GI-5005 THERAPEUTIC VACCINE PLUS PEG-IFN/RIBAVIRIN IMPROVES BIOPSY NECRO-INFLAMMATORY SCORES AND ALT NORMALIZATION AT 48 WEEKS VERSUS PEG-IFN/RIBAVIRIN IN GENOTYPE 1 CHRONIC HCV PATIENTS

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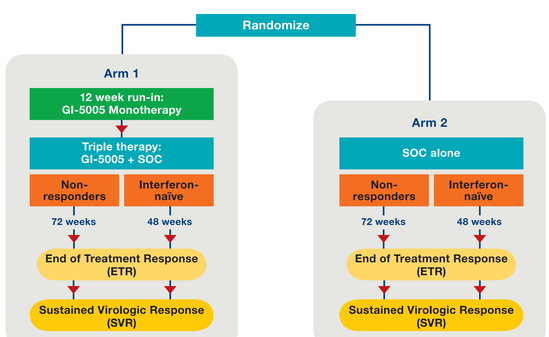
Introduction

Chronic hepatitis C virus (HCV) infection is a health problem that affects 4.8 million people in the U.S. and approximately 180 million people worldwide. The majority of patients exposed to HCV develop chronic infection. However, approximately 20% are able to clear their infection during the acute phase without medical intervention. A strong HCV-specific T cell response has been associated with those spontaneously resolving infections (B. Rehermann 2005 Nat. Rev. Immuno.). The current standard of care (SOC) is pegylated interferon plus ribavirin, which works primarily through the inhibition of viral replication. Only ~40% of HCV genotype 1 patients receiving SOC achieve a sustained virologic response (SVR). Achievement of SVR depends on the patient's ability to clear infected cells from the liver and requires long periods of antiviral suppression by SOC to allow a weak host immune response sufficient time to completely eliminate HCV infected cells.

Substantial gains in the treatment of HCV could be attained through a combination approach that inhibits viral replication (SOC or small molecule antivirals) and enhances HCV-specific cellular immune responses (GI-5005). The GI-5005 Tarmogen® product consists of recombinant *S. cerevisiae* yeast expressing large conserved regions from HCV NS3 and Core proteins. In a randomized, placebo-controlled, phase 1b trial, GI-5005 monotherapy was well tolerated, generated strong HCV-specific T cell responses, and favorably impacted ALT and HCV RNA levels. The GI-5005-02 phase 2 study, described herein, is the first clinical study evaluating GI-5005 in combination with SOC versus SOC alone. We have previously shown in this phase 2 study that GI-5005 plus SOC improved second phase viral kinetics, rapid virologic response (RVR), early virologic response (EVR) rates, as well as ALT normalization and Fibrotest scores. Presented here are the ALT normalization and biopsy data from the GI-5005-02 study.



Phase 2 design

GI-5005-02 is a randomized, open-label phase 2 trial evaluating the efficacy, immunogenicity, and safety of GI-5005 in combination with standard of care (SOC) pegIFN α-2a/ribavirin therapy (triple therapy) vs. SOC alone in subjects with genotype 1 HCV. Treatment naïve subjects in Arm 1 receive GI-5005 monotherapy weekly from day 1 to week 4, a dose at week 8, followed four weeks later by monthly maintenance doses in combination with 48 weeks of SOC (triple therapy). In Arm 1 prior treatment failures receive 12 week monotherapy run-in, followed by 72 weeks of triple therapy. Arm 2 patients received SOC as per the product labels (72 week treatment duration for prior treatment failures). Randomization was stratified by response to prior therapy (interferon-naïve or non-responder). Efficacy endpoints for the trial include viral kinetics, RVR, EVR, ETR, SVR, Fibrotest, biochemical response by ALT reductions and normalization, and histologic improvement by liver biopsy assessment.

Demographics

Variable	Treatment Group		Total (n=140)
	SOC + GI-5005 (n=72)	SOC Alone (n=68)	
Prior Treatment Status			
Naïve	53 (73.6)	49 (72.1)	102 (72.9)
Non-response to prior treatment	19 (26.4)	19 (27.9)	38 (27.1)
Sex			
Male	42 (58.3)	45 (66.2)	87 (62.1)
Female	30 (41.7)	23 (33.8)	53 (37.9)
Race			
White	50 (69.4)	47 (69.1)	97 (69.3)
African American	7 (9.7)	11 (16.2)	18 (12.9)
Hispanic	6 (8.3)	6 (8.8)	12 (8.6)
Asian	6 (8.3)	4 (5.9)	10 (7.1)
Other	3 (4.2)	0 (0.0)	3 (2.1)
Age			
Median (years)	48.0	49.0	48.0
ALT (U/L)[1]			
Mean (SD)	74.4 (41.2)	65.1 (47.3)	70.0 (44.3)
Median	63.0	53.5	57.0
Range	17 to 266	14 to 275	14 to 275
HCV RNA (log_{10} IU/mL)[2]			

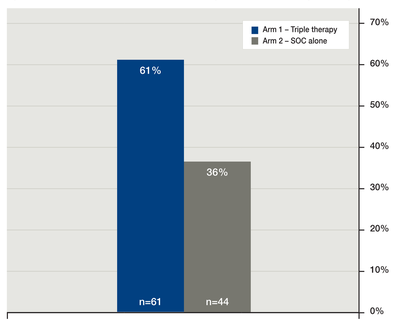
[1] *ALT baseline values taken on Day1 of study therapy* [2] *HCV baseline values were balanced between arms and taken on Day 1 of SOC*

ALT normalization* during treatment period for naïve and prior non-responder patients

Triple therapy significantly improved the proportion of patients who normalized ALT at the end of treatment (all subjects 61% vs 36%, p=0.18), and also showed a substantial advantage for sustained ALT normalization in the post-treatment period for 6 months after completion of therapy (42% vs 21%, p=0.08).

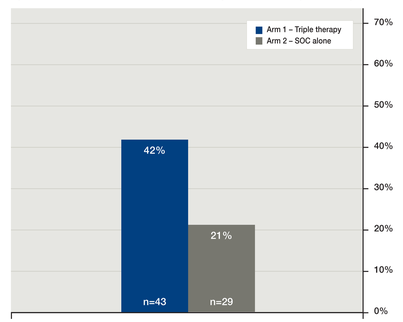
* *ALT normalization defined as 2 consecutive visits <ULN at least 14 days apart for subjects with ALT>ULN at baseline.*

A) ALT normalization at end of treatment (naïve and non-responders)



p=0.018
2-sided Fisher's exact test

B) Sustained ALT normalization 24 weeks post treatment (IFN-naïve)

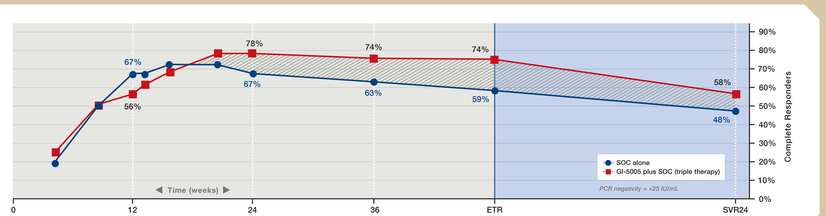


p=0.077
2-sided Fisher's exact test

Time course of viral clearance (IFN-naïve)

The proportion of subjects achieving viral clearance (PCR<25IU/mL) is shown for the naïve subjects from each treatment group during the treatment period and post-treatment periods. Naïve subjects receiving triple therapy showed a 15% advantage for complete virologic response at the end of treatment and a 10% advantage in SVR 6 months after the completion of therapy.

	SVR %	Absolute	Relative	p value
Arm 1 – Triple therapy	58%	10%	21%	0.32
Arm 2 – SOC alone	48%			



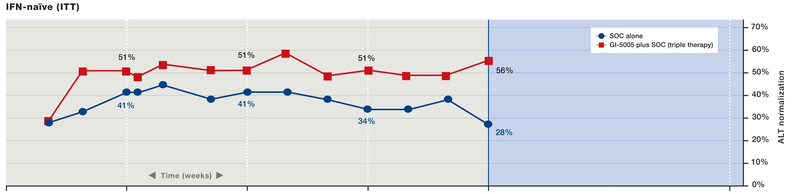
ALT normalization* over time for IFN-naïve and non responder patients

Alanine aminotransferase (ALT) levels in the blood provide a convenient real-time marker of liver injury in patients with chronic HCV infection. Sustained increases in ALT levels may predict a greater level of liver inflammation and necrosis and a more rapid progression to cirrhosis. Normalization of ALT levels for sustained periods of time may reflect an improvement in liver inflammation and may indicate better liver health, overall well being, and reduced risk of progression to cirrhosis.

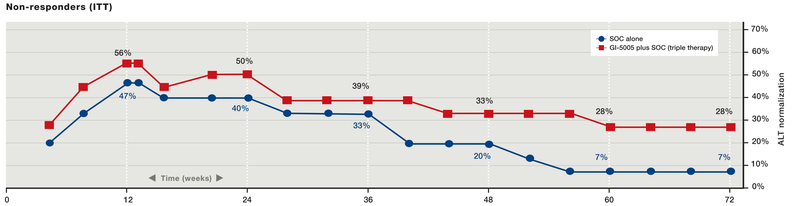
GI-5005 improved ALT normalization in both naïve and non-responder (NR) subjects. This effect was observed in the first 2 months of therapy in both naïve and NR patients and was sustained for the entire treatment period. At end of treatment the naïve GI-5005 patients showed a 2-fold advantage in ALT normalization (56% vs 28%), and the NR GI-5005 patients showed a 4-fold advantage (28% vs 7%).

* *ALT normalization defined as 2 consecutive visits <ULN at least 14 days apart for subjects with ALT>ULN at baseline.*

IFN-naïve (ITT)

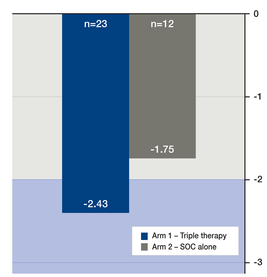


Non-responders (ITT)



Liver biopsy: reduction in necro-inflammation scores

Paired biopsies were collected from consenting subjects (Triple N=23, SOC N=12), blinded with respect to treatment assignment and biopsy sequence (baseline versus 48 weeks), and read by a central pathologist (ZDG). Improvement in 48 week necro-inflammatory (NI) scores was observed in the triple therapy group: mean change Ishak NI TT, -2.43, SOC -1.75. Minimal change in fibrosis was observed in both groups by either Ishak or Knodell index (<0.1 point change). Pearson correlation of average ALT reduction and NI scores was greater for triple therapy compared to SOC: correlation coefficient 0.39, p=0.11 vs SOC 0.09, p=0.88.



Pearson Correlation of ALT and Necro-Inflammation Score

Triple	0.39	p=0.11
SOC	0.09	p=0.88

Conclusions

- GI-5005 significantly improved ALT normalization (61% vs 36%, p=0.018) and was sustained in the post-treatment period (42% vs 21%).
- The advantage for ALT normalization in GI-5005 treated subjects precedes the advantage observed for virologic response and persists for the entire treatment period.
- A larger reduction in necroinflammation score was observed in the biopsies of GI-5005 treated patients compared to SOC alone.
- The reduction in necroinflammation scores were well correlated to ALT reductions in the GI-5005 treated subjects but not in the SOC treated subjects.
- GI-5005 may elicit advantages in ALT normalization and liver biopsy indicative of better liver health independent of the favorable effects observed in virologic response.
- These data support further study of the influence of GI-5005 on liver biopsies as a measure of clinical benefit in addition to virologic response in patients with chronic HCV infection.

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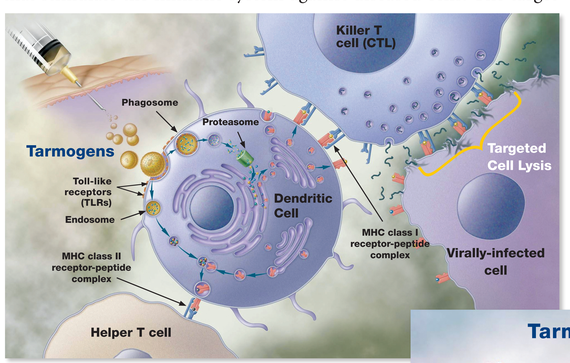
Active immunotherapy with yeast-based Tarmogens

Tarmogens are whole, heat-killed recombinant *Saccharomyces cerevisiae* yeast modified to express one or more protein targets that stimulate the immune system against diseased cells. The target

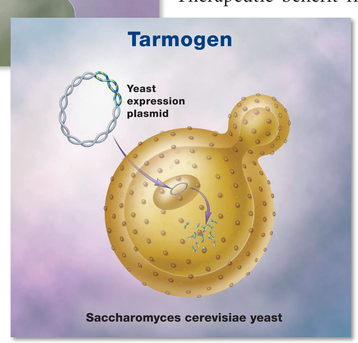


antigens are markers of diseased cells and can be conserved viral proteins, mutated proteins unique to cancer cells, or proteins over-expressed in cancer. To create a new Tarmogen, DNA encoding target protein antigens is engineered into a yeast expression plasmid. The heat-inactivated yeast, with the target protein inside, is administered as the Tarmogen product. Tarmogens stimulate the innate and antigen-specific immune system to produce a highly specific and potent T cell response against the diseased cell, with little or no impact on healthy cells.[1]

Tarmogens are administered subcutaneously and are avidly taken up by antigen presenting cells (APCs), such as dendritic cells and macrophages in a process mediated by Toll-like receptors (TLRs) found on the cell surface. Uptake of Tarmogens activates the APCs and results in their migration to lymph nodes and their production of immune-stimulating cytokines.[2,3]

Tarmogens are degraded inside APCs within hours and the target antigens are presented by MHC class I and II receptors on the APC surface. Tarmogens are initially digested in phagosomes, whereupon the antigens are delivered to the cytosol, and these proteins are cleaved by proteasomes into small peptides. These small peptides are loaded into newly folded MHC class I receptors in the secretory pathway of the APC. The peptide-MHC I receptor complex is shuttled to the surface of the APC, where the antigenic peptides are presented to CD8+ killer T cells (causing activation of these cells). Tarmogens are also digested in endosomes, and the product-associated peptides are loaded into MHC class II receptors for antigen presentation to CD4+ helper T cells (causing activation of these cells).[2,3]

Therapeutic benefit from the Tarmogen is driven by the targeted activation of the immune system. Tarmogens activate killer T cells capable of locating and destroying the target cancer or virally-infected cells. Repeated dosing with Tarmogens further increases the number of T cells available to eliminate diseased cells. In summary, Tarmogens couple the innate immune response to yeast with potent activation of antigen-specific cellular immune responses against cancer cells or virally infected cells.[3-4]



[1] Munson et al. "Coupling Innate and Adaptive Immunity with Yeast-Based Cancer Immunotherapy" Chapter 9; Cancer Vaccines and Tumor Immunity. January 2008

[2] Bernstein et al. "Recombinant Saccharomyces cerevisiae (yeast-CEA) as a potent activator of murine dendritic cells." Vaccine (2008) 26, 509-521.

[3] Remando et al. "Human Dendritic Cell Maturation and Activation by a Heat-Killed Recombinant Yeast Vector Encoding Carcinoembryonic Antigen." Vaccine (2009) 27, 987-994.

[4] Wansley et al. "Vaccination with a Recombinant Saccharomyces cerevisiae Expressing a Tumor Antigen Breaks Immune Tolerance and Elicits Therapeutic Antitumor Responses" Clinical Cancer Research. Clin Can Res (2008) 14,4316-4325.

[5] Haller et al. "Whole recombinant yeast-based immunotherapy induces potent T cell responses targeting HCV NS3 and Core proteins" Vaccine (2007) 25, 1452-1463.

Abstract

GI-5005 THERAPEUTIC VACCINE PLUS PEG-IFN/RIBAVIRIN IMPROVES BIOPSY NECRO-INFLAMMATORY SCORES AND ALT NORMALIZATION AT 48 WEEKS VERSUS PEG-IFN/RIBAVIRIN IN GENOTYPE 1 CHRONIC HCV PATIENTS

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Background and aims: GI-5005 is a whole heat-killed *S. cerevisiae* therapeutic vaccine expressing HCV NS3 and Core antigens. GI-5005 elicits antigen-specific T-cell responses (Hepatology 2007; 46: 816A) with the goal of improving the rate of immune-mediated elimination of HCV-infected hepatocytes.

Methods: Naïve and non-responder (NR) chronic HCV genotype 1 patients were randomized 1:1, and stratified by prior treatment status. Arm 1: GI-5005 monotherapy for 5 weekly doses (day 1 through week 4) followed 4 weeks later by 1 dose at week 8, then monthly subcutaneous doses of 40YU (1 YU = 10^7 yeast) GI-5005, followed by triple therapy (TT) consisting of monthly 40YU GI-5005 doses plus 48 weeks pegIFN α-2a/ribavirin (SOC). Arm 2: SOC alone.

Results: TT was well tolerated with no new toxicities observed. Paired biopsies were collected from consenting subjects (TT N=23, SOC N= 12), blinded with respect to treatment assignment and biopsy sequence (baseline versus 48 weeks), and read by a central pathologist (ZDG). Improvement in 48 week necro-inflammatory (NI) scores was observed in the TT group: mean change Ishak NI TT, -2.43, SOC -1.75; mean change Knodell NI TT -2.57, SOC -2.17. Minimal change in fibrosis was observed in both groups by either Ishak or Knodell index (<0.1 point change). Higher rates of ALT normalization were observed at 48 weeks in TT compared to SOC: TT Naïve 24/44 (55%), SOC Naive 9/29 (31%) p=0.04, TT NR 6/18 (33%) , SOC NR 3/15 (20%) p=0.32. Pearson correlation of average ALT reduction and NI scores was greater for TT compared to SOC: correlation coefficient Knodell TT 0.39, p=0.11 vs SOC 0.09, p=0.88. Ishak TT 0.34, p=0.17 vs SOC 0.20, p=0.75.

Conclusions: Triple therapy (GI-5005 plus pegIFN/ribavirin) improved week 48 biopsy necro-inflammatory scores compared to SOC alone in genotype 1 patients. Improvement in NI scores was correlated with ALT reductions in the Triple group, and indicates that GI-5005 in combination with SOC reduces liver inflammation. These data along with the previously reported 15% treatment advantage for complete virologic response at 48 weeks in naïve subjects (74% vs 59%) support further investigation of GI-5005 triple therapy and novel combination strategies for GI-5005 with STATC agents.