

in the risk for HCC in this population. Data on BMI and a history of diabetes should be available from the patient charts. Therefore, readers would be interested in whether risk factors, such as BMI and diabetes mellitus, contribute to the development of HCC in this population and modify the association between anti-HBc positivity and the development of HCC in individuals with hepatitis C virus–related cirrhosis.

Rohit Loomba, MD, MHS

Marc Ghany, MD

Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
Bethesda, MD 20892

Potential Financial Conflicts of Interest: None disclosed.

References

- Ikeda K, Marusawa H, Osaki Y, Nakamura T, Kitajima N, Yamashita Y, et al. Antibody to hepatitis B core antigen and risk for hepatitis C-related hepatocellular carcinoma: a prospective study. *Ann Intern Med.* 2007;146:649-56. [PMID: 17470833]
- Kusakabe A, Tanaka Y, Orito E, Sugauchi F, Kurbanov F, Sakamoto T, et al. A weak association between occult HBV infection and non-B non-C hepatocellular carcinoma in Japan. *J Gastroenterol.* 2007;42:298-305. [PMID: 17464459]
- El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol.* 2006;4:369-80. [PMID: 16527702]
- Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. *J Hepatol.* 2005;42:218-24. [PMID: 15664247]
- Caldwell SH, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. *Gastroenterology.* 2004;127:S97-103. [PMID: 15508109]

IN RESPONSE: We thank Drs. Loomba and Ghany for their comments. As they pointed out, obesity is widely recognized as a significant risk factor for many types of human cancer, including HCC (1). In our paper, we prospectively analyzed the various clinical factors, including anti-HBc positivity, smoking, and alcohol intake, as risks for the occurrence of HCC in Japanese patients with hepatitis C virus (HCV) infection.

We found that the incidence of HCC in patients with a BMI of 30 kg/m² did not significantly differ from that of patients with a BMI of 25 kg/m² (16.7% vs. 22.1%, respectively; $P = 0.85$). However, the prevalence of obesity among the Japanese population is not as high as that among U.S. and European populations. In fact, only 3.0% of the HCV-positive patients analyzed in our study had a BMI greater than 30.0 kg/m². In contrast, the prevalence of obese individuals with a BMI greater than 30.0 kg/m² in the United States ranges from 13% to 27% (2). A recent U.S. study revealed that the relative risk for HCC was 1.68 times higher among women with a BMI of 35 kg/m² and 4.52 times higher among men with a similarly increased BMI than in reference groups with baseline BMIs of 18.5 kg/m² to 25.0 kg/m² (3). Thus, it seems reasonable to assume that too few Japanese patients with HCV-related chronic liver disease had BMI high enough to evaluate the risk for HCC occurrence.

Similarly, several epidemiologic data showed an increased risk for HCC among patients with diabetes, a condition closely associated with obesity (4). However, only 5.7% of our Japanese patients

with HCV-related chronic liver disease had a diagnosis, with diabetes defined by the use of insulin or oral diabetic medication. Therefore, it was also difficult to analyze the statistical difference of the HCC incidence between patients with and those without diabetes enrolled in our prospective study. In conclusion, we believe that further prospective studies should be done in overweight persons to determine whether high BMI and presence of diabetes could be risks for HCC.

Kazuki Ikeda, MD

Hiroyuki Marusawa, MD, PhD

Tsutomu Chiba, MD, PhD

Kyoto University

Kyoto, Japan 606-8507

Potential Financial Conflicts of Interest: None disclosed.

References

- Caldwell SH, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. *Gastroenterology.* 2004;127:S97-103. [PMID: 15508109]
- McTigue KM, Garrett JM, Popkin BM. The natural history of the development of obesity in a cohort of young U.S. adults between 1981 and 1998. *Ann Intern Med.* 2002;136:857-64. [PMID: 12069559]
- Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003;348:1625-38. [PMID: 12711737]
- El-Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: a case-control study among United States Veterans. *Am J Gastroenterol.* 2001;96:2462-7. [PMID: 11513191]

Tumor Necrosis Factor–Blocking Agents in Polymyalgia Rheumatica and Giant Cell Arteritis

TO THE EDITOR: We agree with the conclusions of the insightful editorial by Luqmani (1) about the 2 randomized, controlled trials (RCTs) of infliximab in polymyalgia rheumatica (2) and giant cell arteritis (GCA) (3), especially that corticosteroids are still the cornerstone of treatment for these 2 related diseases. However, although these 2 studies showed that adding infliximab to prednisone is of no benefit in patients with GCA or polymyalgia rheumatica, a corticosteroid-sparing effect for tumor necrosis factor (TNF) blockers in these 2 conditions cannot be completely excluded. As Luqmani pointed out, the 2 trials were designed to detect a large effect of infliximab because of the drug's expense and possible adverse effects. They were too small to definitively identify small benefits. Another argument can be made for a possible therapeutic benefit for TNF-blocking agents. The 2 RCTs enrolled patients with newly diagnosed polymyalgia rheumatica and GCA. Two open, pilot studies that preceded these RCTs observed the efficacy of infliximab in reducing corticosteroid requirements in patients with long-standing, relapsing polymyalgia rheumatica and GCA (4, 5). In these patients, the potent anti-inflammatory effect of infliximab was demonstrated by the reduction of acute-phase reactants, including interleukin (IL)-6 circulating levels, 2 weeks after the start of therapy. The reduction in IL-6 levels was of particular interest, because the persistence of elevated levels of this cytokine characterized the patients with continued active disease who require higher and more prolonged doses of corticosteroids (4). It is possible that TNF-blocking agents are effective in subsets of patients with polymyalgia rheumatica and GCA char-

acterized by a more chronic, relapsing course. A third recent open study from our group suggests that etanercept may be another useful corticosteroid-sparing agent in patients with polymyalgia rheumatica and refractory disease—that is, patients with more severe disease (6). The efficacy of TNF-blockers in patients with relapsing disease also has a pathophysiologic basis. The elegant study by Hernández-Rodríguez and colleagues (7) showed that high TNF- α production in GCA was associated with longer steroid requirements and relapsing disease. Therefore, before completely excluding a potential therapeutic role for TNF-blockers in polymyalgia rheumatica or GCA, we suggest that RCTs be performed enrolling only patients with relapsing or refractory polymyalgia rheumatica and GCA.

Carlo Salvarani, MD
Arcispedale S. Maria Nuova
Reggio Emilia 42100, Italy

Gene G. Hunder, MD
Mayo Clinic
Rochester, MN 55905

Potential Financial Conflicts of Interest: None disclosed.

References

1. Luqmani R. Treatment of polymyalgia rheumatica and giant cell arteritis: are we any further forward? [Editorial]. *Ann Intern Med.* 2007;146:674-6. [PMID: 17470835]
2. Hoffman GS, Cid MC, Rends-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al.; Influximab-GCA Study Group. Influximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med.* 2007;146:621-30. [PMID: 17470830]
3. Salvarani C, Macchioni P, Manzini C, Paolazzi G, Trotta A, Manganelli P, et al. Influximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. *Ann Intern Med.* 2007;146:631-9. [PMID: 17470831]
4. Salvarani C, Cantini F, Niccoli L, Catanoso MG, Macchioni P, Pulsatelli L, et al. Treatment of refractory polymyalgia rheumatica with influximab: a pilot study. *J Rheumatol.* 2003;30:760-3. [PMID: 12672196]
5. Cantini F, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with influximab: report of four cases. *Arthritis Rheum.* 2001;44:2933-5. [PMID: 11762955]
6. Catanoso MG, Macchioni PL, Boiardi L, Pipitone N, Salvarani C. Treatment of refractory polymyalgia rheumatica with etanercept: an open pilot study. *Arthritis Rheum.* 2007;57:1514-9.
7. Hernández-Rodríguez J, Segarra M, Vilardell C, Sánchez M, García-Martínez A, Esteban MJ, et al. Tissue production of pro-inflammatory cytokines (IL-1beta, TNF-alpha and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. *Rheumatology (Oxford).* 2004;43:294-301. [PMID: 14679293]

IN RESPONSE: I am grateful to Drs. Salvarani and Hunder for raising the issue that their studies of influximab in polymyalgia rheumatica and GCA were not designed to test a small treatment effect of the

agent above that achieved from corticosteroid alone. If there is only a small treatment effect, a cost-benefit analysis is likely to conclude that influximab does not have a clinically or statistically significant role in the management of polymyalgia rheumatica or GCA. If, on the other hand, the study demonstrated that severe complications, such as sight loss in GCA, could be prevented or that steroid toxicity could be avoided by using much lower doses of steroid, these would be more compelling reasons to reconsider the use of this agent in these diseases.

There is a separate question about whether influximab has a role in the management of patients who have relapsing or resistant disease, in whom the authors point out that benefits have been seen, albeit in pilot studies. Reduction in IL-6 levels as a result of suppressing TNF and associated with clinical benefit would suggest that a more direct attack on IL-6 might be more logical, especially because the persistence of IL-6 in temporal biopsy specimens is predictive of disease persistence. There would certainly be support for a study looking at the management of resistant polymyalgia rheumatica and GCA with anti-TNF therapy or anti-IL-6 therapy.

We may be able to identify at onset patients in whom standard therapy with corticosteroids is likely to fail and stratify them to receive additional anti-TNF or anti-IL-6. It is becoming more realistic to perform cytokine profiles in clinical practice and thereby identify patients who are most likely to require more aggressive therapy and those who may benefit from much milder therapy. In the control groups for these 2 studies, several patients responded well to short-duration corticosteroid therapy.

Raashid A. Luqmani, DM
University of Oxford
Oxford OX3 7LD, United Kingdom

Potential Financial Conflicts of Interest: None disclosed.

CORRECTION

Correction: Strengthening the Reporting of Observational Studies in Epidemiology Statement

In the recent Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (1), Dr. Drummond Rennie was inadvertently left out of the Acknowledgment section. Dr. Rennie has contributed to the project since the beginning. The authors are grateful for his support and pleased to acknowledge it.

Reference

1. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med.* 2007;147:573-7.