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Editorial

Partial virological response to nucleos(t)ide analogues in naïve patients with chronic hepatitis B: From guidelines to field practice ☆

Pietro Lampertico*

First Division of Gastroenterology, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Via Francesco Sforza 35, 20122 Milan, Italy

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According to the recent EASL HBV Clinical Practice Guidelines, partial virological responders (PVR) to nucleos(t)ide analogues (NUC) are patients with more than 1 log decline of viremia compared to baseline but still have detectable serum levels of HBV DNA by real-time PCR assay (>10–15 IU/ml) at Week 24 or 48, depending on the genetic barrier of the anti-HBV drug [1]. Though the prevalence of partial virological response according to this new definition is not known exactly, the rates of patients with detectable HBV DNA by sensitive assay, i.e. >60–80 IU/ml (equivalent to approximately 300 or 400 copies/ml), at Week 24 for lamivudine (LMV) and telbivudine (LDT) and at Week 48 for adefovir (ADV), entecavir (ETV) and tenofovir (TDF) have been delineated in different, independent studies (see Figure).

The clinical relevance of NUC partial virological response relates to the high risk these patients face of developing resistance to long-term anti-HBV treatment, particularly when first (LMV) and second generation (LDT, ADV) drugs are involved [1]. Conversely, for PVR on third generation NUCs like ETV and TDF, carrying a lower risk of resistance to long-term monotherapy, the association between residual viremia at Week 48 and secondary treatment failure during follow-up has not been fully established [1]. Despite the strong rationale for adapting antiviral therapy, at least for selected NUCs, evidence-based algorithms for rescuing these patients have not been developed, apart from expert opinions. The paper by Reijenders et al. in this issue of the Journal is the first to evaluate the efficacy of ETV in NUC- naïve partial virological responders to ADV monotherapy [2].

Twenty-nine to 68% of the patients on LMV monotherapy were PVR at Week 24, showing an increased risk of developing drug resistance in follow-up, thus requiring early adaptation of antiviral therapy (see Figure) [3,4]. To assess whether PVR to LMV would benefit by switching to LDT, 246 HBeAg-positive and negative patients previously treated with LMV for 3–12 months at the time of screening, with HBV DNA >3 log copies/ml and compensated liver disease, were randomized to switch to LDT treatment ($n = 122$) or continue LMV ($n = 124$) for one year [5]. The extent of HBV suppression at Week 24 was greater in LDT-treated patients than in patients who continued on LMV (mean −1.90 log copies/ml vs. −0.90 log copies/ml, $p = 0.002$) although HBV was equally undetectable in the two groups (40% vs. 31%, $p = 0.14$). While these findings suggest a partial benefit of early adaptation, at least for the first 24 weeks, LDT monotherapy might not be the best strategy to manage PVR to LMV, because the two drugs share a similar cross-resistance profile despite LDT having a slightly better genetic barrier to resistance than LMV [1].

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☆ PL is on the speaker's bureau and/or advisory board of: Bristol-Meyers Squibb, Roche, GlaxoSmithKline, Gilead Sciences and Novartis.

* Tel.: +39 0255035432; fax: +39 0250320410.
E-mail address: pietro.lampertico@unimi.it.

Abbreviations: HBV, hepatitis B virus; PVR, partial virological responders; NUC, nucleos(t)ide analogues; LMV, lamivudine; LDT, telbivudine; ADV, adefovir; ETV, entecavir; TDF, tenofovir; FTC, emtrićitabine.

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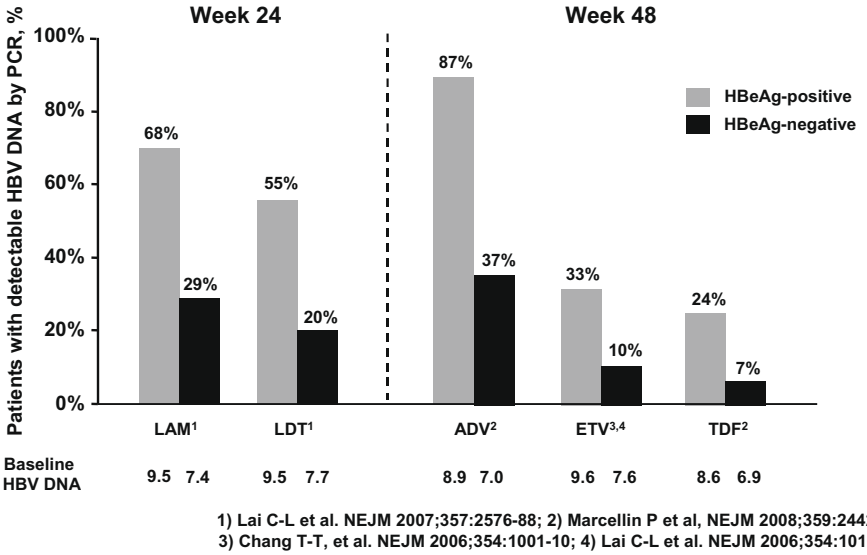

Figure. Rates of partial virological responders (PVR), defined as patients with detectable HBV DNA by PCR assay at Week 24 for LMV and LDT and Week 48 for ADV, ETV, TDF. Viremia was quantified by Roche Cobas Amplicor PCR assay with a lower detection limit of 300 copies/ml for LMV, LDT and ETV and by Roche Cobas Taq-Man PCR assay with a lower detection limit of 400 copies/ml for TDF. Studies were not head-to-head. Baseline HBV DNA was expressed as log copies/ml.

On LDT therapy, more HBeAg-positive than HBeAg-negative patients (55 vs. 20%) showed detectable HBV DNA at Week 24 (see Figure) [4] and though PVR had a well defined increased risk of LDT resistance at Week 104 [5], no studies that assess the best rescue strategy in these patients, are available.

Of patients on ADV monotherapy, 37% of HBeAg-negative patients and 87% of the HBeAg-positive patients showed partial virological responses at Week 48 (see Figure) [6]. The 49% risk of developing ADV resistance at Week 192 for HBeAg-negative patients with >3 log copies/ml of HBV DNA at Week 48 was significantly higher than the 6% risk of those with lower viremia [7], suggesting the need for early adaptation of antiviral therapy in the former group. The management of PVR to ADV has been investigated in 5 studies with TDF, ETV or LDT as monotherapies. TDF emerges as an option in these patients as partial virological response to ADV reflects low potency of this drug rather than the emergence of resistant strains. Among ADV PVR at Week 48, viral suppression (<400 copies/ml HBV DNA) was achieved at Week 96 in 82% of HBeAg-positive and in all HBeAg-negative patients who were switched to TDF monotherapy at Week 48 [8,9], suggesting that TDF suppressed HBV replication in most ADV PVR within 48 weeks of therapy. Because of its potency, high genetic barrier and different cross-resistance profile, ETV was also assessed as a potential rescue therapy for ADV PVR in two studies. This issue of the Journal describes six LMV-naïve, HBeAg-positive patients with HBV DNA >5 log copies/ml after 17 (12–31) months of ADV monotherapy, in the absence of ADV-related mutations, who were switched to ETV 1.0 mg [2]. Viral load, which was 7.1 (6.1–10.1) log copies/ml at baseline, declined by 3.4 (2.4–5.8) log copies/ml after 48 weeks, with one patient only becoming PCR negative at month 12, and no patient showing HBeAg loss in the absence of virological breakthrough or ETV resistance. Virological response to ETV rescue was surprisingly lower than expected despite the reinforced dosage of 1.0 mg instead of 0.5 as recommended for LMV-naïve patients, the high genetic barrier of ETV and the different cross-resistance profile of this drug compared to ADV. These findings were challenged by a study presented at the AASLD 2008 meeting, where twenty-nine patients with incomplete viral suppression on ADV, defined as failure to achieve a 2 log reduction of viral load at Week 24 or HBV DNA undetectability at Week 48, were switched to ETV [10]. At baseline, median age was 49 years, 61% were male, 55% HBeAg-positive, median time on ADV prior to switching was 80 weeks (16–237) and median HBV DNA was 4.4 (2.4–8.2) log IU/ml. The rates of virological response, i.e. serum HBV DNA <60–100 IU/ml, were 55, 77 and 82% after 24, 48 and 96 weeks of therapy, suggesting a satisfactory response to ETV switch. The apparently contradictory results of these two studies might depend on relevant variables, like the definition of partial virological response and more importantly, the baseline level of HBV DNA at the time of switch, which was approximately 7 log copies/ml in the former study and 4.4 log IU/ml in the latter. LDT could represent an alternative approach to the management of ADV PVR because of its potency, although a switch to a lower genetic barrier drug may expose patients to developing drug resistance in the long term. In a prospective controlled study, 46

HBeAg-positive, Asian patients with a baseline HBV DNA of 9.5 log copies/ml, were treated with ADV for 24 weeks to be subsequently switched to LDT monotherapy [11]. The proportion of patients with undetectable viremia increased from 12% at the time of LDT switch (Week 24) to 54% at Week 52, i.e. after 24 additional weeks of LDT, compared to an increase of HBV DNA undectability rates from 12% to 40% in a parallel group of 44 patients with similar baseline features who continued ADV monotherapy. By exploratory analysis, the 78% of ADV suboptimal responders, defined by HBV DNA level $\geqslant$3 log copies/ml at Week 24, who switched from ADV to LDT, displayed an additional reduction of 2.1 log copies/ml of HBV DNA between Weeks 24 and 52, compared with 0.8 log copies/ml for patients continuing ADV through Week 52, although the proportion of HBV DNA PCR-negative patients was similar between groups (42% vs. 24%; $p = 0.11$).

Ten to 33% of patients on ETV monotherapy for 48 weeks showed a partial virological response, i.e. HBV DNA >300 copies/ml by Roche Cobas Amplicor PCR assay (see Figure) [12,13]. Though there is no clear-cut evidence that ETV PVR at Week 48 are likely to develop resistance in the subsequent years, ETV-resistant strains developed in two LMV-naïve patients with incomplete suppression at Week 48 [14,15], suggesting that even partial virological response to a 3rd generation NUC like ETV, entails a residual risk of secondary treatment failure. Full papers assessing the best strategy to treat these patients have not been published so far but a recent abstract shed some light on this issue [16]. Among 236 patients with chronic hepatitis B receiving ETV monotherapy for a mean of 68 weeks (53–126), 7 patients (3%) had suboptimal responses to ETV (<1 log HBV DNA reduction in 6 months), requiring a switch to TDF monotherapy. All patients were Chinese, 5 LMV-naïve, 5 males, and 5 HBeAg-positive with a mean HBV DNA level of approximately 4 log copies/ml and none with antiviral resistance at the time of TDF switch. All patients achieved HBV DNA <160 copies/ml within 24 weeks of TDF monotherapy without evidence for a virological breakthrough during a mean of 34.8 (16–76) weeks.

In the recently published Phase III study on TDF, the 48-week rates of partial virological response, i.e. the proportion of patients with >400 copies/ml of HBV DNA by Roche Cobas Taq-Man PCR assay, were 7% for HBeAg-negative and 24% for HBeAg-positive patients (see Figure) [6]. The clinical outcome of TDF PVR is unknown, but no patient developed TDF resistance through Week 96, the rates of HBV DNA suppression progressively increased during the second year of therapy, while patients with incomplete viral suppression at Week 72, i.e. >400 copies/ml of HBV DNA, were offered a rescue therapy with add-on FTC [8,9]. The 28 HBeAg-positive patients (13 ADV-TDF and 15 TDF-TDF) who started on combination therapy with FTC and TDF, had a HBV DNA decline from 4.36 to 3.57 log copies/ml within 16 weeks of treatment, whereas 4 (14%) patients only cleared HBV DNA [9]. While these data suggest a slow response to the nucleoside analogue in TDF PVR after 72 weeks of therapy, the short duration of additional combination treatment and the lack of an individual virological profile from patients who were rescued with FTC + TDF and from those who continued on TDF monotherapy, does not allow for any definitive conclusion.

In summary, with the EASL HBV Clinical Practice Guidelines setting the stage for a new definition of PVR, i.e. patients with detectable HBV DNA by real-time PCR assay (>10–15 IU/ml) at Week 24 or 48, hepatologists are forced to reassess the efficacy of currently available therapeutics providing evidence-based studies to improve the management of these patients. The risk for PVR to develop resistance in the subsequent months has been clearly demonstrated following LMV, LDT and ADV, to such an extent that EASL suggested either to switch to a more potent drug (ETV or TDF) or add a more potent drug that does not share cross-resistance, i.e. TDF to LMV or LDT, or ETV to ADV [1]. Conversely, the risk of secondary treatment failure for patients with residual viremia at Week 48 following compounds with high genetic barrier like ETV and TDF, has not been demonstrated, though it is plausible on virological grounds and suggested by preliminary clinical data [14,15]. This is a relevant clinical issue both in terms of added cost and uncertain safety data for add-on strategy, as well as added risk of resistance in case of switch to strategy or long-term maintained monotherapy. The uncertainty on this issue is reflected in the EASL guidelines, where some of the experts suggested to add the other drug in order to prevent resistance in the long term, although the long-term safety of ETV and TDF in combination is unknown [1], while others suggested either switch to or continuation of monotherapy. Alternative options include to delay from Week 48 to Week 72 the time point for this therapeutic decision or, on the basis of kinetics or pattern of serum HBV DNA, stratify PVR at Week 48 according to the risk of developing HBV resistance to third generation NUCs like ETV and TDF, and deliver a prompt rescue therapy to those PVR who do not show a progressive, continuous decline of viremia [17]. Though the mechanisms accounting for partial virological response to last generation anti-HBV drugs in NUC- naïve patients are poorly understood, the longer time to undetectability in patients with higher baseline viral load is a likely explanation. To date, other poorly understood events like intestinal absorption, cell entry and hepatocyte phosphorylation rates of the drug may impact not only virological response to the first drug but also on that of the rescue drug. Finally, the importance of the selection

of drug-resistant strains which is negligible for ETV or TDF PVR in the registration trials, might be greater in field practice studies where patient adherence and compliance may be suboptimal.

The study by Reijnders et al. in this issue of the Journal adds to the available evidence on the management of NUC PVR, but more work is needed on issues like assessing the rates of partial virological response to ETV and TDF in clinical practice, risk of a flat HBV DNA kinetics, drug resistance, and validation of the best antiviral algorithms. While results of ongoing clinical trials focusing on the rescue strategy of PVR are awaited, the EASL HBV Clinical Practice Guidelines have proposed a rescue strategy for NUC PVR which represents a clinically and virologically sound approach.

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