PHARMACOGENOMIC ANALYSIS REVEALS IMPROVED VIROLOGIC RESPONSE IN ALL *IL-28* B GENOTYPES IN NAÏVE GENOTYPE 1 CHRONIC HCV PATIENTS TREATED WITH GI-5005 THERAPEUTIC VACCINE PLUS PEG-IFN/RIBAVIRIN

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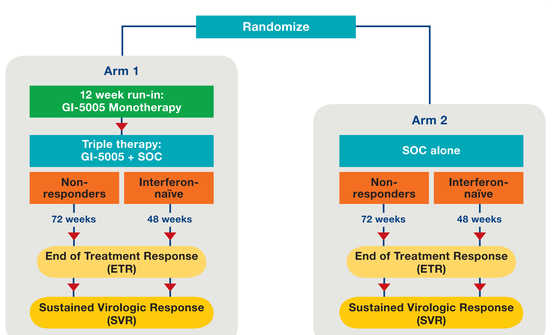
Introduction

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.

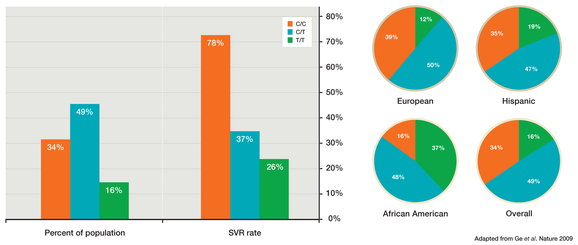
Substantial gains in the treatment of HCV could be attained through a combination approach that inhibits viral replication (SOC or small molecule antivirals) and enhances HCV-specific cellular immune responses (GI-5005). The GI-5005 Tarmogen® product consists of recombinant *S. cerevisiae* yeast expressing 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) and early virologic response (EVR) rates, as well as ALT normalization and Fibrotest scores. Presented here are the complete virologic response at end of treatment (ETR) and sustained virologic response (SVR) data in naïve patients grouped by *IL-28* B genotype.



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-α2a/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.

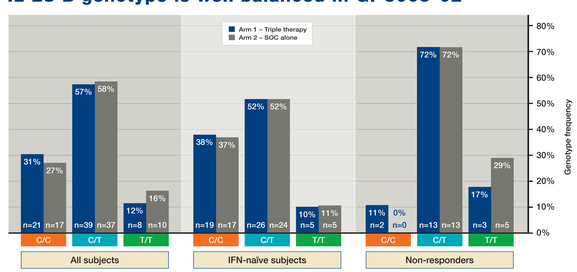
Historical *IL-28* B data predicts response to IFN therapy



Adapted from Ge *et al.* Nature 2009

In a recent study published by Ge, et al. 2009 genome wide sequence analysis revealed that genetic variations at a single locus (rs12979860 located 3kb upstream of the *IL-28* B gene) predicts response to pegIFN/ribavirin therapy. Three genotypes were described: C/C (highly responsive) C/T (moderately responsive), and T/T (poorly responsive). The overall frequencies as well as race specific frequencies of the *IL-28* B genotypes are shown above. In another recent article (Thomas et al, 2009), spontaneous clearance of HCV in the acute setting also correlated to these *IL-28* B genotypes.

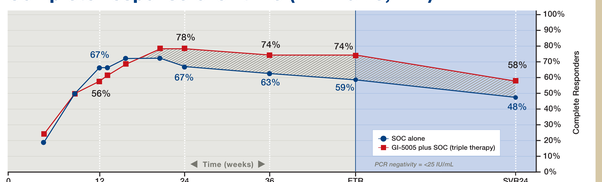
IL-28 B genotype is well balanced in GI-5005-02



GI-5005-02 demographics

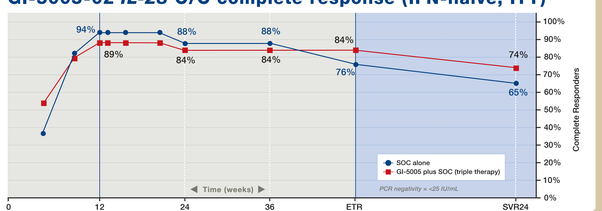
Variable	Treatment Group		Total (n=140)
	SOC + GI-5005 (n=72)	SOC Alone (n=68)	
Prior Treatment Status			
Naïve	53 (73.6)	49 (72.1)	102 (72.9)
Non-response to prior treatment	19 (26.4)	19 (27.9)	38 (27.1)
Sex			
Male	42 (58.3)	45 (66.2)	87 (62.1)
Female	30 (41.7)	23 (33.8)	53 (37.9)
Race			
White	50 (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
Range	20 to 74	20 to 68	20 to 74

Complete response over time (IFN-naïve, ITT)

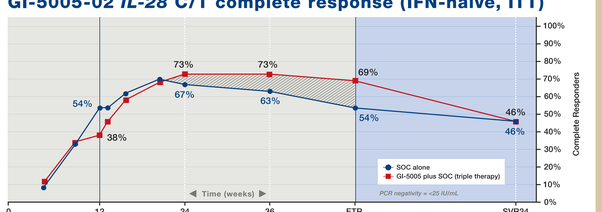


	SVR %	Absolute improvement	Relative improvement	p value
Arm 1 – Triple therapy	58%	10%	21%	0.32
Arm 2 – SOC alone	48%			

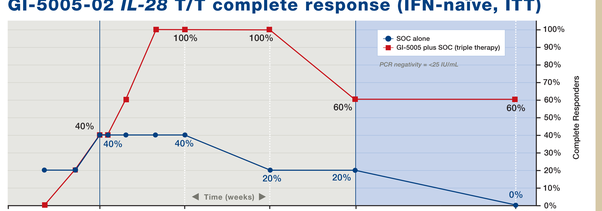
GI-5005-02 *IL-28* C/C complete response (IFN-naïve, ITT)



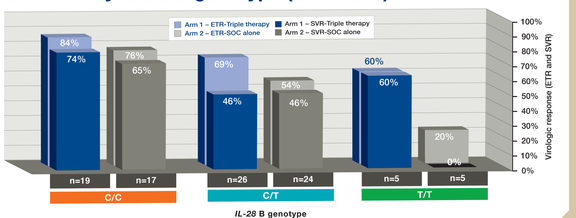
GI-5005-02 *IL-28* C/T complete response (IFN-naïve, ITT)



GI-5005-02 *IL-28* T/T complete response (IFN-naïve, ITT)



ETR/SVR by *IL-28* B genotype (IFN-naïve)



Discussion

The discovery of the *IL-28* B genotypes (Ge et al., 2009) and their predictive value for spontaneous clearance of HCV (Thomas et al., 2009) and response to pegIFN/ribavirin therapy (Ge et al. 2009) are significant breakthroughs in the understanding of the molecular biology of HCV. The role of *IL-28* B variants in acute clearance of HCV strongly suggests that it is a marker of the immune capacity of the patient, and influences response to interferon therapy based on the immune differences in the *IL-28* B subgroups. *IL-28* B testing in GI-5005-02 showed excellent balance between the GI-5005 triple therapy and SOC groups. Furthermore, important differences were noted for the different *IL-28* B genotypes related to the timing and magnitude of viral clearance and SVR. GI-5005 triple therapy improved end of treatment viral clearance in all *IL-28* B genotypes (C/C; 84% vs 76%, C/T; 69% vs 54%, T/T; 60% vs 20%) and improved SVR in the C/C (74% vs 65%) and T/T groups (60% vs 0%).

The pattern of response in the C/T group suggests an important role for response guided therapy due to the fact that an advantage of 15% in response was observed at end of treatment but not at 6 months post-treatment. The majority of GI-5005 treated C/T patients who relapsed in the post-treatment period cleared HCV virus after 12 weeks of therapy, suggesting that they would have benefited by a lengthened duration of treatment. The greatest favorable treatment effect for GI-5005 was observed in the T/T group with an advantage in end of treatment viral clearance of 40% and an advantage in SVR of 60%. This may reflect an immune deficiency inherent in the T/T group, and suggests that GI-5005 can stimulate HCV specific immunity in a manner that compensates for this deficit.

Conclusions

- Genetic variants near the *IL-28* B locus predict spontaneous clearance of HCV as well as response to pegIFN/ribavirin.
- GI-5005 improved end of treatment (ETR) responses in all *IL-28* B genotypes, with the greatest effect in T/T subjects (60% vs 20%).
- GI-5005 improved SVR in C/C and T/T patients, with the greatest effect in T/T subjects (60% vs 0%).
- *IL-28* B testing will be a critical baseline demographic to consider in future trial design.
- The immune based mechanism of GI-5005 may offer unique treatment advantages in different *IL-28* B genotypes, with the greatest impact observed in the poorest responding group (*IL-28* B T/T).
- These data support further study of GI-5005 in combination with pegIFN/ribavirin as well as direct acting antivirals in *IL-28* B defined populations.

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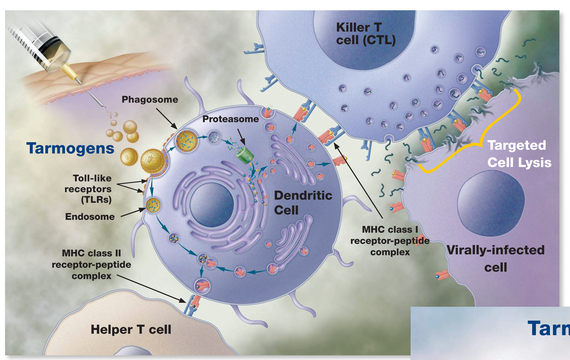
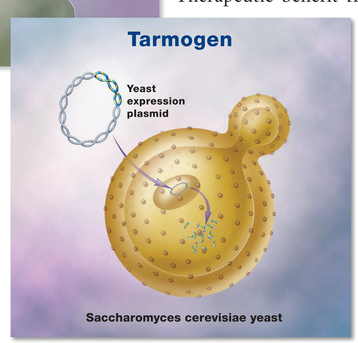
Active immunotherapy with yeast-based Tarmogens

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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Background and aims: *IL-28* B genotypes (CC,CT,TT) predict sustained virologic response (SVR) to standard of care (SOC) PegIFN/ribavirin and spontaneous clearance of acute HCV. Since GI-5005 generates HCV-specific T-cells involved in spontaneous HCV clearance, we assessed the influence of *IL-28* B on end of treatment (ETR) and SVR responses to GI-5005 plus SOC in naïve genotype-1 chronic HCV.

Methods: Patients were randomized 1:1, and stratified by prior treatment status. Arm1-Triple(n=50):GI-5005 monotherapy for 5 weekly doses (day 1 through week 4) followed 4 weeks later by 1 dose at week 8, then monthly GI-5005 with 48 weeks pegIFNα-2a/ribavirin. Arm2-SOC(n=46): 48 weeks SOC. The *IL-28* B locus was PCR amplified from patient genomic DNA and genotyped by bi-directional sequencing.

Table1: Influence of *IL-28* B Alleles on ETR48 and SVR24

IL-28 B genotype	Endpoint	Triple	SOC	Δ
All {nt=50, nsoc=46}	ETR	74%	59%	15%
	SVR24	58%	48%	10%
C/C {nt=19 (38%), nsoc=17 (37%)}	ETR	84%	76%	8%
	SVR24	74%	65%	9%
C/T {nt= 26 (52%), nsoc=24 (52%)}	ETR	69%	54%	15%
	SVR24	46%	46%	0%
T/T {nt= 5 (10%), nsoc= 5 (11%)}	ETR	60%	20%	40%
	SVR24	60%	0%	60%

Table 2: Influence of *IL-28* B Alleles on Kinetics of HCV Clearance and SVR24

IL-28 B genotype	SVR when first RNA negative D1-D29 (RVR)		SVR when first RNA negative D30-D85 (cEVR)		SVR when first RNA negative D86-D337 (Slow Responder)	
	Triple	SOC	Triple	SOC	Triple	SOC
CC	10/10 (100%)	5/6 (83%)	4/7 (57%)	6/10 (60%)	0/0	0/0
CT	2/3 (67%)	1/2 (50%)	7/7 (100%)	8/11 (73%)	3/10 (30%)	2/5 (40%)
TT	0/0	0/1	1/2 (50%)	0/1	2/3 (67%)	0/0
All	12/13 (92%)	6/9 (67%)	12/16 (75%)	14/22 (64%)	5/13 (38%)	2/5 (40%)

Results: *IL-28* B genotypes were balanced in both arms. Results shown in Tables 1 and 2.

Conclusions: harmacogenomic analyses can provide valuable insights into therapeutic trial results. Triple therapy improved ETR regardless of *IL-28* B genotype; delivering more CC and CT RVRs and more CC and CT slow responders. The effect of GI-5005 on SVR is greatest in patients with the poorest prognosis genotype (TT). *IL-28* B genotyping suggests that the GI-5005 therapeutic vaccine augments response in those with unfavorable *IL-28* B types.