Article commented


**COMMENT**

Chronic hepatitis C infections appears to progress more rapidly in men than in women, and cirrhosis is predominately a disease of men and postmenopausal women. Several studies have shown that estrogens specifically Estradiol is a potent endogenous antioxidant that may slow fibrosis progression.¹ One study revealed that menopause appears to be associated with accelerated liver fibrosis progression in HCV-infected women, an effect that may be prevented with hormone replacement therapy, even pregnancy may have a beneficial impact on the long-term progression of liver fibrosis.² Another study revealed that non alcoholic liver disease is more prevalent in postmenopausal than premenopausal women.³ Raloxifene is an oral selective estrogen receptor modulator that directly protect hepatocytes and control liver fibrosis.⁴

In a recent issue of *Journal of Hepatology*, Furusyo, *et al.*,⁵ shown that raloxifene can improve sustained virological response (SVR) in postmenopausal Japanese women with chronic hepatitis C genotype 1b infection. This prospective open label study of 223 postmenopausal women were randomized into two groups: raloxifene hydrochloride (60 mg/day) plus standard of care (SOC) with rivabirin/pegylated interferon and SOC only. There were not differences in fibrosis, body mass index, IL28B gen with major allele genotype, or age between both groups. The end of treatment response (ETR) and SVR rate in the raloxifene/SOC group were 88.7% (n = 35) and 61.3% (n = 38) respectively, compared with 68.9 (n = 42) and 34.4% (n = 21) respectively in the SOC only group, being significantly higher in the first group for SVR (p = 0.0051) and for ETR (p = 0.0312). Relapse rates after treatment were lower in the raloxifene/SOC group (30.9%, 17 of 55) than in the SOC only group (50%, 21 of 42), however there were not statistically significant (p = 0.0890). The SVR rate in patients with IL28 gene (rs8099917) genotype TT in the raloxifene/SOC group was 72.5% (n = 37) compared with 39.2% (n = 20) in the SOC group alone. However there was no difference in SVR rates between the two treatment groups in genotype GG or GT (9.1% and 10%). There were only six patients that discontinued treatment during the study in the raloxifene/SOC group due to general malaise, retinopathy and depression. No thrombosis event was detected in any group. Also no differences between the two treatment groups were observed with changes in serum aminotransferase levels, hemoglobin, platelet or white blood cells counts during treatment.

In conclusion this prospective, randomized, controlled study reveal that raloxifene improved the efficacy of SOC treatment for postmenopausal women with chronic hepatitis C, suggesting that it may be a promising candidate as adjuvant therapy is such patients. The major limitation of the study is that it was only proven in Japanese women and consequently should be tested in other ethnical populations.

There are many hypothesis to explain the different response to between pre and postmenopausal women in hepatitis C virus treatment: the toxic intrahepatic iron deposition that is characteristic of chronic hepatitis C infection is lower premenopausal women through their physiologic blood loss compared to postmenopausal women.⁶ Estradiol levels are
higher in premenopausal women and this hormone has seen to block lipid oxidation reactions in liver. Tamoxifen is also an estrogen receptor agonist has been shown to suppress hepatitis C virus replication and this suggests that raloxifene could have the same antiviral mechanism.

The ILB28 gene was a crucial factor to have a SVR in postmenopausal women with chronic hepatitis C virus. In a metanalysis of 4,252 patients with chronic hepatitis C from different ethnicities were analyzed for IL28B and response with SOC treatment and they demonstrate that IL28B (rs129797860) major allele CC and (rs8099917) major allele TT are strong SVR predictors for SOC treatment in chronic hepatitis C infection, regardless of ethnicity. Therefore it is important to determine IL28B gene in patients receiving SOC treatment and focusing more in this subgroup of patients that in future studies could receive raloxifene as an adjuvant therapy.

It would be interesting to compare this new promising adjuvant therapy with the new antiviral drugs like telaprevir and boceprevir on SVR rates in postmenopausal women with chronic hepatitis C genotype 1 infection. There are no studies focusing these new agents on this subgroup of patients. The increase SVR rate with the protease inhibitors in general population are 29% in boceprevir and 31% in telaprevir that is very similar rate observed in the study with raloxifene. Therefore more studies are needed to establish of raloxifene could be an option as an adjuvant therapy in postmenopausal women receiving SOC treatment alone or even SOC plus protease inhibitors. The cost-effectiveness of treating postmenopausal women either with a protease inhibitor or raloxifene, the estrogen receptor agonist could be a less expensive option and probably has similar SVR rates for this particular subgroup of patients.

REFERENCES