Nitazoxanide for the treatment of chronic hepatitis C: New opportunities but new challenges?

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Background & Aims: Sustained virologic response (SVR) rates of 50%–60% have been achieved in patients with chronic hepatitis C genotype 4 treated with peginterferon plus ribavirin. The safety and efficacy of nitazoxanide plus peginterferon alfa-2a, with or without ribavirin, were evaluated in a randomized controlled trial at 2 centers in Egypt. Methods: Previously untreated patients with chronic hepatitis C and genotype 4 infection were assigned randomly to groups that were given standard of care (peginterferon alfa-2a and ribavirin for 48 weeks, n = 40), nitazoxanide monotherapy for 12 weeks followed by nitazoxanide plus peginterferon alfa-2a for 36 weeks (n = 28), or nitazoxanide monotherapy for 12 weeks followed by nitazoxanide plus peginterferon alfa-2a and ribavirin for 36 weeks (n = 28). Therapy included nitazoxanide (500 mg) twice daily, peginterferon alfa-2a (180 μg) once weekly, and weight-based ribavirin (1000–1200 mg/day). Results: The percentages of rapid virologic response (RVR), defined as undetectable HCV RNA at week 4 of combination therapy, and SVR were significantly higher in patients given the triple therapy compared with the standard of care (64% vs 38%, P = .048; and 79% vs 50%, P = .023; respectively). Patients given nitazoxanide plus peginterferon alfa-2a had intermediate rates of RVR (54%) and SVR (61%). Adverse events were similar across treatment groups except for higher rates of anemia in the groups receiving ribavirin.

Conclusions: The combination of nitazoxanide, peginterferon alfa-2a, and ribavirin increased the percentages of patients with RVR and SVR, compared with patients given peginterferon plus ribavirin, without an increase in adverse events.

Treatment of chronic hepatitis C has significantly improved over the last two decades as - depending on the HCV genotype - 40-90% of patients achieve a sustained virological response (SVR). However, treatment with pegylated interferon alfa (PEG-IFN) and ribavirin (RBV) is still associated with frequent and sometimes severe side effects and many patients cannot be treated because of contraindications.1 A major step forward in the therapy of HCV infection is expected by the approval of new direct inhibitors of HCV replication. Several compounds, mainly inhibitors of the HCV NS3/4A protease and NS5B polymerase, are currently in phase II and III trials and the first HCV protease inhibitors will hopefully be licensed in 2011/12.2,3 The far majority of the new antiviral drugs are currently developed only for HCV genotype 1 infection - although at least one third of the world’s HCV population is infected with other genotypes. Thus, there is an urgent need to explore alternative treatment options also for non-genotype 1-infected patients. E.g. HCV genotype 4 is endemic in Northern Africa, and response rates to treatment with PEG-IFN and RBV are much lower in patients with genotype 4 than in HCV genotype 2 or 3 infected patients. In this context, the study by Rossignol and coworkers published in the 3rd issue (Volume 136) of Gastroenterology is of interest, suggesting that adding Nitazoxanide (NTZ) to standard PEG-IFN/RBV combination therapy may significantly improve response rates in Egyptian HCV genotype 4 infected patients.4 Nitazoxanide, a synthetic antiprotozoal agent, is licensed in the United States for the treatment of infections with Cryptosporidium parvum and Giardia lamblia. Antiviral properties of this compound were discovered when patients with acquired immune deficiency syndrome (AIDS) coinfected with hepatitis B and C were...
treated for cryptosporidiosis. These findings were confirmed by in vitro studies demonstrating that NTZ and its active metabolite Tizoxanide show antiviral activity against HCV genotype 1a and 1b in the HCV replicon system. A potential mechanism of action for NTZ has recently been suggested. The double-stranded RNA-activated protein kinase (PKR) mediates antiviral actions of IFN by phosphorylation of eukaryotic initiation factor-2 alpha (eIF2alpha). NTZ modulates this pathway by an increase of the phosphorylation of double-stranded RNA-activated protein kinase (PKR) and of intracellular levels of phosphorylated eukaryotic initiation factor-2 alpha (eIF2alpha).

A phase II pilot trial explored NTZ monotherapy in Egyptian hepatitis C patients infected with HCV genotype 4. HCV-RNA became undetectable in 7 out of 23 patients who all had a rather low viral load before treatment ($\leq 400,000$ IU/mL). Interestingly, 4 patients achieved a sustained virological response after 24 weeks of NTZ treatment. The current study by Rossignol and coworkers represented the next step in the investigation of NTZ for the treatment of hepatitis C as combination of NTZ with standard PEG-IFN/RBV treatment and PEG-IFN alone was explored. The trial was conducted in two Egyptian centers and included 96 treatment-naïve patients – all were infected with HCV genotype 4. Patients were randomized in one of three arms, a control arm with pegylated interferon alfa-2a and ribavirin for 48 weeks (n = 40), and two arms with a 12 week lead-in monotherapy with NTZ followed by 36 week course of NTZ in combination with pegylated interferon with (n = 28) or without ribavirin (n = 28). Sustained virological response rates in the control arm were only 50%, which is relatively low as compared to most other previous HCV genotype 4 trials. Importantly, 79% of the patients receiving triple therapy with NTZ and PEG-IFN/RBV achieved a SVR which reached statistical significance although patients in the triple therapy arm were treated for only 36 weeks with PEG-IFN. Of note, patients receiving NTZ and PEG-IFN without RBV also showed a surprisingly high SVR of 61%.

Although these data are promising, several issues need to be considered. First of all, the overall number of patients treated was rather small and patient characteristics differed to other hepatitis C patient cohorts. E.g., only five of the 96 patients had advanced fibrosis or cirrhosis (Ishak F4-6), a factor that very likely contributed to the high response rates. Similarly, only three patients were black which is of importance as black patients respond weaker to IFN-based treatments. Finally, only very few women were treated (8% of the patients). In addition, there were some differences in patients characteristics between the study arms as the body mass index was significantly lower in patients who received PEG-IFN, RBV and NTZ as compared to the control group - which also could have been contributed to the better response in the triple therapy arm although the BMI was not an independent factor associated with SVR. Nevertheless, it is quite obvious that another independent trial in a non-Egyptian cohort is needed to investigate NTZ in genotype 4 patients.

The antiviral efficacy of NTZ was confirmed during the 12 week lead-in phase when NTZ was administered alone. NTZ induced a modest but significant HCV-RNA decline of $-0.27 \log_{10}$ which is in line with the previous monotherapy study. However, only 2 out of 53 patients treated with NTZ monotherapy had a decline of more than 1 $\log_{10}$ and just one patient achieved a complete response (HCV-RNA negative) after 12 weeks, which is in contrast to previous trial where 6 out of 23 patients (26%) were HCV-RNA-negative after 12 weeks. Thus, it is very unlikely that NTZ monotherapy will have any role in future treatment algorithms of chronic hepatitis C.

Another interesting finding of the study was that NTZ did not only increase early virological responses but was also associated with lower relapse rates as only 4 out of 43 NTZ-treated patients relapsed compared to 10 out of 30 patients treated in the standard therapy arm. Since response rates of NTZ and PEG-IFN without RBV were even slightly higher than with standard treatment, it would be of interest to explore the potential role of NTZ in patients who do not tolerate RBV.

The obvious next question is if NTZ is also effective in other HCV genotypes. Very recently, data on NTZ treatment of patients infected with HCV genotype 1 were presented during the late breaker session of the annual meeting of the European association for the study of the liver (EASL) 2009 in Copenhagen. Bacon and coworkers showed interim results in treatment naïve patients receiving PEG-IFN/RBV plus NTZ (n = 75) or placebo (n = 37). The NTZ lead-in phase was shorter with only 4 weeks. Complete early virological response (cEVR) and EVR rates were higher in patients with an HCV-RNA level at baseline of $> 600,000$ IU/mL, who were treated with NTZ (n = 67) compared to placebo (n = 31) (57% vs. 39%, and 79% vs. 61%, respectively). Another study by Shiffman and coworkers presented more disappointing data on genotype 1 nonresponder patients. The study design was identical to the study by Bacon et al. (NTZ arm 42 patients, placebo arm 20 patients). Interestingly only 6/42 (14%) NTZ treated patients compared to 0/20 placebo treated patients had undetectable HCV-RNA levels at week 24 of combination therapy. These rather low response rates in nonresponder patients suggest that indeed the intracellular mode-of-action of NTZ is similar to interferon-alfa. Thus, NTZ will probably and unfortunately not be of major benefit for the large group of nonresponder patients who urgently need alternative treatment options to prevent clinical events caused by chronic hepatitis C.

There are several open questions on NTZ that have to be answered in future studies. (i) Is there really a need for NTZ pre-treatment to enhance the efficacy of interferon
alpha as suggested by in vitro studies and if so how long should this lead-in-phase be (4 weeks, 12 weeks, shorter or even longer)? (ii) What is the optimal dose of NTZ for the treatment of hepatitis C? So far, most trials in hepatitis C patients have used NTZ 500 mg twice daily (bid). Recently data on a new NTZ controlled release 675 mg tablet was presented at the annual meeting of the Asian Pacific Association for the Study of the Liver (APASL) in Hong Kong. 675 mg and 1,350 mg bid dose regimens were studied. Viral load reduction in treatment naïve genotype 4 patients after 4 weeks of NTZ treatment (1,350 mg or 675 mg bid) followed by 4 weeks of combination with PEG-IFN plus RBV was slightly increased in the high dose arm (5.45 log_{10} and 5.25 log_{10}, respectively). Further data of this trial will be of interest. (iii) Will NTZ cause additional side effects and add another level of complexity to treatment? So far, side effects were similar between NTZ- and placebo-treated patients, which is in line with the FDA Drug information stating that less than 1% of patients who received NTZ for the treatment of diarrhea caused by Giardia lamblia or Cryptosporidium parvum in placebo-controlled trials discontinued therapy because of an adverse event (www.fda.gov). Importantly, NTZ was also tolerated at doses of 1375 mg (bid), which is in line with a former study investigating doses of 1,000 mg (bid) in the treatment of cryptosporidial diarrhea in AIDS patients. However, these data need to be confirmed in larger combination treatment trials with interferon alfa. (iv) Does NTZ really reduce relapse rates which would give interesting insights in the mode of action of the drug and open new options for patients who do not tolerate recommended doses of RBV due to side effects like anemia? (v) Will SVR rates for genotype 1 patients treated with NTZ be higher as compared to the current standard of care, and would NTZ also be beneficial in patients with HCV genotype 2 and 3 infection? (vi) What is the tolerability and efficacy of NTZ in other special patient populations including elderly patients, patients with advanced liver disease, patients after liver transplantation, and HIV- or HBV-coinfected patients? (vii) Finally, and maybe most interestingly, will nitazoxanide be effective in combination with new direct antiviral compounds against HCV enabling an all oral treatment without the need for interferon alfa?

In conclusion, the data presented by Rossignol and colleagues are definitely of interest and may open new opportunities for the treatment of HCV-infected patients. However, it is far too early to use nitazoxanide outside of clinical trials. In particular the apparently poorer response rates in nonresponder patients and the lack of data in non-genotype 4 patients currently represent major limitations. Thus, additional, well controlled trials are needed before nitazoxanide can be recommended for the treatment of chronic hepatitis C. We always should keep in mind: all that glitters is not gold!

References