Results of a clinical trial suggest that treatment based on alisporivir (Debio 025/DEB 025, Novartis), an oral host-targeting cyclophilin inhibitor, might be an effective interferon (IFN)-free alternative for individuals with genotype 2 or 3 (G2/3) hepatitis C virus (HCV) infection. IFN therapy is associated with significant adverse events (AEs), including flu-like symptoms, fatigue, and nausea, all of which can have a significant impact on treatment adherence and, therefore, response rates and disease control.

Alisporivir is attractive as a therapy for HCV infection because it is an oral agent, has potent activity for all HCV genotypes, and has demonstrated a high barrier to viral resistance, Dr. Pawlotsky said.

The international, multicenter, open-label study, led by Dr. Pawlotsky and colleagues, included 334 treatment-naive G2/3 HCV patients, randomly assigned, in a 2:2:2:1:1 ratio, to one of five treatment arms as follows:

- alisporivir 1,000 mg daily as monotherapy (ALV1,000) (n = 82)
- alisporivir 600 mg daily plus ribavirin (R) (ALV600R) (n = 84)
- alisporivir 800 mg daily plus R (ALV800R) (n = 94)
- alisporivir 600 mg daily plus pegylated interferon (P) (ALV + P) (n = 39)
- Pegylated interferon plus ribavirin (PR) (n = 35)

In week 1, all alisporivir patients received 600 mg twice daily. Patients receiving alisporivir as IFN-free treatment who achieved undetectable HCV–RNA levels (below 25 IU/mL) at week 4 continued with initial treatment. Patients with detectable HCV–RNA levels were given add-on IFN and continued with ALV plus PR triple therapy from week 6 to week 24. Dr. Pawlotsky reported a greater than 3 log reduction in mean HCV–RNA levels over the first 4 weeks with alisporivir-based, IFN-free therapy. Rapid virological responses (RVRs) were also achieved by 28% of the ALV1,000 patients, by 37% of ALV600R patients, and by 42% of those in the ALV800R group. Patients achieving RVRs with IFN-free treatment maintained responses to week 12, with a minimal incidence of viral rebound.

From weeks 4 to 6, the proportion of patients who achieved undetectable HCV–RNA levels with alisporivir-based, IFN-free therapy further increased to 32%, 49%, and 46% in the ALV1000, ALV600R, and ALV800R groups, respectively.

More patients had undetectable HCV–RNA levels with alisporivir plus ribavirin than with alisporivir alone. The rate was 71% for patients with lower baseline HCV–RNA levels (less than 800,000 IU/mL). However, for alisporivir patients who did not achieve RVRs by week 4, add-on IFN as triple therapy (alisporivir 600 mg daily + PR + IFN) from week 6 resulted in rapid HCV clearance, with more than 90% of patients having undetectable HCV–RNA levels at week 12.

Markedly lower rates of flu-like symptoms (fatigue, pyrexia, myalgia, and arthralgia) were reported with alisporivir-based, IFN-free therapy, compared with treatment that included IFN. Overall, fewer AEs were reported in the alisporivir arm. There were no reports of grade 3 or 4 anemia.

Dr. Pawlotsky commented, “Alisporivir once daily shows promise to become the first interferon-free oral treatment for a substantial proportion of treatment-naive G2/3 HCV patients.”

Everolimus and Reduction or Elimination of Tacrolimus in Liver Transplantation: 12-Month, Phase 3 Results

- Faouzi Saliba, MD, Head, Liver Transplant Intensive Care Unit, Paul Brousse Hospital, Paris, France

Calcineurin inhibitor (CNI) treatment, although the standard of care in liver transplantation, contributes to acute and chronic renal dysfunction. Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), is devoid of nephrotoxicity and allows substantially reduced use of CNIs. Dr. Saliba’s study evaluated whether reducing or eliminating the CNI tacrolimus with everolimus-based immunosuppression would
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**Telaprevir (Incivo) in Cirrhosis: A Subanalysis of REALIZE Phase 3**

**Telaprevir (Incivo) in Cirrhosis: A Subanalysis of REALIZE Phase 3**

Stanislas Pol, MD, Université Paris Descartes, Cochin Hospital, Paris, France

Patients with cirrhosis that is caused by genotype 1 hepatitis C virus (G1 HCV) infection have low sustained virological response (SVR) rates with peginterferon (P) and ribavirin (R) therapy, explained Dr. Pol, before reporting results of the REALIZE phase 3 trial. This study included 578 patients, 143 with cirrhosis, who were randomly assigned to receive peginterferon/ribavirin (PR) alone or one of two regimens of telaprevir (Incivo, Janssen) plus PR for 48 weeks, as follows:

- either 12 weeks of telaprevir and PR plus 36 weeks of PR alone, or
- 4 weeks of PR alone, followed by 12 weeks of telaprevir plus PR and 32 weeks of PR alone (PR48)

REALIZE enrolled patients with G1 HCV infection, some with compensated Child Class A cirrhosis who had not achieved SVRs after one or more previous treatments with PR. Patients with cirrhosis were slightly older and more likely to be prior null responders.

Telaprevir plus PR was associated with higher SVR rates than PR alone in patients with cirrhosis. Severe fibrosis at baseline was generally associated with lower responses.

SVR rates, stratified according to no, minimal, or portal fibrosis, bridging fibrosis, or cirrhosis were 87%, 85%, and 84%, respectively, in prior relapsed patients receiving telaprevir regimens, compared with 32%, 13%, and 7%, respectively, for patients receiving placebo plus PR48.

Among previous partial responders, SVR rates were 77%, 56%, and 34% for telaprevir-containing regimens, respectively, and 18%, 0%, and 20% for placebo plus PR48, respectively. In prior null responders, SVR rates were 41%, 42%, and 14%, respectively, for telaprevir regimens and 6%, 0%, and 10%, respectively, for placebo plus PR48.

Failure to achieve SVRs was reported in 53% of patients with cirrhosis and in 27% of patients without cirrhosis.

The most common AEs in patients receiving telaprevir-containing regimens were rash, pruritus, and fatigue. Discontinuation rates attributable to AEs during telaprevir treatment were 7% among patients with cirrhosis and 4% among patients without cirrhosis.

Although anemia led to few discontinuations (below 1% in both cirrhotic and non-cirrhotic patients), Dr. Pol acknowledged that the rapid occurrence of anemia has been problematic in some assessments. He concluded that telaprevir plus PR, compared with PR alone, led to higher SVR rates in treatment-experienced patients with cirrhosis. The analysis also showed high SVR rates and low rates of virological failure irrespective of the patient’s cirrhosis status.

Dr. Pol disclosed that he has been an advisory board member for Pharmasset, Gilead, Janssen-Cilag, and Boehringer-Ingelheim, and Roche.

**BI 201335 Plus Peginterferon alfa-2a/Ribavirin For Hepatitis C: SILEN-C3 Results at 12 and 24 Weeks**

Douglas Dieterich, MD, Mount Sinai School of Medicine, New York, N.Y.

A daily 120-mg dose of Boehringer Ingelheim’s BI 201335, a next-generation protease inhibitor, achieved high rates of sustained virological responses (SVRs) among treatment-naive subjects with chronic genotype 1 hepatitis C virus (G1 HCV) infection in the SILEN-C3 trial—even though 16% of the patients had cirrhosis. In addition, more than 70% of patients achieved extended rapid virological responses (RVRs), defined as a viral load of less than 25 IU/mL after 24 weeks of treatment.

Investigators for SILEN-C3, an open-label, phase 2B trial, randomly assigned 159 subjects to receive 120 mg BI 201335 daily for either 12 or 24 weeks. Liver cirrhosis was present in 25 of 160 patients (16%) who were initially enrolled. Both groups received 24 weeks of pegylated interferon alfa-2a and ribavirin (PR). Patients who did not achieve extended RVRs at...
week 4, as well as those whose levels of HCV–RNA were undetected at weeks 8 to 18, continued with PR up to week 48.

Among patients assigned to receive 12 weeks of BI 201335, 72% and 65% achieved extended RVRs and SVRs, respectively. In the 24-week arm, 82% and 73% of patients achieved extended RVRs and SVRs, respectively. Viral breakthrough was reported in 12.3% and 6.4% of patients at 12 and 24 weeks. Non-responses were noted for 7.4% and 5.1% of patients, respectively, and relapses were noted in 11.1% and 10.3%, respectively, at 12 and 24 weeks.

Severe AEs occurred in 8% and 9% of the 12- and 24-week treatment arms, respectively, with discontinuation rates of 4% and 6%, respectively. The most common AE was nausea (in 41% and 23% of patients after 12 and 24 weeks, respectively), followed by asthenia (33% and 25%) and fatigue (30% and 20%). Anemia occurred in 10% and 18% of patients who received BI 201335 for 12 and 24 weeks, respectively.

Dr. Dieterich concluded, “120 mg of BI 201335 achieved high sustained viral response rates, even including the patients with cirrhosis.” Safety and tolerability, he added, were favorable in both treatment arms. Phase 3 testing of 120 mg daily and 240 mg daily BI 201335 is ongoing.

Dr. Dieterich has disclosed financial relationships with Boehringer Ingelheim.

American College of Rheumatology Annual Meeting

Nearly 16,000 rheumatologists and other specialists in treating bone and joint disorders attended this year’s American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) meeting in Chicago from November 5 to 9, 2011. Key sessions on psoriatic arthritis and rheumatoid arthritis are summarized.

Oral Apremilast With and Without Methotrexate For Psoriatic Arthritis: 12-Week Results

- Georg A. Schett, MD, Friedrigh–Alexander University Erlangen-Nuremberg, Nuremberg, Germany
- Scott Zashin, MD, Clinical Professor, University of Texas Southwestern Medical Center, Dallas, Texas

“Because a large proportion of patients with psoriatic arthritis are treated with methotrexate, the comparable efficacy and tolerability of apremilast as monotherapy or in combination with methotrexate are of interest,” said Dr. Schett. who presented results of a clinical trial designed to look specifically at how treatment with the investigational oral agent was affected by methotrexate.

Apremilast (CC-10004, Celgene) is a novel, orally available small molecule. Phosphodiesterase 4 (PDE4) is expressed in cells that mediate the immune response. Apremilast specifically targets PDE4, thereby increasing cellular cyclic adenosine monophosphate (cAMP), which in turn modulates multiple pro-inflammatory and anti-inflammatory mediators.

In the phase 2 randomized, multicenter study, patients with active psoriatic arthritis were randomly assigned to receive placebo, apremilast 20 mg twice daily, or apremilast 40 mg once daily for 12 weeks. Stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and methotrexate were allowed.

The substudy included 89 patients who received methotrexate and 115 patients who did not. Among the 29 patients receiving placebo plus methotrexate, 10.3% achieved an American College of Rheumatology 20% (ACR 20) improvement in disease status, compared with 12.8% of the 39 patients taking only placebo.

Among the 30 patients taking apremilast 20 mg twice daily who also received methotrexate, 46.7% achieved an ACR 20, compared with 41.0% of the 39 patients who received only apremilast. Among the 30 patients who received methotrexate and apremilast 40 mg once daily, 36.7% achieved an ACR 20, whereas 35.1% of the 37 patients receiving apremilast 40 mg achieved an ACR 20 at week 12.

None of the comparisons revealed significant differences, Dr. Schett said, suggesting that neither benefits nor risks were associated with the apremilast/methotrexate combination. Gastrointestinal complaints (diarrhea and vomiting), the most commonly reported AEs, tended to occur more frequently in the methotrexate-treated subjects.

“Apremilast is effective in the treatment of psoriatic arthritis, in patients both treated and not treated with methotrexate,” said Dr. Schett.

Dr. Zashin commented in an interview that patients with psoriatic arthritis would favor the oral formulation.

“It’s really a breakthrough for these patients,” he said. “If approved, apremilast would be first-line treatment as a biologic for patients who resist injections or infusions.”

He noted further that a pilot study of oral apremilast in ankylosing spondylitis also had encouraging results, which were presented at the meeting by Ejaz Pathan.

Etanercept (Enbrel) for Rheumatoid Arthritis: An Observational Cohort After Five Years

- Duncan Porter, MD, Senior Lecturer, University of Glasgow, Scotland
- Daniel Lewis, MD, Lecturer in Rheumatology, Monash University, Melbourne, Australia

When tumor necrosis factor (TNF) inhibitors first came on the market, according to Dr. Lewis, “We were scared to death that we were going to see a lot of cancer.” That fear has not been borne out, he said in an interview, and experience has shown that the agents control rheumatoid arthritis (RA) and other diseases for long periods.

Dr. Porter’s study looked at outcomes in the large British Society of Rheumatology Biologics Register in patients receiving anti-TNF agents for RA for 5 years. Among the enrolled subjects, 3,470 patients received etanercept (Enbrel, Amgen/Pfizer), and 1,365 patients received disease-modifying anti-rheumatic drugs (DMARDs). Patients who received DMARDs were about 59 years of age, significantly older than the mean

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age of those receiving etanercept (55.4 years). About 25% of patients in both groups were men.

In the 5-year analysis, there was a trend toward a lower risk of death in patients receiving etanercept (13.1 per 1,000 patient-years vs. 22.7 per 1,000 patient-years for DMARDs; \( P = 0.096 \)). Malignancy rates were also lower with etanercept (13.6 per 1,000 patient-years) than with the other drugs (23 per 1,000 patient-years) (\( P = 0.023 \)). Cardiovascular events, experienced at a rate of 11 per 1,000 patient-years with etanercept, compared favorably with the rate of 19.7 per 1,000 patient-years for those receiving DMARDs (\( P = 0.002 \)).

The evaluation, Dr. Porter concluded, showed therapy with etanercept to be effective and not associated with an increased risk of serious infections, malignancy, cardiovascular events, or death when compared with a DMARD reference group.

Comparisons of Abatacept (Orencia), Adalimumab (Humira), Etanercept (Enbrel), and Infliximab (Remicade) in Rheumatoid Arthritis

Yusuf Yazici, MD, Assistant Professor of Medicine, New York University Hospital for Joint Diseases and Medicine, New York, N.Y.

Gerd-Rudiger Burmester, MD, Director, Rheumatology Clinic, Charite Universitatmedezin, Berlin, Germany

In an analysis of the New York University Arthritis Registry Monitoring Database, which has tracked rheumatoid arthritis (RA) patients since 2005, subjects who were treated with biologic agents early in the course of disease responded better than those who were treated later. No differences between biologic agents, however, were found in terms of the proportion of responders or in time to response.

Among 385 cases in which the treatment course was determined, a single biologic agent was given to 272 patients, as follows: 148 individuals received etanercept (Enbrel, Amgen/Pfizer); 114, abatacept (Orencia, Bristol-Myers Squibb); 85, adalimumab (Humira, Abbott); and 38, infliximab (Remicade, Janssen-Ortho-Biotech). Patient outcomes were based on changes in scores from the Routine Assessment of Patient Index Data (RAPID3). A 3.6-point improvement in scores was considered clinically important.

RA symptoms were reduced meaningfully among 65% of patients treated with abatacept, 64% of patients receiving adalimumab, 62% of the etanercept patients, and 45% of the infliximab group. Further, 75% of responses to the biologic agents occurred within the first 9 months of therapy, and 90% of responses occurred within 20 months.

Although infliximab and abatacept differed marginally in a univariate model (\( P = 0.050 \)), adjustments for age and disease duration erased the statistical significance of these variations.

Dr. Yazici concluded, “With no difference in clinical outcomes or response time, most treatment decisions may be based on ease of use, safety data, and long-term survival of respective biologic agents when they are being considered for rheumatoid arthritis treatment.”

Commenting on the findings, Dr. Burmester said, “The most important thing for our patients is to get them into treatment early with these drugs.”