GI-5005 IMMUNOTHERAPY PLUS PEG-IFN/RIBAVIRIN VERSUS PEG-IFN/RIBAVIRIN IN GENOTYPE 1 CHRONIC HCV SUBJECTS; PRELIMINARY PHASE 2 EVR ANALYSES

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Introduction

Chronic hepatitis C virus (HCV) infection is a worldwide health problem that affects 4.8 million people in the US and approximately 180 million people worldwide. The majority of patients exposed to HCV develop chronic infection. However, approximately 20% of people exposed to hepatitis C virus (HCV) are able to clear their infection during the acute phase without medical intervention. A strong and broadly directed HCV-specific T cell response has been associated with these spontaneously resolving infections (B. Rehermann 2005 Nat. Rev. Immuno.).

The current standard of care (SOC) for patients chronically infected with HCV is pegylated interferon plus ribavirin, which works primarily through the inhibition of viral replication. While SOC can often deliver substantial reductions in serum virus levels during the first days of therapy (first phase viral kinetic clearance), only 50% of HCV genotype 1 patients receiving SOC achieve a sustained virologic response (SVR defined as serum negativity for HCV RNA by PCR assay lasting 6 months after the completion of 48 weeks of therapy). Achievement of SVR depends on the patient's ability to clear infected cells from the liver and requires long periods of SOC treatment for a weak host immune response to completely eliminate HCV infected cells (second phase viral kinetic clearance). Therapies that improve the T cell immune response would be predicted to improve the rate of clearance of HCV infected liver cells and lead to improvement of early virologic markers as well as improved rates of remission (SVR); see Figure 1a.

Figure 1a

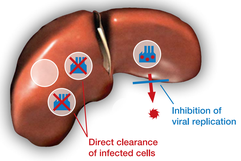
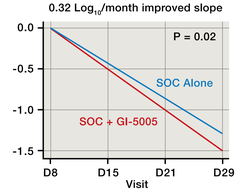
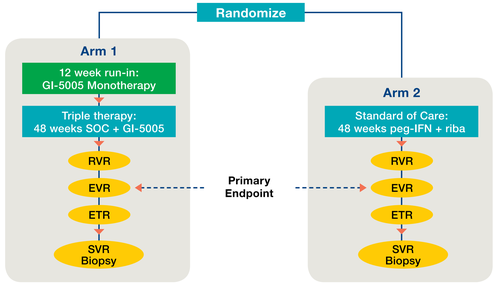


Figure 1b: Triple therapy vs. SOC alone



Substantial gains in the treatment of HCV should be attainable through a combination approach that includes inhibition of viral replication (SOC or small molecule antivirals) with a product that generates enhanced complementary HCV-specific cellular immune responses. The objective of the GI-5005-02 study is to evaluate whether the ability of the GI-5005 Tarmogen® product to produce an HCV-specific T cell immune response enhances the clearance of infected cells from the liver in the setting of inhibited viral replication. This will potentially improve established virologic endpoints, and ultimately, clinical outcomes. In the current phase 2 trial (GI-5005-02) we have previously shown that GI-5005 plus SOC improved second phase viral kinetics by 0.3 log_{10}/month in all patient subgroups and rapid virologic response (RVR) >2-fold in high viral load naïve patients (McHutchison et al. AASLD 2008 Poster); see Figure 1b.

The GI-5005 Tarmogen product consists of recombinant *S. cerevisiae* yeast expressing a fusion protein of large conserved regions from the HCV NS3 and Core proteins. In a randomized, placebo-controlled phase 1b trial, GI-5005 monotherapy was well tolerated, generated broadly targeted HCV-specific T cell responses and favorably impacted clinically relevant markers such as ALT and HCV RNA levels. The GI-5005-02 study, described herein, is the first clinical study evaluating GI-5005 in combination with SOC versus SOC alone.



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 SOC vs. SOC alone in subjects with genotype 1 HCV. Treatment naïve subjects in Arm 1 receive monotherapy GI-5005 for 12 weeks (5 weekly plus by 2 monthly doses), followed by 48 weeks of triple therapy (GI-5005 administered monthly). Prior treatment failures in Arm 1 receive 12 week monotherapy run-in, followed by 72 weeks of triple therapy. Arm 2 patients receive Pegasys/ribavirin as per the product labels. The primary endpoint for the trial is early virologic response (EVR) at week 12. Secondary endpoints include viral kinetics, RVR, ETR, SVR, ALT normalization, serum fibrosis markers (Fibrotest), serum necrosis markers (Actitest), and histologic improvement by liver biopsy assessment.

Demographics

The triple therapy and SOC groups were well balanced for age, gender, race, HCV RNA at baseline (median 6.72 log_{10} IU/mL in triple vs. 6.79 log_{10} IU/mL in SOC), ALT at baseline (median 63.0 U/L in triple vs. 53.5 U/L in SOC), and prior response to SOC (73.6% naïve in triple vs. 72.1% naive in SOC.

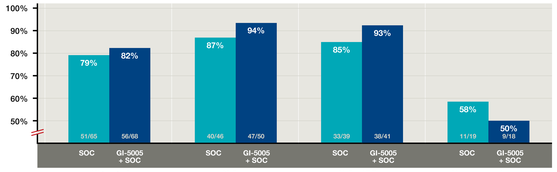
Safety summary

During the 12 week GI-5005 monotherapy phase no patients discontinued therapy due to adverse events. Comparable numbers of patients from the triple therapy group and SOC group discontinued therapy due to adverse events; 9/65% (13.8%) SOC group discontinued SOC, 5/69 (7.7%) triple therapy group discontinued SOC, 6/69 (8.7%) triple therapy group discontinued GI-5005.

While 8/69 (11.6%) SAEs were observed in the triple therapy group compared to 3/65 (4.6%) in the SOC group, several events in the triple therapy group were clearly unrelated to therapy (1 cat bite, and 2 events of substance abuse).

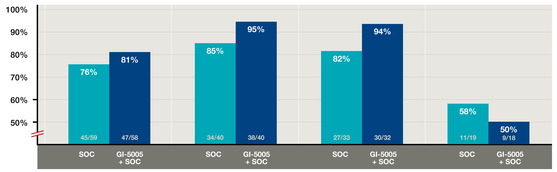
The most common (>20%) treatment-emergent non-serious adverse events observed in the triple therapy group included (listed alphabetically by term) Anemia (21.7%), Depression (20.3%), Fatigue (50.7%), Headache (37.7%), flu-like illness (18.8%), Injection site reaction (23.2%), Insomnia (23.2%), Irritability (21.7%), Nausea (36.2%), Pyrexia (26.1%), Rash (23.2%). The incidence of these events was comparable to that observed in the SOC group.

EVR (all regions)



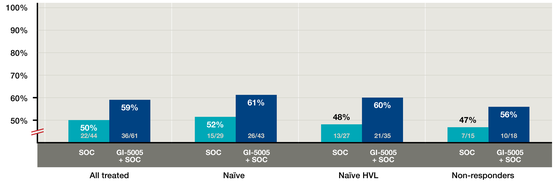
Early virologic response (EVR) is defined as a >2 log10 reduction of HCV RNA from baseline by 12 weeks.

EVR (U.S.)



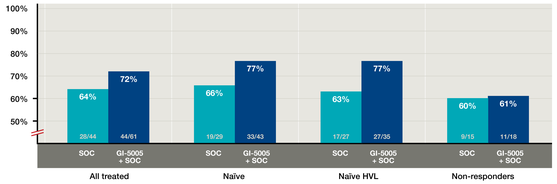
Early virologic response (EVR) is defined as a >2 log10 reduction of HCV RNA from baseline by 12 weeks.

ALT normalization by 12 weeks

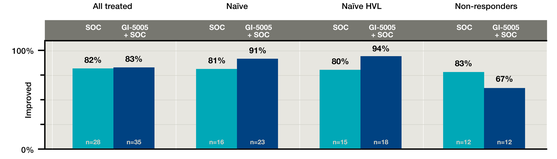


ALT normalization is defined as at least 2 ALT values < ULN on consecutive study visits for patients with ALT >ULN at Day 1.

ALT normalization by 24 weeks

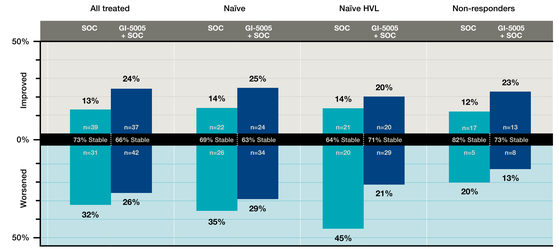


Actitest at 24 weeks



The proportion of patients who improved from moderate to minimal necrosis or from severe to moderate or minimal necrosis as measured by Actitest.

Fibrotest at 24 weeks



The proportion of patients who improved from moderate to minimal fibrosis or from severe to moderate or minimal fibrosis as measured by Fibrotest.

Conclusions

- GI-5005 is well tolerated with triple therapy showing comparable discontinuation rates compared to SOC
- Triple therapy demonstrated 8-12% improvement in EVR rates compared to SOC alone in treatment naïve patient subgroups
- Triple therapy demonstrated a 10-15% improvement in ALT normalization in treatment naïve patient subgroups
- Triple therapy demonstrated increased proportions (up to 2-fold) of patients with categorically improved serum fibrotest scores and a decreased proportion (as much as 50% reduction) of patients with categorically worsened serum fibrotest scores compared to SOC
- Triple therapy demonstrated up to a 14% advantage in naïve patient subgroups with categorically improved serum Actitest scores compared to SOC
- Improvements in viral kinetics, RVR, and EVR may lead to an advantage in virologic response for triple therapy compared to SOC as measured by SVR
- Improvements in ALT normalization, Fibrotest, and Actitest scores may lead to an advantage for liver histology for triple therapy compared to SOC as measured by paired biopsy assessment
- Combination of GI-5005 with different inhibitors of viral replication, such as small molecule polymerase and protease inhibitors may result in the future ability to spare or eliminate components of the current standard of care (pegylated IFN or ribavirin).

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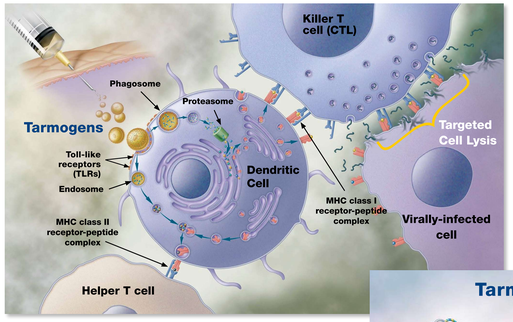
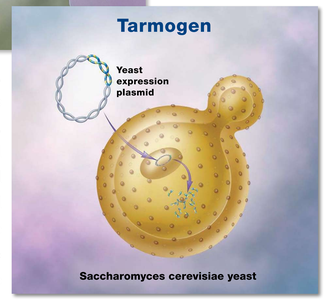
Active immunotherapy with yeast-based Tarmogens

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

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European Association for the Study of Liver Diseases, Annual Meeting, Copenhagen, Denmark, April 2009.

Background and aims

GI-5005 is a whole heat-killed S. cerevisiae immunotherapy expressing HCV NS3 and Core antigens. GI-5005 has been designed to elicit antigen-specific T-cell responses with the goal of improving the rate of immune clearance of HCV. HCV genotype 1 patients enrolled in a trial comparing pegylated interferon plus ribavirin with and without GI-5005 were compared in a prior interim analysis; RVRs for triple therapy compared to SOC alone were >2 fold more frequent (Hepatology 2008; 48: 1023A). Interim EVR data are presented here.

Methods

Naïve and non-responder chronic HCV genotype 1 patients were eligible (null responders and relapsers were excluded), and were randomized 1:1 and stratified by prior virologic response in this open label trial; Arm 1- GI-5005 monotherapy run-in consisting of five weekly followed by 2 monthly subcutaneous (SC) doses of 40YU (1 YU = 10,000,000 yeast) GI-5005 over 12 weeks, followed by triple therapy consisting of monthly 40YU GI-5005 doses plus 48 weeks pegIFN/ribavirin (SOC), Arm 2- SOC alone.

Results

At this time, 52/72 triple therapy subjects and 65/68 SOC subjects were evaluable for EVR (> 2 log10 reduction in HCV RNA at week 12, with last observation carried forward). Triple therapy showed a trend for improved EVR in all naïve subjects (34/36 {94.4%} vs. 40/46 {87%} p=0.23) and naïve subjects with high baseline viral load (>600,000IU/mL) (28/30 {93.3%} vs. 35/41 {85.4%} p=0.26). EVR was comparable for triple therapy and SOC in the small subset of prior non-responder subjects. GI-5005 has been well-tolerated, with no GI-5005 related serious adverse events or dose limiting toxicities to date.

Conclusions

Triple therapy with GI-5005 plus pegIFN/ribavirin was well tolerated and preliminary data indicate improved EVR rates, despite an unusually high EVR rate in the SOC group. These data are consistent with the HCV-specific cellular immune responses observed in the GI-5005-01 phase 1 trial and the improved week 4 RVR in the current trial. This therapeutic approach and the mechanism of GI-5005 support further investigation and development of combination therapy strategies in chronic HCV infection. Complete cohort data for naives and non-responders will be included at the time of presentation.