Hepatites

22

Similar SVR rates in IL28B CC, CT or TT prior relapser, partial - or null - responder patients treated with telaprevir/peginterferon/ribavirin: retrospective analysis of the REALIZE study

Roberto Focaccia, Stanislas Pol, Stefan Zeuzem , Pietro Andreone, Eric J. Lawitz, Stuart Roberts, Zobair Younossi, Graham R. Foster, Kleber Dias do Prado, Décio Diament, Jeroen Aerssens, Eric J. Lawitz, Andrzej Horban, Paul J. Pockros
Université Paris Descartes (INSERM Unité 567) et Assistance Publique – Hôpitaux de Paris, Cochin Hospital Paris, França; Tibotec BVBA, Beerse, Bélgica; Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, Alemanha; Università di Bologna, Bolonha, Itália; Alamo Medical Research, San Antonio, Texas, EUA; Department of Gastroenterology, Alfred Hospital, Melbourne, Austrália; Center for Liver Disease, Inova Fairfax Hospital, Falls Church, Virgínia, EUA; Queen Mary University of London, Institute of Cell and Molecular Science, Londres, Reino Unido; Instituto de Doenças Infecciosas Emílio Ribas, São Paulo, Brasil; Medical University of Warsaw, Wolska, Warsaw, Polônia

Background: IL28B polymorphisms are linked to differences in SVR rates in HCV treatment-naïve patients treated with pegylated interferon (P) and ribavirin (R). REALIZE is a Phase 3 study that compared the efficacy, safety and tolerability of telaprevir (T), with or without a lead-in (LI), in combination with PR against PR alone in prior treatment-failure patients including relapsers, partial responders and null responders (NR). Both T12/PR48 arms were superior to control in all three patient categories. The relationship between IL28B genotype and SVR was investigated retrospectively. **Methods:** 527/662 (80%) patients enrolled in REALIZE consented to genetic testing. This represented 72%, 76% and 98% of the total relapsers, partial responders, and NR, respectively. Genotype rs12979860 was determined using a TaqMan allelic discrimination assay validated against Sanger sequencing on 50 independent samples. This was a retrospective study based on patients who consented to genetic testing prior to the discovery of IL28B, thus, sample size was not based on formal statistical considerations. **Results:** Overall, 94% were caucasian and 4% were black. Eighteen percent of patients were IL28B CC, 61% CT and 21% TT. By prior response category, the highest proportion of IL28B TT patients was among prior NR (28%), while the highest frequency of CC patients occurred among prior relapsers (27%). The observed IL28B genotype frequencies indicate that the population was not in Hardy-Weinberg equilibrium ($Chi^2 = 28$, $p < 0.0001$). IL28B genotypes were well balanced across all arms, with exception of a higher frequency of TTs in the placebo arm. Since no differences were observed between the two T arms, a pooled analysis is presented. In overall population, SVR in the T12/PR48 group was 79% for CC genotype, 60% for Ct and 61% for TT; in the Pbo/PR48 group frequencies were: CC 29%, CT 16% and TT 13%. Among prior relapsers, frequencies were: CC 88%, CT 86%, TT 85% for the T12/PR48 group and CC 33%, CT 20%, and TT 30% for the Pbo/PR48 group; partial responders SVR% for the T12/PR48 group was: CC 63%, CT 58%, and TT 71%; for the placebo group: CC 20%, CT 20% and TT 0%. In the prior null responders SVR on the T12/PR48 group was as follows: CC 0%, CT 29%, and TT 31%; in the placebo group was: CC 0%, CT 6% and TT 7%. **Conclusions:** Differences in SVR rates among IL28B CC, CT and CC patients were only evident when the three patient subpopulations were pooled; however, SVR among CT and TT patients were still high. In this retrospective analysis, IL28B genotype did not

contribute to outcome prediction in prior treatment-experienced patients treated with a telaprevir-based regimen, and thus may be of limited utility in this setting.

23

REALIZE trial final results: telaprevir-based regimen for genotype 1 hepatitis C virus infection in patients with prior null response, partial response or relapse to peginterferon/ ribavirin

Roberto Focaccia, Stefan Zeuzem, Pietro Andreone, Stanislas Pol, Eric J. Lawitz, Moises Diago, Stuart Roberts, Kleber Dias do Prado, Décio Diament, Zobair M. Younossi
Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, Alemanha; Università di Bologna, Bolonha, Itália; Université Paris Descartes (INSERM Unité 567) et Assistance Publique – Hôpitaux de Paris, Cochin Hospital, Paris, França; Alamo Medical Research, San Antonio, Texas, EUA; Hospital General de Valencia, Valência, Espanha; Department of Gastroenterology, Alfred Hospital, Melbourne, Austrália; Instituto de Doenças Infecciosas Emílio Ribas, São Paulo, Brasil; Center for Liver Disease, Inova Fairfax Hospital, Falls Church, Virgínia, EUA; Queen Mary University of London, Institute of Cell and Molecular Science, Londres, Reino Unido; Medical University of Warsaw, Wolska, Warsaw, Polônia; Scripps Clinic and The Scripps Research Institute, La Jolla, Califórnia, EUA

Background: The Phase 3 study REALIZE evaluated telaprevir (T) in combination with pegylated-IFNα-2a (P) and ribavirin (R) in well-characterized prior PR treatment-failure patients. **Methods:** REALIZE was a randomized, international, multicentre, double-blind, placebo-controlled trial to evaluate the efficacy, safety and tolerability of T (750 mg q8h) plus P (180 µg/w) and R (1000- 1200 mg/d) compared with PR alone in G1 HCV-infected patients with prior PR treatment failure including non-responders (null- and partial-responders) and relapses. The treatment arms (randomized 2:2:1, stratified by viral load and type of prior response) were: 1) T/PR for 12 weeks, followed by PR for 36 weeks (T12/PR48); 2) PR for 4 weeks followed by T/PR for 12 weeks, then PR for 32 weeks (lead-in T12/PR48); 3) PR for 48 weeks (Pbo/PR48). The primary objective was to evaluate the superior efficacy of the T/PR arms for non-responders and relapses. Secondary objectives: evaluation of a lead-in and efficacy in prior null- and partial-responders separately. HCV RNA was quantified with the COBAS TaqMan® v2.0 assay (LLOQ = 25I U/mL). ESAs were not allowed for anemia management. **Results:** 662 treated. 70% of patients were male, 93% were caucasian, 26% had cirrhosis, and 89% had baseline HCV RNA ≥ 800,000 IU/mL. The RVS was significantly higher in the two telaprevir groups than in the control group for patients who had a previous relapse (83% in the T12PR48 group, 88% in the lead-in T12PR48 group, and 24% in the control group) and for those who did not have a previous sustained response (41%, 41%, and 9%, respectively), including those who had a partial response (59%, 54%, and 15%, respectively) and those who had no response (29%, 33%, and 5%,respectively), or according to the stage of liver fibrosis or baseline viral load. The rate of RVS was also significantly higher for the pooled subgroup of patients who had either a relapse or a partial response in the telaprevir groups than in the control group (78% vs 21%). RVS were similar in the T12PR48 group and the lead-in T12PR48 for patients who had a relapse or no response or a partial response to previous therapy. Overall, the rates of RVS were 64% in the T12PR48 group, 66% in the lead-in T12PR48 group, and 17% in the control group. The differences in the rates of RVS were 47% between the T12PR48 group and the control group, and 50% between lead-in T12PR48 group and the control group. **Conclusions:** T/PR demonstrated superior efficacy compared with PR in all prior treatment-failure populations studied including null- and partial-responders. A lead-in did not have a significant impact on SVR rates. The safety profile of T/PR in prior treatment-failure patients was consistent with that observed in treatment-naïve patients.

24

Tratamento com interferon peguilado é superior a interferon genérico em infecção crônica pelos genótipos 2 ou 3 do vírus da hepatite C?

Aline Gonzalez Vigani, Eduardo Sellan Gonçales, Maria Helena Postal Pavan, Flavia Genari Raquel Tozzo, Maria Silvia Kroll Lazarini, Viviane Fais, Neiva Sellan Gonçales, Fernando Lopes Gonçales Jr.
Grupo de Estudos das Hepatites Virais – Disciplina de Moléstias Infecciosas – Universidade Estadual de Campinas, UNICAMP

Justificativa e Objetivos: De acordo com o protocolo brasileiro de tratamento das hepatites virais, pacientes com infecção pelo genótipo 1 do vírus da hepatite C (VHC) devem ser tratados com interferon peguilado α 2a ou 2b e ribavirina (RBV) e pacientes com infecção pelos genótipos 2 ou 3 com interferon α convencional genérico e RBV. Dados da literatura demonstram que pacientes com infecção pelo genótipo 1 apresentam taxas de resposta virológica sustentada (RVS) superiores quando tratados com interferon peguilado α 2a ou 2b e RBV em comparação com interferon α 2a ou 2b e RBV. Pacientes com infecção pelos genótipos 2 ou 3 apresentam taxas de RVS semelhantes quando tratados com interferon peguilado α 2a ou 2b e RBV ou interferon α 2a ou 2b e RBV. O objetivo deste estudo é avaliar se pacientes com infecção pelos genótipos 2 ou 3 apresentam taxas de RVS semelhantes quando tratados com interferon peguilado α 2a ou 2b e RBV ou interferon α convencional genérico, utilizado no Brasil, e RBV. **Métodos:** Incluídos pacientes com infecção crônica pelo genótipos 2 ou 3 do VHC e tratados com interferon peguilado α 2a (180 µg/semana) ou 2b (1,5 µg/kg/semana) e RBV ou interferon α convencional genérico (3 milhões UI, três vezes/semana) e RBV, no período de 2005 a 2010 no ambulatório de Moléstias Infecciosas – Hepatites Virais do Hospital de Clínicas da UNICAMP. Através da revisão dos prontuários médicos foram obtidas informações demográficas, laboratoriais e taxa de RVS. **Resultados:** Foram incluídos 171 pacientes. Cinquenta e oito (33,9%) pacientes foram tratados com interferon peguilado α 2a ou 2b e RBV e 113 (66,1%) receberam tratamento com interferon α convencional genérico e RBV. As taxas de RVS foram, respectivamente, 79,3 % e 48,7 %, p = 0,0001. Não foram observadas diferenças significativas relativas a dados demográficos, laboratoriais e histológicos entre as duas populações. As taxas de RVS em pacientes tratados com interferon peguilado e RBV foram superiores àquelas entre pacientes tratados com interferon α convencional genérico e RBV tanto em populações com fibrose hepática leve ou moderada, taxa de RVS respectivamente de 81,8% *versus* 56,6%, p = 0,01, como entre aqueles com fibrose avançada, taxa de RVS respectivamente de 76% *versus* 39,2%, p = 0,002. **Conclusões:** Tratamento com interferon peguilado e RBV é significativamente superior ao tratamento com interferon genérico e RBV entre pacientes com infecção pelos genótipos 2 e 3 do VHC.