

Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naïve patients with chronic hepatitis B

List of abbreviations:

ADV	Adefovir dipivoxil
CHB	Chronic hepatitis B
CI	Confidence interval
CrI	Credible [Bayesian probability] interval
DIC	Deviance information criterion
ETV	Entecavir
HBeAg	Hepatitis B e antigen
HBV	Hepatitis B virus
LAM	Lamivudine
LdT	Telbivudine
Log-OR	Natural log of the odds ratio
MTC	Mixed treatment comparison
OR	Odds ratio
RCT	Randomised controlled trial
SD	Standard deviation
TDF	Tenofovir disoproxil fumarate

Abstract

Background/aims: Five nucleoside/nucleotide treatments are now available for chronic hepatitis B (CHB). This meta-analysis aimed to assess the relative efficacy of adefovir, entecavir, lamivudine, telbivudine, tenofovir disoproxil fumarate (TDF) and nucleos(t)ide combinations in the treatment of CHB.

Methods: A systematic review of MEDLINE and the Cochrane library was conducted to identify all studies evaluating these nucleos(t)ides in adults with CHB. Randomised controlled trials were included in the meta-analysis if they reported the proportion of patients with <1,000 copies/mL hepatitis B virus (HBV) DNA or HBeAg loss/seroconversion at one year. Bayesian mixed treatment comparison meta-analyses were conducted in WinBUGS to assess relative efficacy.

Results: A random-effects meta-analysis of trials on treatment-naïve patients with HBeAg-positive CHB demonstrated that 94% of patients will achieve HBV DNA <300 copies/mL after one year with TDF, compared with 73% for entecavir, 50% for adefovir and 38% for lamivudine. There was a 97.7% probability that TDF enabled a greater proportion of patients to achieve HBV DNA <300 copies/mL at one year than all other treatments considered in the analysis. TDF was significantly superior to all nucleos(t)ides for this outcome at the 0.05 level. There were no statistically significant differences between nucleos(t)ides in HBeAg seroconversion at one year, based on a fixed-effects meta-analysis in the same population. More trials on HBeAg-negative and drug-resistant patients are required to facilitate meta-analyses for these sub-groups.

Conclusions: In nucleos(t)ide-naïve patients with HBeAg-positive CHB, TDF is associated with the highest probability of achieving undetectable HBV DNA at one year of all nucleos(t)ides considered.

1. Introduction

Chronic hepatitis B (CHB) comprises liver inflammation and damage caused by the hepatitis B virus (HBV), which can lead to cirrhosis and hepatocellular carcinoma [1]. Eight drugs are now licensed in the UK for use in CHB: the nucleosides entecavir (ETV), lamivudine (LAM) and telbivudine (LdT); the nucleotides adefovir dipivoxil (ADV) and tenofovir disoproxil fumarate (TDF); and peginterferon-alpha-2a, interferon-alpha-2a and interferon-alpha-2b [2].

Although numerous trials have evaluated the efficacy of the three newest agents (ETV, LdT and TDF) compared with LAM or ADV [3-10], no head-to-head randomised controlled trials (RCTs) have yet compared ETV, LdT and TDF directly. Estimates of relative efficacy are required to inform clinical decisions about patient management, national and local treatment guidelines and economic evaluations assessing the cost-effectiveness of the different treatment options.

A previous meta-analysis pooled the results of studies evaluating ADV, ETV, LAM and placebo [11] and concluded that ETV was superior to both ADV and LAM. However, the analysis was primarily based on the absolute effects observed in individual arms of different trials [11] and therefore did not take account of the relative treatment effects observed in each study. Furthermore, the analysis did not assess the efficacy of LdT or TDF or include studies published since 2004.

Standard meta-analytical techniques evaluate the relative efficacy of one treatment compared with a single comparator [12]. However, mixed treatment comparison (MTC) methods have recently been developed that estimate the relative efficacy of any number of different treatments by taking account of the entire network of RCT evidence [12-15]. MTC is also known as network meta-analysis and multiple-treatments meta-analysis and is now recommended by the National Institute for Health and Clinical Excellence (NICE) [16].

We set out to use MTC to assess the relative efficacy of the following nucleos(t)ides in the treatment of CHB in terms of achieving viral suppression and seroconversion: ADV; ETV; LAM; LdT; TDF; placebo; and combinations of these drugs.

2. Methods

2.1. Systematic review

MEDLINE/PubMed and the Cochrane library were searched on 31st August 2007; additional studies were identified through manufacturer/conference websites and citations within published review articles.

The systematic review used broad, pre-specified inclusion criteria to identify all relevant studies evaluating nucleos(t)ides in the treatment of CHB; these inclusion criteria are available on request. The wider review included non-randomised studies as well as RCTs on diverse populations in order to provide data inputs for a model-based economic evaluation [17] as well as identifying RCTs for meta-analysis.

Studies identified in the systematic review were considered for meta-analysis if they met the inclusion criteria shown in Table 1. Meta-analyses were planned on four patient subgroups: nucleos(t)ide-naïve patients with (a) HBeAg-positive or (b) HBeAg-negative CHB; and patients who were resistant/refractory to one or more nucleos(t)ides at baseline with (c) HBeAg-positive or (d) HBeAg-negative CHB. However, this paper focuses on the results of analyses on HBeAg-positive nucleos(t)ide-naïve patients.

2.2. Data extraction

Data were extracted from journal articles, study reports, conference abstracts, summaries of product characteristics and (where available) clinical study reports. Data were extracted by one researcher and all data used in the meta-analysis were checked against the original sources by two other researchers. Any typos or discrepancies between the extracted data and the source material were resolved through reference to the original sources.

Data were extracted on the number/proportion of patients with HBeAg loss, HBeAg seroconversion and HBV DNA levels undetectable by polymerase chain reaction (PCR) after one year of treatment (range: 40-72 weeks). In cases where no available data source reported the number of patients

meeting a particular endpoint, patient numbers were calculated from percentages and were not rounded. All outcomes were recorded as reported by the trial, whether intent-to-treat or per protocol in order to maximise the amount of data available for the meta-analysis; however, all but two trials included in the analysis of HBeAg-positive CHB presented intent-to-treat data (Table 2).

2.3. Allowance for missing data

Meta-analyses were conducted on two outcomes: the probability of HBeAg seroconversion and the probability of achieving HBV DNA <300 copies/mL after one year's treatment. These outcomes were chosen to provide transition probabilities for a model-based economic evaluation [17]. A threshold of 300 copies/mL was used since this is the threshold most commonly reported in trials using PCR. Since a wide range of HBV DNA thresholds have been used in the literature and as some studies report HBeAg loss but not HBeAg seroconversion, statistical transformations were used to estimate these parameters from data on closely-related outcome measures so that all available data could be meta-analysed. Combining data on different outcomes without making appropriate adjustments could introduce bias into the analysis; in particular, since two studies observed that no placebo-treated patients achieved HBV DNA <400 copies/mL [18, 19], combining data on different thresholds without adjusting for this is likely to have biased analyses in favour of TDF and ADV.

Data on the number of patients with HBeAg loss were converted into estimates of the number undergoing HBeAg seroconversion by assuming that 92% of patients losing HBeAg will also undergo HBeAg seroconversion within the same year, based on data extracted from the three largest trials reporting both measures, where the ratio of seroconversion to loss ranged from 88% to 100% [3, 20, 21].

Data on the proportion of patients in the two main TDF trials [9, 10, 21, 22] who had HBV DNA below one of four different thresholds (169, 300, 400 and 1,000 copies/mL) were used to estimate a statistical model to predict the number of patients with HBV DNA levels <300 copies/mL from the number of patients meeting other HBV DNA targets (details available on request). The model fitting the data best ($R^2=0.7554$) was:

$$n_Y = N[(n_X / N) - 0.0538\text{Ln}(\text{ThresholdX}) + 0.0538\text{Ln}(\text{ThresholdY})] \quad (1)$$

Where:

ThresholdX = Threshold HBV DNA level (in copies/mL) for which data are available; if data on several thresholds are available, the threshold closest to Threshold Y should be used.

n_X = The number of patients in this trial with HBV DNA below Threshold X

n_Y = The number of patients in this trial with HBV DNA below Threshold Y

N = Total number of patients with HBV DNA measurements

ThresholdY = Threshold HBV DNA level of interest (in copies/mL).

This equation was validated against data from the BEHOLD A1463022 trial [3] and was used to estimate the number of patients with HBV DNA <300 copies/mL for use in the meta-analysis in cases where trials used other thresholds. In cases where the equation predicted negative numbers (for example if no patients had HBV DNA <400 copies/mL), it was assumed that no patients would have HBV DNA <300 copies/mL. Equation 1 may also be used for other purposes where it is necessary to convert between HBV DNA thresholds between 169 and 1,000 copies/mL.

2.4. Statistical methods

The techniques of Bayesian MTC meta-analysis [12, 13, 15] were used to assess the relative efficacy of the nucleos(t)ides. MTC techniques allow all evidence to be taken into account, whether direct (from head-to-head RCTs) or indirect (calculated from trials with common comparators). These methods use the principles underpinning standard indirect comparisons [23, 24] and are based on relative treatment effects (in this case the natural log of the odds ratio, log-OR) in order to preserve trial randomisation and minimise bias.

MTC was conducted using WinBUGS Version 1.4 (MRC Biostatistics Unit, Cambridge, UK) [25], which uses Bayesian Markov chain Monte Carlo Gibbs sampling methods to fit user-defined models. We used statistical models for fixed and random-effects MTC analyses (shown in Appendix 1) that were developed by Bristol University and allow for trials with up to three treatment arms [13, 14, 26, 27].

As with all meta-analyses, MTC may be conducted using either fixed or random-effects models. Random-effects models allow for the possibility that the true treatment effect may differ between trials [12]. We used random-effects models when there was evidence of heterogeneity or when fixed-effects models fitted the data poorly. Model fit was assessed based on residual deviance [28] and deviance information criteria (DIC) [25].

LAM was used as the baseline drug since it has been evaluated in the largest number of RCTs. The absolute probability of responding to LAM was based on the crude average probability of response across the LAM arms of all trials evaluating this treatment; the probability of responding to other treatments was calculated from this figure and the log-ORs for each treatment relative to LAM (Appendix 1).

Differences between treatments were considered significantly significant at the 0.05 level if the 95% credible (Bayesian probability) interval (CrI) for the log-OR did not cross zero. We also calculated the probability that each treatment was best based on the proportion of Markov chain iterations in which that treatment had the highest probability of viral suppression/HBeAg seroconversion. All p-values represent Bayesian p-values. Treatment effects based on head-to-head trials were estimated using pairwise frequentist meta-analyses conducted in Stata Version 10.0 (StataCorp, College Station, Texas) using the metan command; the same methods were used to calculate the odds ratio for viral suppression in HBeAg-negative patients compared with HBeAg-positive patients.

The impact of using fixed and random-effects models, alternative priors, adding/removing trials and making no adjustment for HBV DNA threshold was evaluated in sensitivity analyses.

In common with previous research [13, 27, 29, 30], non-informative prior distributions were used for all treatment effects and the odds of responding to LAM to ensure that the results were primarily driven by the data (Appendix 1). However, sensitivity analyses suggested that the posterior estimates of the uncertainty around treatment effects (but not the posterior means) were sensitive to the priors used. Informative half-normal priors [31] were therefore used for the between-studies SD in order to allow this external data to help inform the between-studies SD; these distributions were based on a meta-

analysis of interferon trials identified in a published systematic review [32]; see Appendix 2 for more details.

Although reasonable convergence was achieved after a burn-in of 100,000 simulations, between 500,000 and 925,000 burn-in simulations were conducted for the main analyses to ensure that robust results were generated. For all analyses, results were based on a further 20,000 sampled simulations of two chains using different initial values.

Additional details of the methods used, data on model fit or convergence and results of sensitivity analyses are available from the authors on request.

3. Results

3.1. Studies identified

Of the 1,272 publications identified through electronic searches, 77 RCTs and 46 non-randomised studies met the inclusion criteria for the wider systematic review (Fig. 1); details available from the authors on request. For the purposes of this analysis, the HBeAg-positive and HBeAg-negative subgroups of the GLOBE trial comparing LdT and LAM [33] were counted as two separate studies.

Twenty-three 23 RCTs met the narrower inclusion criteria for the meta-analysis [3-6, 8-10, 18, 19, 33-49]. Thirteen studies were included in the analysis of treatment-naïve patients with HBeAg-positive CHB [3-6, 8, 9, 18, 33-38], four were on treatment-naïve HBeAg-negative CHB [10, 19, 33, 39], five were on LAM-refractory patients with HBeAg-positive CHB [40-48] and one was on LAM-refractory HBeAg-negative CHB [49] (Fig. 2).

3.2. HBeAg-positive treatment-naïve patients

Thirteen trials met the inclusion criteria for the analysis of HBeAg-positive, treatment-naïve patients. The trials used similar methods and comparable patient populations (Table 2), although one recruited patients with hepatitis D virus co-infection [38] and one used an older, less sensitive, PCR assay to measure viral load [37].

Ten studies [3-6, 8, 9, 18, 33, 36, 37] on HBeAg-positive treatment-naïve patients reported the proportion of patients with undetectable HBV DNA by PCR after one year of therapy. Although model fit was similar for fixed and random-effects models (DIC=141-144), a random-effects model was used to meta-analyse data on this outcome as there was evidence of heterogeneity from previous studies (Appendix 2) and the current meta-analysis (between-studies SD: 0.470 [95% CrI: 0.026, 1.166]).

In this analysis, TDF had a significantly higher probability of undetectable HBV DNA at one year than any other nucleos(t)ide considered in the analysis ($p < 0.05$; Tables 3-4, Fig. 3). There was found to be a 97.7% probability that TDF enabled a greater proportion of patients to achieve HBV DNA < 300 copies/mL than all other treatments considered in the analysis (Table 4). All nucleos(t)ide therapies

and combinations were found to be significantly more effective than placebo for this outcome and ETV, LdT and TDF were also significantly more effective than LAM ($p < 0.05$; Table 3). Sensitivity analyses suggested that using a wide uniform prior distribution for the between-studies SD increased the width of 95% CrI but did not affect mean treatment effects. Fixed-effects models were found to have greater statistical power than random-effects models, although the results were otherwise similar.

All 13 trials on nucleos(t)ide-naïve HBeAg-positive CHB that met the inclusion criteria reported the proportion of patients with HBeAg loss/seroconversion after one year of therapy [3-6, 8, 9, 18, 33-38]. For HBeAg seroconversion, there was less heterogeneity (between-studies SD: 0.315 [95% CrI: 0.012, 1.008] with a uniform prior [range: 0, 10]) and both fixed and random-effects models fitted the data well (DIC: 158-159); this outcome was therefore analysed using a fixed-effects meta-analysis.

This analysis found no significant differences between nucleos(t)ides in the incidence of HBeAg seroconversion, although all treatments other than LdT plus LAM were significantly superior to placebo at the 0.05 level (Table 5). ADV plus LAM had the highest probability of HBeAg seroconversion and had a 40% probability of having the highest probability of this outcome overall, compared with 32% for TDF, 15% for LdT and 7% for ETV (Table 4).

For both HBV DNA and HBeAg seroconversion, some counterintuitive findings were obtained for combination therapies since only two small RCTs evaluating nucleos(t)ide combination therapies in treatment-naïve patients met inclusion criteria [8, 36]. As one trial found LdT+LAM to be non-significantly inferior to LdT monotherapy for both viral suppression and HBeAg seroconversion [8] and another found ADV+LAM to be non-significantly inferior to LAM in terms of viral suppression [36] ($p > 0.05$), similar non-significant trends were observed in the meta-analysis. However, these findings for combination therapies should be interpreted cautiously due to the small patient numbers.

3.3. Results for other subgroups

Four studies met the inclusion criteria for the analysis of nucleos(t)ide-naïve patients with HBeAg-negative CHB [10, 19, 33, 39], although these did not form a connected network (Fig. 2), so could not

be used in isolation to estimate the efficacy of TDF relative to ETV or LdT. These four trials were each conducted alongside a trial on patients with HBeAg-positive nucleos(t)ide-naïve CHB [3, 9, 18, 33] that evaluated the same treatments using identical methods and identical inclusion criteria other than HBeAg status, viral load and ALT and/or the proportion of cirrhotic or nucleos(t)ide-experienced patients enrolled.

Outcomes in each arm of the studies of HBeAg-negative patients were compared with those in the HBeAg-positive trials conducted alongside them in a *post hoc* fixed-effects meta-analysis. This suggested that the odds of achieving HBV DNA <300 copies/mL are 1.51 (95% CI: 1.35, 1.67) fold higher for HBeAg-negative patients than HBeAg-positive patients, with little variation in odds ratios between trials or treatments.

Six RCTs on nucleos(t)ide-refractory patients were identified, which all considered LAM-refractory patients [40-49]. Three of the six trials specifically recruited patients with YMDD mutations at baseline [43, 44, 48], while the remainder recruited patients with viraemia despite ≥24 weeks of LAM therapy. Only one trial evaluated a cohort that was predominantly HBeAg-negative [49].

However, no RCTs meeting the inclusion criteria evaluated either TDF or LdT in LAM-refractory patients with HBV mono-infection, although two RCTs have evaluated TDF in LAM-refractory patients co-infected with HIV [50, 51] and an RCT published since the search date has evaluated use of TDF in HBV mono-infected patients who have failed ADV, of whom 57% had previously received LAM [52]. Furthermore, 12% of the patients participating in studies 102 and 103 had received prior therapy with LAM or emtricitabine [53]. Since there was insufficient RCT evidence to evaluate treatment effects for all nucleos(t)ides in LAM-refractory patients with HBV mono-infection, the results of meta-analyses on these populations are not presented here. However, results for a secondary analysis that included HIV co-infected patients are reported elsewhere [17].

4. Discussion

MTC meta-analyses found there to be a 98% probability that TDF enables a higher proportion of patients to achieve HBV DNA levels <300 copies/mL at one year than any other licensed nucleos(t)ide. All nucleos(t)ides significantly increased the probability of HBeAg seroconversion by one year relative to placebo, although no significant differences in HBeAg seroconversion were observed between nucleos(t)ides.

The systematic review demonstrated that there is currently insufficient evidence to compare the efficacy of all nucleos(t)ides in LAM-refractory patients or those with HBeAg-negative CHB. A *post hoc* analysis suggested that across all treatments the odds of viral suppression in HBeAg-negative patients are around 1.5 times higher than in HBeAg-positive patients. However, this finding must be interpreted with caution as it is based on comparisons between matched pairs of studies rather than within RCTs, which means that the observed difference could be attributable to selection bias or confounding factors (such as baseline viral load or alanine aminotransferase [ALT] levels, genotype, age or duration of infection) rather than being a direct consequence of HBeAg status.

Although several meta-analyses have assessed the efficacy of interferons in CHB [32, 54-57], our systematic review identified only one published meta-analysis of RCTs evaluating nucleos(t)ides in patients with CHB [11]. This previous study did not include TDF. For the other nucleos(t)ides, it reported similar results, but suggested that LAM was significantly superior to ADV, whereas we observed a non-significant trend towards inferiority. The previous analysis does not appear to have been based on relative treatment effects and may therefore be prone to bias due to differences between studies.

In the current analysis, the efficacy of each treatment was calculated using the relative treatment effects from individual trials and was based on recognised statistical methods for conducting indirect comparisons with minimal bias and preserving the randomisation within each RCT [23, 24]. Since the analysis was based on measures of *relative* efficacy and makes adjustments to allow for inconsistency between trials, the meta-analysis estimates of the proportion of patients responding to

treatment (Table 4) do not necessarily match those observed in clinical trials, but are based on unbiased estimates of differences between treatments. By contrast, “naïve” indirect comparisons (whereby the outcomes for each treatment are based on the average of the outcomes observed in the arms of separate studies in which that treatment was used) ignore the randomisation within each RCT and have been shown to be prone to bias and to underestimate the degree of uncertainty around the averages outcome for each treatment [24].

However, although conducting indirect comparisons based on the relative treatment effects observed in each trial minimises the risk of bias, the treatment effects observed in trials may differ from the true treatment effects by chance. This is particularly true for the comparison between TDF and ADV, which is based on a single study (103) in which only 12% (11/90) of ADV-treated patients achieved HBV DNA <300 copies/mL [9, 21]. It is possible that the log-OR for TDF relative to ADV that was observed in Study 103 may, by chance, be higher than the true difference between these drugs; if this is the case, repeating our meta-analysis in the future with more data may yield a lower estimate of the probability of responding to TDF. However, since Study 103 used appropriate methods for randomisation and blinding, the treatment effect it observed is unlikely to systematically differ from the true treatment effect and is therefore unlikely to have introduced any bias into the meta-analysis.

Interferon-alpha and peginterferon-alpha were excluded from this analysis as they are generally given as first-line therapy to patients who have a particularly high chance of responding to and tolerating treatment and as the outcome of interferon therapy is most appropriately assessed 24 weeks after end of treatment. Including interferons would have increased the amount of data available, but would also have greatly increased the complexity and/or heterogeneity within the analysis due to the wide array of formulations and dosing schedules. Furthermore, since peginterferon-alpha has been found to produce a lower probability of HBV DNA <400 copies/mL than LAM immediately after a 48-week course of treatment [20], it is likely that interferons would have been found to be less effective than TDF and other newer nucleos(t)ides.

Although MTC could also be used for outcomes such as ALT normalisation or histological improvement, it was not possible to conduct meta-analyses of less common outcomes, such as

hepatitis B surface antigen (HBsAg) seroconversion or the incidence or progression of cirrhosis, since few RCTs reported such outcomes.

The analysis suggested that there was a substantial degree of heterogeneity in the effect of treatment on viral suppression. The observed heterogeneity may be due to factors that differed between studies, such as viral load, age, HBV genotype, ALT or the duration or mode of infection. In principle, such heterogeneity could be explored through meta-regression; however, the limited number of trials and relatively large number of treatments within the evidence network means that such analyses would have had limited power to detect the effect of covariates – particularly for variables that are not reported by all trials.

As with all meta-analyses, the subset of trials available for analysis may be affected by publication bias; however, this cannot be assessed at present, as methods for identifying publication bias in MTC have not yet been developed. Imputation of missing data helped to minimise bias by allowing us to include all potentially-relevant data in the analysis, although one limitation of the imputation methods we used is that they did not enable the uncertainty around imputed values to be taken into account in the MTC. Since missing data affects meta-analyses in all disease areas, further work is required to develop and make recommendations on the appropriate methods for imputing missing values in MTC.

The systematic review highlighted a paucity of studies evaluating nucleos(t)ide combinations. Since ADV+LAM and LdT+LAM are each supported by just one small RCT in HBeAg-positive nucleos(t)ide naïve patients, outcomes for these treatments must be interpreted with caution. Furthermore, there is a need for more studies on HBeAg-negative patients and for trials evaluating TDF and LdT in patients who are resistant to LAM or other nucleos(t)ides. Additional studies comparing treatments for HBeAg-positive treatment-naïve CHB would also enable future meta-analyses to provide more accurate estimates of treatment effects. We conducted further literature searches in March 2010 to identify whether any additional trials have been published since the search date for the systematic review (August 2007); these identified only two studies that would have met our inclusion criteria [58, 59], which are highly unlikely to have changed the conclusions of the analysis.

Based on the RCT evidence currently available, this analysis finds that among licensed nucleosides, TDF has the highest probability of achieving viral suppression at one year. In addition to short-term potency, it is necessary to take account of the drug resistance profile, incidence of HBsAg seroconversion, durability of response and cost of each treatment when deciding on the optimal treatment for CHB. The results of MTC can be readily used alongside information on these other factors within decision-analytical models that assess cost-effectiveness, since MTC allows the relative efficacy of multiple treatments to be evaluated in the same analysis and enables direct estimation of transition probabilities. The accompanying paper [17] uses the results of this meta-analysis and other evidence sources, taking into account differences in cost and resistance rates as well as long-term efficacy, and finds first-line TDF to be the most cost-effective treatment for CHB in a UK setting. The evidence on the efficacy, safety and cost-effectiveness of TDF has recently been reviewed by NICE, who have recommended TDF for use in England and Wales within its licence indication [60].

Conclusions

In conclusion, this meta-analysis demonstrates that in HBeAg-positive nucleos(t)ide-naïve patients, TDF has a higher probability of achieving undetectable HBV DNA at one year than any other nucleos(t)ide currently licensed for CHB in the UK. The probability of HBeAg seroconversion was not found to differ significantly between nucleos(t)ides. More trials on nucleos(t)ide combinations, HBeAg-negative CHB and patients resistant to one or more nucleos(t)ides are required to assess the benefits of combination therapy and evaluate relative efficacy in other populations.

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