

1. Madrid AH, Bueno MG, Rebollo JM, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. *Circulation* 2002;106:331-6.
2. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005;45:1832-9.
3. Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: inhibition of renin-angiotensin system prevents new-onset atrial fibrillation. *Am Heart J* 2006;152:217-22.
4. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. *J Am Coll Cardiol* 2003;41:2197-204.

THE AUTHORS REPLY: Smit and Van Gelder raise the question of the timing of the administration of valsartan in the evaluation of its effects. We reported the results of two additional analyses involving patients who were in sinus rhythm at 15 days (as prespecified in the protocol)¹ and at 8 weeks (a post hoc analysis) after randomization. No trend in favor of valsartan was apparent. In the 8-week analysis, atrial fibrillation recurred at 1 year in 42.7% of patients in the valsartan group, as compared with 44.0% of those in the placebo group (hazard ratio, 0.96; 96% confidence interval, 0.80 to 1.14; $P=0.62$).

With respect to the duration of the history of atrial fibrillation, we do not have this information for the patients in our study. However, we performed a subgroup analysis as to whether the duration of the last episode of atrial fibrillation had an effect on the results. We did not observe

any difference in the effect of valsartan between patients with episodes lasting more than 48 hours and those with shorter episodes.

As Tomoda correctly points out, the efficacy of RAAS blockade in the primary prevention of atrial fibrillation is still an open issue, with current evidence coming from post hoc analyses of large trials, databases, and overviews. Thus, a large, randomized clinical trial of such therapy in the primary prevention of atrial fibrillation may be appropriate. However, such a trial is likely to be difficult to carry out because of the broadening range of use of RAAS inhibitors in a variety of cardiovascular conditions.

Marcello Disertori, M.D.

Santa Chiara Hospital
38100 Trento, Italy

Roberto Latini, M.D.

Mario Negri Institute for Pharmacological Research
20156 Milan, Italy

Aldo P. Maggioni, M.D.

Italian Association of Hospital Cardiologists Research Center
50121 Florence, Italy
maggioni@anmco.it

for the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation (GISSI-AF) Investigators

1. Disertori M, Latini R, Maggioni AP, et al. Rationale and design of the GISSI-Atrial Fibrillation trial: a randomized, prospective, multicentre study on the use of valsartan, an angiotensin II AT1-receptor blocker, in the prevention of atrial fibrillation recurrence. *J Cardiovasc Med (Hagerstown)* 2006;7:29-38.

Telaprevir for Chronic HCV Infection

TO THE EDITOR: McHutchison et al. and Hézode et al. (April 30 issue) found an important effect of adding telaprevir to current antiviral therapy.^{1,2} Nevertheless, the results of the Protease Inhibition for Viral Evaluation (PROVE) trials (ClinicalTrials.gov numbers, NCT00336479 and NCT00372385) are disappointing, since they demonstrate the risk of serious side effects resulting from high dosing of a new molecule, with profound consequences for efficacy. Combined data from all telaprevir regimens in both trials show a significant difference in sustained virologic response between patients completing and those discontinuing treatment (78% and 25%, respectively; $P<0.001$). Although telaprevir had an acceptable initial side-effect

profile, the extended administration of high doses of telaprevir was accompanied by a high rate of treatment discontinuation, mainly because of unexpected rash and more severe anemia.

The first study of telaprevir showed similar initial viral declines with different dosages; viral breakthrough occurred in the lower dosing regimen.³ The fear of selection of telaprevir-resistant variants can be negated, since mutant viruses are sensitive to peginterferon.⁴

We are concerned that major decisions in the development of new antiviral agents are primarily based on the reduction of hepatitis C virus (HCV) RNA levels and on the highest tolerated doses in short phase 1 trials. Subsequent trials

should incorporate lower, albeit effective, dosages to reduce the risk of adverse events and to enhance treatment adherence, which might improve efficacy further.

Adriaan J.P. van der Meer, M.D.

Robert J. de Knecht, M.D.

Erasmus Medical Center
3015 CE Rotterdam, the Netherlands
a.vandermeer@erasmusmc.nl

Dr. de Knecht reports serving on an advisory board for Schering-Plough and receiving research funding from Schering-Plough, Roche, and Vertex. No other potential conflict of interest relevant to this letter was reported.

1. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009;360:1827-38.
2. Hézode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009;360:1839-50.
3. Reesink HW, Zeuzem S, Weegink CJ, et al. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase Ib, placebo-controlled, randomized study. *Gastroenterology* 2006;131:997-1002.
4. Kieffer TL, Sarrazin C, Miller JS, et al. Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. *Hepatology* 2007;46:631-9.

TO THE EDITOR: Two phase 2 trials showed that in patients infected with chronic HCV genotype 1, the sustained virologic response rate with peginterferon plus ribavirin therapy for 48 weeks was 41 to 46%, whereas the response rate with the addition of 12 weeks of telaprevir to combination therapy for 24 weeks was 61 to 69%. The accompanying editorial by Hoofnagle¹ thus suggested that this advance will permit future therapy to be limited to 24 weeks. Nevertheless, this suggestion might not be able to be extrapolated to Asian patients with HCV genotype 1 infection. First, the Asian population was under-represented (<5%) in both studies. Second, for patients with genotype 1 infection, Asians who have received combination therapy for 48 weeks have substantially higher rapid and sustained virologic response rates than do whites (44 to 63% vs. 11 to 13% for rapid rates and 76 to 79% vs. 41 to 46% for sustained rates),^{2,3} which could be explained by the kinetics of an effective early viral response.⁴ Moreover, 24-week combination therapy also results in a sustained virologic response rate of 56 to 59% in Asians. Further studies are awaited to see whether the addition of telaprevir could limit HCV therapy to 12 weeks in Asian patients who have not previously received treatment.

Jia-Horng Kao, M.D., Ph.D.

National Taiwan University Hospital
Taipei 10002, Taiwan
kaojh@ntu.edu.tw

1. Hoofnagle JH. A step forward in therapy for hepatitis C. *N Engl J Med* 2009;360:1899-901.
2. Yu ML, Dai CY, Huang JF, et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. *Hepatology* 2008;47:1884-93.
3. Liu CH, Liu CJ, Lin CL, et al. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. *Clin Infect Dis* 2008;47:1260-9.
4. Hsu CS, Liu CJ, Lai MY, Chen PJ, Kao JH, Chen DS. Early viral kinetics during treatment of chronic hepatitis C virus infection with pegylated interferon alpha plus ribavirin in Taiwan. *Inter-virology* 2007;50:310-5.

THE AUTHORS REPLY: Van der Meer and de Knecht have rightly pointed out that the addition of a new agent to an existing treatment regimen would be expected to result in additional side effects, which would be the price for potential improvements in efficacy and shortened treatment durations. The telaprevir groups in the PROVE1 and PROVE2 studies did have higher rates of discontinuation due to adverse events than did the control groups. Rash was the main reason for the additional discontinuations; 7% of patients had rashes that were considered severe. Rashes resulted in hospitalization for 9 of 338 patients who were exposed to telaprevir; 2 patients also received one or two doses of intravenous corticosteroids. These were the first studies in which a severe rash was seen, and a management plan was included in subsequent studies.

The suggestion of using lower dosages of telaprevir is not supported by the scientific data. Dose selection was not based on the highest tolerated doses but on the dose that best prevented the emergence of telaprevir-resistant variants. Although telaprevir-resistant variants remain sensitive to the antiviral effect of interferon in vitro, the important factor in vivo is the extent and timing of the patient's response to interferon. In the phase 1 study cited, selection of telaprevir-resistant variants was correlated with lower trough concentrations of telaprevir.¹ When telaprevir was combined with interferon and ribavirin in the PROVE studies, the viral breakthroughs observed were associated with lower telaprevir and interferon levels.² Therefore, lower exposure to telaprevir may increase the incidence of viral breakthrough and diminish the clinical benefit of

the triple combination. An analysis of the relationships between the pharmacokinetics of telaprevir and either severe rash or a decrease in the hemoglobin level (to <9.5 g per deciliter [5.9 mmol per liter]) shows no consistent reason for an improved adverse-event profile in cases of a lower dose (unpublished data).

Therefore, efforts should be directed at adverse-event awareness, monitoring, and management so that patients are able to complete treatment and maximize their chance of a successful and safe response to therapy.

We also agree with Kao. New HCV therapies that are in development should be studied in populations with favorable responses to therapy (Asians) and in populations with less favorable responses to therapy (blacks and Latinos) to fully characterize their efficacy and safety.

John McHutchison, M.D.

Duke University
Durham, NC 27715
mchut001@mc.duke.edu

Jean-Michel Pawlotsky, M.D., Ph.D.

Henri Mondor University Hospital
94010 Créteil, France

Stefan Zeuzem, M.D.

J.W. Goethe University Hospital
60590 Frankfurt, Germany

for the PROVE1 and PROVE2 Study Teams

1. Reesink HW, Zeuzem S, Weegink CJ, et al. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase Ib, placebo-controlled, randomized study. *Gastroenterology* 2006; 131:997-1002.

2. Jacobson IM, Everson GT, Gordon SC, et al. Interim analysis from a phase 2 study of telaprevir with peginterferon alfa-2a and ribavirin in treatment-naïve subjects with hepatitis C. *Hepatology* 2007;46:Suppl 1:315A. abstract.

Asthma in Pregnancy

TO THE EDITOR: In their review article on asthma in pregnancy (April 30 issue),¹ Schatz and Dombrowski state that leukotriene-receptor antagonists may be considered as an alternative to inhaled corticosteroids in pregnancy. However, current guidelines by the British Thoracic Society² advocate against starting these agents during pregnancy. Given the limited safety data available on leukotriene-receptor antagonists and the literature regarding the safety of inhaled corticosteroids during pregnancy,^{3,4} use of the corticosteroids would seem a better approach in cases of mild asthma.

Stuart Schembri, M.D.

Perth Royal Infirmary
Perth PH1 1NX, United Kingdom
sschembri@nhs.net

1. Schatz M, Dombrowski M. Asthma in pregnancy. *N Engl J Med* 2009;360:1862-9.

2. British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. *Thorax* 2008;63:Suppl 4:iv1-iv121.

3. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 1997;100:301-6.

4. Dombrowski M, Thom E, McNellis D. Maternal-Fetal Medicine Units (MFMU) studies of inhaled corticosteroids during pregnancy. *J Allergy Clin Immunol* 1999;103:S356-S359.

all levels of persistent asthma during pregnancy, as noted in Tables 2 and 5 of our article. However, because of reassuring data from studies in animals (Food and Drug Administration Pregnancy Category B) and at least some reassuring published data about humans,¹ we and the most recent pregnancy-specific guidelines of the National Asthma Education and Prevention Program² have not considered leukotriene-receptor antagonists to be contraindicated during pregnancy. As “alternative controller medications” for step 2 of asthma therapy, they provide alternatives in circumstances in which inhaled corticosteroids have not been effective, have not been tolerated, or are declined by the patient for other reasons. We also state in Table 5 of our article that another circumstance in which leukotriene-receptor antagonists may be considered for use during pregnancy is when they have been providing good control of asthma before pregnancy.

Michael Schatz, M.D., M.S.

Kaiser Permanente Medical Center
San Diego, CA 92111
michael.x.schatz@kp.org

Mitchell P. Dombrowski, M.D.

St. John Hospital
Detroit, MI 48236

1. Bakhireva LN, Jones KL, Schatz M, et al. Safety of leukotri-

THE AUTHORS REPLY: We agree that inhaled corticosteroids are the preferred controller therapy for