Combination therapies, and even fixed drug combinations, seem logical in several clinical situations. One common example is difficult-to-treat diseases, and combination therapy is already considered the standard of care for conditions like hepatitis C. Other situations include where one drug in a combination potentiates the effect of the other (e.g., trimethoprim and sulphamethoxazole); where one drug reduces the dose required of the other, in order to decrease potential adverse effects; and, probably most importantly, where the risk and consequences of development of resistance with monotherapy are high (e.g. in the treatment of tuberculosis and HIV).

Proponents of combination therapy for chronic hepatitis B (CHB) believe that a single antiviral agent is unlikely to be sufficient for eradication of CHB infection and may result in development of drug-resistant mutants. With LAM monotherapy, three of four patients develop resistance by five years. In treatment-naive patients with CHB, telbivudine monotherapy results in undetectable HBV DNA in 60% of HBeAg-positive and 88% of HBeAg-negative patients at 1 year, but is associated with genotypic resistance in 5% and 25% of HBeAg-positive and 2.3% and 11% of HBeAg-negative patients after 1 and 2 years of treatment, respectively; hence, it is no longer recommended as first-line therapy for CHB. ADV has limited potency and is generally used as add-on therapy.

The first combination of a nucleoside and nucleotide analogue was LAM with adefovir (ADV). A meta-analysis including six studies concluded that this combination was superior in inhibiting HBV replication and preventing drug resistance as compared to ADV alone for LAM-resistant CHB patients. This combination also reduced resistance to LAM when both drugs were given to treatment-naive patients. The combination was recommended by the American Association for Study of Liver Diseases (AASLD) as one of the first-line therapies for patients with decompensated cirrhosis due to CHB.

Initial studies on combination therapy using lamivudine (LAM) and interferon yielded conflicting results. At least two studies showed marginal superiority of combination therapy over monotherapy with regard to HBeAg seroconversion rate. Subsequently, at least four studies comparing pegylated interferon and LAM combination therapy to monotherapy showed superior end-of-therapy response with the combination, but not at 6 months’ follow-up. Another trial studying combination therapy with telbivudine and peg-interferon had to be terminated prematurely because of unacceptably high rate of peripheral neuropathy.

The scene changed with the emergence of potent antiviral agents with high genetic barrier to resistance, like entecavir and tenofovir. With these drugs, the likelihood of emergence of resistance over the long term has been shown to be low. Tenofovir monotherapy, for example, is associated with HBV DNA loss in 76% of naive HBeAg-positive and 93% of HBeAg-negative patients at 1 year, and is not associated with any genotypic resistance at the end of five years of therapy.
Combination of entecavir and tenofovir was tried in 57 patients with advanced liver disease who had previously not responded to or had developed resistance to a median of three lines of antiviral therapy; it was shown to be effective, with undetectable HBV DNA in 51 patients within 6 months. Tenofovir and emtricitabine combination proved effective in patients with LAM and/or ADV resistance.

In this edition of JAPI, Panda has published a real-life study of a combination of telbivudine and tenofovir in 21 treatment-naive patients with CHB. Unfortunately, only 10 patients completed the follow-up period of 48 weeks. Probably the most important but unstated message here is the general pattern of poor follow-up that is observed in this country and the lack of awareness among patients about the importance of treatment compliance, especially in CHB. This leads to dismal efficacy results on intention-to-treat analysis. The author acknowledged the fact that even with per-protocol analysis, combination therapy in this study was not superior to previously published results with monotherapy.

The implied justification for undertaking this study was evidence that combinations may work better than monotherapy in patients with high viral loads, and the fear of development of resistance with monotherapy. Unfortunately, in this study, viral load was not evaluated as a discriminating factor, and the follow-up duration was not adequate to evaluate resistance at least for tenofovir, considering the known absent resistance to this drug over a 5-year period. The other indications for combination therapy listed earlier in this commentary are also not fulfilled by this combination. A meaningful future study should include a larger sample size, maybe with a combination of entecavir and tenofovir compared against tenofovir or entecavir monotherapy as control arm, and follow-up of much over five years. Of course, the justification for the increased cost of such a combination therapy should be considered in a resource-limited country like ours.

References