Surrogate endpoints and non-inferiority trials in chronic viral hepatitis

To the Editor:

We read with great interest the recent article by Dr. Garattini and Dr. Bertelè [1]. We would just like to comment on the authors' statement that "Quality of life, morbidity and mortality should always be the primary hard end-points for evaluating new drugs". We believe that this rule should be applied with caution in the field of chronic viral hepatitis because of the slow progression of this disease and the availability of surrogate virological end-points. For example, we know that the quality of life and survival of chronic hepatitis B patients can be improved if HBV replication is suppressed in a sustained manner [2]. Also in HCV-related chronic liver disease, a sustained virological response, namely HCV clearance 6 months after treatment withdrawal, is associated with increased survival and a low rate of progression towards decompensation or hepatocellular carcinoma [3–6]. A trial, comparing the effects of different drugs in the setting of HBV-related or HCV-related chronic hepatitis with survival as end-point, would be considered poorly ethical. Indeed, it would take several decades to demonstrate the superiority of one drug over another, and patients would be deprived of the best treatment strategy for a prolonged period. Obviously, toxicity and adverse events must be carefully monitored in trials with a surrogate endpoint. Therefore, we agree with Dr. Garattini and Dr. Bertelè that "in some cases an endpoint that closely correlates with a hard end-point can be used as a surrogate" and suggest that this is the case of treatment of chronic viral hepatitis.

The authors also advocate the use of superiority rather than non-inferiority-designed randomized controlled trials. On the whole, we share this view, but again a caveat applies in the setting of therapy with nucleoside/nucleotide analogues of hepatitis B. In fact, it is well known that prolonged administration of analogues is associated with the emergence of resistant mutations. Resistant variants cause viral rebound and the loss of histological and clinical benefits associated with viral suppression [7]. Analogues entecavir and tenofovir have high antiviral power (77–94% undetectability after 2 years of therapy) and a low rate of mutation emergence. To date, the rate of resistance to entecavir has been as low as 1.2% at 6 years and null for tenofovir at 3 years. However, what will happen in patients treated for 20 or 30 years? Resistance to analogues will probably increase in the long term. Consequently, new drugs with similar antiviral powers and resistance rates as entecavir and tenofovir, but with different resistance profiles might be useful weapons in the fight against HBV. Such drugs may be effective in patients who responded poorly to previous compounds. Moreover, the availability of multiple non-inferior drugs would give the physician a better opportunity to "customize" treatment for individual patients. Lastly, new non-inferior drugs with lower costs than previous drugs would be welcome.

In non-inferior trials, it is important that the margin of non-inferiority is based on clinical grounds. In fact, using a wide margin of non-inferiority, a clearly inferior treatment would be considered non-inferior. In other words, a wide non-inferiority margin does not allow us to translate into the clinical setting what is "non-inferior" from a statistical point of view.

References

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