences).

PE-labeled mouse anti-human Foxp3 antibody (clone: 236A/E7, BD Biosciences).

Table 1. Characteristics of study subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (range)</td>
<td>58.0 (43.5–70.8)</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>22 (65)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Race: White</td>
<td>36 (90)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>BMI: mean (range)</td>
<td>27.4 (18.1–43.5)</td>
</tr>
<tr>
<td>Family history of colorectal cancer</td>
<td>8 (20.0)</td>
</tr>
</tbody>
</table>

Advanced adenoma: N (%) | 37 (77.5) |
| Size ≥ 1 cm              | 18 (45) |
| Tubulovillous/villous    | 6 (15) |
| High-grade dysplasia     | 572 (824, 168–3,499) |

| Time from most recent advanced adenoma to receipt of vaccine, days, median (mean, range) |

N = 40 (includes 1 patient treated only on week 0).

In a first-degree relative.

May meet more than 1 criterion.

Statistical analysis
The association of 2 variables was assessed as follows: Fisher exact test for 2 categorical variables; Wilcoxon rank sum test for 1 continuous and 1 dichotomous variable; and Spearman rank correlation test for 2 continuous variables. A 2-sided P value less than 0.05 was considered indicative of a true association, but no corrections were applied for multiple comparisons.

Results
MUC1 vaccine is immunogenic
Of the 46 subjects who consented to participate, 6 did not receive vaccine: 4 had abnormal screening laboratory tests, 1 did not meet criteria for an advanced adenoma, and 1 declined to participate. One patient dropped out after receiving the first injection because of travel distance, leaving a total of 39 evaluable subjects. The characteristics of the study subjects are presented in Table 1. The mean age was 58 years and 55% were men. Most subjects met the criteria of having an advanced adenoma by having an adenoma that measured 1 cm or more. The median time between the most recent diagnosis of an advanced adenoma and receipt of the first dose of vaccine was 572 days (range, 168–3,499).

Figure 1A shows that week 12 IgG/prevaccination IgG ratio 2.0 or more was observed in 17 of 39 subjects (43.6%; range in ratio among responders, 2.2–36.3). Antibody
have elevated ANA at week 52. Retesting of prevaccination serum showed the ANA to have been elevated before vaccination and at all other time points along with SSA and Ro antigens, leading us to conclude that the initial immunofluorescence-based ANA test at enrollment was falsely negative. One patient at 11 months postvaccination developed clinical hypothyroidism with an elevated thyroid-stimulating hormone (TSH) of 27.2 (normal levels < 5). Testing of serum prevaccination showed a TSH level of 3.5, however, with significantly elevated thyroglobulin and thyroid peroxidase antibody levels, consistent with Hashimoto’s thyroiditis, leading us to conclude that the condition predated vaccination.

The vaccine elicited a memory response

A booster injection at 52 weeks to evaluate the long-term memory response was administered to 37 subjects. Of those who responded (ratio ≥2) at week 12 and received a booster injection at week 52, 12 of 16 (75.0%) had a response to the booster. Of the 4 subjects who did not respond to the booster, 3 had persistently high levels of antibody at week 52 (OD of 0.42, 2.72, and 3.61). One patient, although classified as a responder at week 12, had a low tier antibody response (0.02 at baseline and 0.07 at week 12) and did not respond to the booster. Of the 21 subjects who were nonresponders at week 12 and received a booster injection, 2 (9.5%) responded to the booster by increasing antibody levels at week 54 by 2-fold, however, the antibody levels achieved were relatively low and did not exceed OD of 0.21.

Response to the vaccine correlated with prevaccination levels of circulating MDSC but not T regulatory cells

Comparing vaccine responders to nonresponders (Table 1) we found no association of response with age ($P = 0.75$), family history of colorectal cancer ($P = 1.0$), body mass index (BMI; $P = 0.37$), the criterion for advanced adenoma ($P = 0.71$ for size 1 cm or more, 0.75 for villous, and 0.68 for high-grade dysplasia), or with the length of time from adenoma removal to vaccination ($P = 0.94$). Women were more likely to respond to the vaccine (11 of 18, 61%) than men (6 of 21, 29%), but this was of borderline significance ($P = 0.06$). There was no association between response and HLA-DR (Supplementary Table S1) or HLA-DQ (Supplementary Table S2) types, which were similar in frequency to general population.

When analyzing subjects’ PBMC by flow cytometry (Fig. 2A) we observed a presence of a nonlymphoid cell population in nonresponders that were very low or absent in responders. Phenotypic analysis identified these cells as CD11b+/low, CD33+/low, and HLA-DR+/low MDSCs (42). Nonresponders ($N = 19$) had a significantly higher percentage of these cells prevaccination as compared with responders ($N = 12$; $P < 0.05$) whose MDSC levels were similar to healthy, age-matched controls ($N = 19$; Fig. 2B).

Abnormally high percentages of these cells had been described in the blood and at the tumor site in many different malignancies and correlated with high-level

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Figure 1. Vaccine elicited anti-MUC1 IgG responses. A, ratio of week 12/week 0 anti-MUC1 IgG in ascending order. Subjects with ratio more than 2 were considered responders (black bars) and those with ratio less than 2 were nonresponders (white bar). Data are presented as OD 405 values for 1:40 dilution of plasma. Dashed line represents ratio less than 2 were nonresponders (white bar). Data are presented more than 2 were considered responders (black bars) and those with 12/week 0 anti-MUC1 IgG in ascending order. Subjects with ratio 1:2,560 (Supplementary Fig. S1).

B, time and kinetics of anti-MUC1 IgG development in responders. Phenotypic analysis identified these cells as CD11b+/low, CD33+/low, and HLA-DR+/low MDSCs (42). Nonresponders ($N = 19$) had a significantly higher percentage of these cells prevaccination as compared with responders ($N = 12$; $P < 0.05$) whose MDSC levels were similar to healthy, age-matched controls ($N = 19$; Fig. 2B).
suppression of both innate and immune antitumor effector mechanisms (43). Their presence in the setting of premalignant disease, and especially in individuals with only a history of premalignant disease, had not been explored. We evaluated the functional consequence of increased MDSCs on the T-cell effector function in 3 vaccinated subjects, 1 responder with low percentage of MDSC and 2 nonresponders with higher percentage of MDSC, by measuring T-cell responses to stimulation with anti-CD3 and anti-CD28 antibody before and after MDSC depletion from the PBMC. Figure 3A shows successful depletion of MDSCs with magnetic beads conjugated to antibody against CD15, a cell surface fucosyl transferase expressed on MDSC (44, 45). Figure 3B shows that T cells from the 2 nonresponders produce significantly higher amounts of INF-γ after CD15⁺ MDSC depletion, whereas the same depletion procedure conducted on the PBMC of a responder had no effect on the T-cell response.

Tregs (46) are another cell population known to suppress antitumor adaptive immunity, including in colon cancer (47). There were no differences in Tregs between responders and nonresponders, and when the levels in both groups were compared with healthy controls there was no difference (Fig. 4).
of 16 patients (6.25%) developed IgG and only a 2.16-fold increase from prevaccination OD of 0.168 to postvaccination OD of 0.368 (32). In contrast, in this trial in the premalignant setting, of the nearly 44% that responded, more than 76% had greater than a 4-fold increase and more than 47% had more than a 9-fold increase in antibody titer. Furthermore, the highest IgG OD value that we measured in the pancreatic cancer trial was 0.561 in 1 patient’s plasma at 1:20 dilution. In this study in the premalignant setting, the majority of responders had postvaccination OD values more than 10 at a plasma dilution of 1:40, the highest being an OD of 36.3.

Anti-MUC1 IgG levels measured at week 12, after the first 3 injections, in most patients decreased over time, as would be expected of a response to an antigen that is cleared from the system. We tested the ability of the vaccine to elicit a memory response by giving a booster injection at 1 year and the levels of IgG increased again. The response to the booster injection was another indication, in addition to isotype switching, that the vaccine had elicited a T-cell response and T-cell memory participating in the response to the booster injection.

Importantly, development of high titer of anti-MUC1 antibodies was not associated with significant adverse events. In particular, we observed no incidence of clinical autoimmune disease developing subsequent to vaccination and there was no increase in ANA titer over 1 year of observation. The inability to induce a significant anti-MUC1 immune response in patients with cancer made the safety of a high-titer response impossible to assess. In this trial, even the subjects that had more than a 30-fold increase in IgG titer had no evidence of clinical adverse effect. We have reported previously that healthy individuals can have an immune response against MUC1 (measured by anti-MUC1 IgG levels) presumably elicited via exposure to abnormal forms of MUC1 induced by acute inflammatory conditions, such as mastitis or mumps. Anti-MUC1 immunity in these individuals correlated with positive outcomes, such as lower risk of cancer, rather than being detrimental (54–57). While the beneficial clinical effects of the MUC1 vaccine will need to be tested in future-randomized trials, our results here clearly show that the vaccine-elicited anti-MUC1 immune response is not seemingly detrimental to the patient’s overall health.

Our study was carried out in a population at increased risk for colorectal cancer by virtue of having a history of advanced adenoma. We expected that these subjects would not harbor the same immunosuppressive environment as patients with cancer, such as increased numbers of immunosuppressive Tregs (58). Surprisingly, we observed significantly higher levels of MDSCs in prevaccination PBMC in subjects who did not respond to the vaccine as compared with those who did. Abnormally high percentages of these cells had been described in the blood and at the tumor site in many different malignancies and correlated with high-level suppression of both innate and immune antitumor effector mechanisms (43). Higher levels of MDSC in the setting of premalignant disease, and especially in
individuals with only a history of premalignant disease, has not been previously explored or described. Increased MDSCs, such as Tregs, have been primarily associated with advanced cancer (43) and some chronic infections (59, 60) in which they have been shown to suppress adaptive immunity by producing arginase 1, inducible nitric oxide synthase (iNOS), nitric oxide (NO), and reactive oxygen species (ROS; refs. 42, 45). In mice MDSCs increase during the development of spontaneous inflammatory bowel disease (IBD; refs. 37, 61) and pancreatic cancer (62). Increased MDSCs have also been reported in humans with IBD (61). It is not known if development of IBD or premalignant polyps causes an increase in MDSC or is preceded by an increase in MDSC. We also do not know why some subjects with advanced adenoma have significantly increased levels of MDSC and others do not. What is clear, however, is that a response to the vaccine is compromised by the presence of MDSC. Further research on a much larger sample may establish MDSCs as biomarkers for selection of subjects who are likely to respond to vaccines or other forms of immunotherapy that depend on activating endogenous immunity.

Cancer vaccines given in the therapeutic setting are beginning to assume greater role in the overall care of patients with cancer and despite compromised immunogenicity in advanced disease, there is evidence from phase III clinical trials of their positive impact on disease-free and overall survival in prostate cancer (63), melanoma (64), and follicular lymphoma (65). Ours is the first study to administer a cancer vaccine against a TAA in the prophylactic setting, in subjects at high risk for subsequent malignancy. The vaccine proved to be highly immunogenic, much more so than has been previously observed when similar type vaccines were administered to patients with cancer, raising hope that this increased immunogenicity will translate to a highly effective antitumor response. The vaccine was well tolerated without evidence of autoimmunity in these immunocompetent hosts. Unlike the majority of peptide vaccines that are restricted to 1 or only a limited number of HLA types, MUC1 100 mer peptide was immunogenic in individuals of most HLA-DR and HLA-DQ types precluding the need for HLA-typing before vaccination. Immunogenicity of the vaccine can be monitored by a simple and inexpensive ELISA for MUC1-specific IgG. Subsequent studies will include evaluation of whether the vaccine can impact a clinical endpoint, such as reducing adenoma recurrence leading to colon cancer prevention.

Disclosure of Potential Conflicts of Interest
A.M. Salazar is CEO of Oncovir, Inc. and has ownership interest (including patents) in Oncovir, Inc. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Kimura, D.M. Potter, R.E. Schoen, O.J. Finn
Writing, review, and/or revision of the manuscript: T. Kimura, K. Islam, D.M. Potter, A.M. Salazar, R.E. Schoen, O.J. Finn
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