Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B infection

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of tenofovir disoproxil fumarate for the treatment of chronic hepatitis B, in accordance with the licensed indication, based upon the evidence submission from Gilead to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submitted clinical evidence included two international randomised controlled trials (RCTs) comparing tenofovir with adefovir, and a mixed treatment comparison (MTC) using Bayesian methodology to compare tenofovir with other nucleos(t)ide analogues using direct and indirect RCT evidence. There were no statistically significant differences between tenofovir and adefovir in overall adverse events although, in hepatitis B 'e' antigen (HBeAg)-positive patients, there was a higher incidence of mild nausea in the tenofovir treatment group. The primary outcome, 'complete response', was a composite end point defined as histology response and hepatitis B virus DNA below 400 copies/ml. For both HBeAg-positive and HBeAg-negative patients, a significantly greater proportion had a complete response after 48 weeks with tenofovir than with adefovir. There was no statistically significant difference in histological response in either group of patients compared with adefovir. The MTC could only generate results for HBeAg positive nucleos(t)ide naive patients as there was insufficient evidence for other subgroups. The probability of achieving undetectable HBV DNA with tenofovir was found to be significantly higher than that for all other treatments considered in the analysis at the

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

0.05 level. The analysis demonstrated that there is a 98% probability that tenofovir is the most potent nucleos(t)ide in terms of this outcome. The manufacturer's submission concluded that tenofovir is a cost-effective option as first-line treatment. For HBeAg-positive patients, tenofovir followed by lamivudine has an incremental cost-effective ratio (ICER) of £9940 per quality-adjusted life-year (QALY) gained, compared with lamivudine followed by tenofovir. A more appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine has an ICER of £13,619 per QALY gained, compared with lamivudine followed by tenofovir. For HBeAg-negative patients, tenofovir followed by lamivudine has an ICER of £9811 per QALY gained, compared with best supportive care. A more clinically appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine has an ICER of £13,854 per QALY gained, compared with tenofovir followed by lamivudine. The ERG uncovered a number of errors in the submission and these ICERs approximately doubled when the analysis was corrected and reran. The guidance issued by NICE on 22 July 2009 states that tenofovir disoproxil, within its marketing authorisation is recommended as an option for the treatment of people with chronic HBe-Ag-positive or HBe-Ag-negative hepatitis B in whom antiviral treatment is indicated.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B'.[2]

Description of the underlying health problem

Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus (HBV). It is transmitted through blood-to-blood contact (e.g. through sharing of blood-contaminated needles by drug users) and sexual contact. It is also transmitted vertically from mother to infant, during or soon after birth. Infected individuals develop an acute infection, which may or may not result in symptoms. The majority of those infected during adulthood make a full recovery and acquire immunity from future infection. About only 2–10% of infected adults will develop chronic hepatitis B (CHB), defined as viraemia and hepatic inflammation that persists for more than 6 months after acute infection with HBV. In contrast, almost 100% of infected neonates and about 50% of infected young children will develop CHB if infected with HBV.

According to whether hepatitis B 'e' antigen (HBeAg) is secreted, active infection can be described as HBeAg-positive or HBeAg-negative. HBeAg is an indicator of viral replication, although some variant forms of the virus do not express HBeAg. The response to treatment and rates of progression differ between the two forms. People can be infected with the so-called HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form of the virus. Chronic infection with mutant strains of HBV that do not produce the 'e' antigen (that is, HBeAg-negative) is associated with a fluctuating course and a poor prognosis.

The Department of Health estimated that about 180,000 people in the UK had CHB in 2002, but recent data from the Hepatitis B Foundation estimated that approximately 326,000 people are currently infected in the UK. There are about 7700 new cases of CHB each year. Of these, around 300 people were infected within the UK; the remainder (mainly immigrants to the UK) were infected abroad.

The progression to cirrhosis occurs at an annual rate of 2–5.5%, with a cumulative 5-year rate of

progression of 8–20% in HBeAg-positive CHB and an annual rate of 8–10% in HBeAg-negative CHB.

Scope of the evidence review group report

The ERG critically evaluated the evidence submission from Gilead on the use of tenofovir for the treatment of CHB. Tenofovir has a marketing authorisation in the UK for the treatment of chronic HBV infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

The population considered in the scope was adults with active CHB according to the licensed indication. Patient subgroups included those with HBeAg-positive and HBeAg-negative CHB; and those who are treatment (nucleoside analogue) naive or refractory to lamivudine. Patients with co-infections (e.g. HIV) were excluded in accordance with the scope. The intervention was tenofovir alone or in combination with other therapies.

Comparators included lamivudine, adefovir dipivoxil, entecavir and telbivudine.

Outcomes included HBeAg/hepatitis B surface antigen (HbsAg) seroconversion rate, virological response (HBV DNA); histological improvement (liver inflammation and fibrosis); biochemical response (e.g. ALT levels); development of viral resistance; and adverse events. Outcomes included in the scope and decision problem, but not reported in the submission include time-to-treatment failure, survival and health-related quality of life.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG checked the literature searches and applied the NICE critical appraisal checklist to the included studies and checked the quality of the manufacturer's submission with the Centre for Reviews and Dissemination (CRD) quality assessment criteria for a systematic review. Searches were rerun in PubMed from August 2007 to 3 December 2008 and results screened for potentially relevant randomised controlled trials (RCTs) of tenofovir. In addition, the ERG checked and provided commentary on the manufacturer's model using standard checklists. The ERG conducted an amended base-case analysis, a one-way sensitivity analysis, a scenario analysis and a probabilistic sensitivity analysis to correct for errors in the manufacturer's economic model.

Results

Summary of submitted clinical evidence

The evidence in the manufacturer's submission comprised (i) a systematic review which included two international RCTs comparing tenofovir with adefovir,[3,4] and (ii) and a mixed treatment comparison (MTC) using Bayesian methodology to compare tenofovir with other nucleos(t)ide analogues using direct and indirect RCT evidence.

Two RCTs compared tenofovir with adefovir (one in HBeAg-positive patients, one in HBeAg-negative patients), and a third RCT compared tenofovir with tenofovir plus emtricitabine. The latter RCT was considered by the ERG to be beyond the scope of the appraisal and not considered further. The primary outcome, 'complete response', was a composite end point defined as histology response (greater than two-point Knodell necroinflammatory score without worsening in fibrosis) and HBV DNA below 400 copies/ml. For both HBeAg-positive and HBeAg-negative patients, a significantly greater proportion had a complete response after 48 weeks with tenofovir than with adefovir. There was no statistically significant difference in histological response in either group of patients compared with adefovir.

In both HBeAg-positive and HBeAg-negative patients, significantly more patients receiving tenofovir than adefovir had reductions in HBV DNA levels below 400, 300 and 169 copies/ml, and the mean reduction from baseline in plasma HBV DNA was significantly greater with tenofovir than adefovir. There were statistically significant differences between tenofovir and adefovir in ALT response (although no difference in the proportion of HBeAg-negative patients with normalised ALT levels at 48 weeks). A similar proportion of HBeAg-positive patients experienced HBeAg loss and seroconversion at week 48 in the tenofovir

and adefovir groups. No HBeAg-negative patients experienced HBsAg loss or seroconverted to anti-hepatitis B surface antibody (HBs) by week 48. Significantly more HBeAg-positive patients achieved HBsAg loss at 48 weeks with tenofovir than with adefovir. No cases of virologic HBV resistance have been identified.

There were no statistically significant differences between tenofovir and adefovir in overall adverse events in either group of patients although, in HBeAg-positive patients, there was a greater incidence of study drug-related adverse events with tenofovir. The manufacturer's submission attributes this to a higher incidence of mild nausea in the tenofovir treatment group. The most common adverse events were headache, nasopharyngitis, back pain, nausea, fatigue and abdominal pain.

An MTC was conducted on two outcomes: the probability of HBeAg seroconversion and the probability of achieving HBV DNA of less than 300 copies/ml after 1 year of treatment.

Of four subgroups considered, results could only be generated for HBeAg-positive nucleos(t)ide naive patients (13 RCTs). There was insufficient RCT evidence to construct an MTC for HBeAg-negative nucleos(t)ide naive patients, or HBeAg-positive or HBeAg-negative lamivudine refractory patients.

The probability of achieving undetectable HBV DNA with tenofovir was found to be significantly higher than that for all other comparators considered in the analysis at the 0.05 level. The analysis demonstrated that there is a 98% probability that tenofovir is the most potent nucleos(t)ide in terms of this outcome. All nucleos(t)ides were associated with a significantly higher chance of achieving undetectable HBV DNA than placebo. Tenofovir, entecavir and telbivudine were also found to be significantly superior to lamivudine at the 0.05 level.

All treatments other than telbivudine plus lamivudine in combination were found to significantly increase the probability of HBeAg seroconversion at 1 year relative to placebo at the 0.05 level. However, this analysis identified no statistically significant differences between the nucleos(t)ides for this outcome.

Summary of submitted cost-effectiveness evidence

The manufacturer's cost-effectiveness analysis adopted a Markov state transition model to estimate the incremental costs and consequences of a range of treatment strategies that include tenofovir and other antiviral drugs. Evidence on the efficacy of tenofovir, lamivudine, adefovir and entecavir (alone or in combination, when appropriate) in terms of reducing viral load and HBeAg seroconversion were taken from the MTC which also estimated baseline outcomes for best supportive care (BSC) (based on outcomes in the placebo arms of included RCTs). These outcomes are associated with reduced probability of progression to advanced liver disease and may also be associated with improved quality of life.

The model was used to simulate cohorts of patients with HBeAg-positive and HBeAg-negative CHB, at treatment initiation, separately. The model was structured to allow HBeAg-negative CHB to emerge in HBeAg-positive patients, following reactivation of disease in patients who had achieved HBeAg seroconversion. In all other respects the model was structurally similar to those adopted for previous economic evaluations, including that used in the previous NICE assessment of adefovir for the treatment of CHB.

The model adopted a lifetime horizon and was used to extrapolate lifetime costs and quality-adjusted life-years (QALYs) for patients treated with tenofovir (alone or in combination) and each of the included comparators. The analysis assumed that once patients develop resistance to their current antiviral drug, they will either switch to a new drug or add a new drug to their treatment. The model was used to evaluate single-agent and combination therapies adopted as first-, second- or third-line treatment, with BSC retained as the final treatment option for patients who have developed resistance to all antiviral agents available in each treatment strategy. Of the 211 treatment strategies evaluated (including BSC) cost-effective strategies were selected using the cost-effectiveness frontier and incremental cost-effectiveness ratios (ICERs) calculated against the next best alternative.

The manufacturer's submission concluded that tenofovir is a cost-effective option as first-line treatment. For HBeAg-positive patients, tenofovir followed by lamivudine has an ICER of £9940 per QALY gained, compared with lamivudine followed

by tenofovir. This implied switching treatments on development of resistance to first-line therapy, which is not supported by clinical guidelines as an appropriate clinical strategy. A more appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine had an ICER of £13,619 (incorrectly reported in the manufacturer's submission as £10,055 which is the ICER for tenofovir followed by tenofovir plus lamivudine, compared with lamivudine followed by tenofovir) per QALY gained, compared with lamivudine followed by tenofovir.

The manufacturer's submission reported that for HBeAg-negative patients, tenofovir followed by lamivudine had an ICER of £9811 per QALY gained, compared with BSC. A more clinically appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine had an ICER of £13,854 per QALY gained, compared with tenofovir followed by lamivudine.

In the ERG base-case analysis, amended to correct for errors in the manufacturer's model, these ICERs approximately doubled.

Commentary on the robustness of submitted evidence

Strengths

The two tenofovir RCTs were of good methodological quality and measured outcomes that are appropriate and clinically relevant, although health-related quality of life was not reported. The manufacturer's submission provided a detailed account of their procedures for the MTC, although much of this is reported in an academic-in-confidence appendix.

The economic model is structurally consistent with models adopted for previous economic evaluations. The manufacturer's submission reported that the structure of the model was discussed with clinicians with relevant expertise. The methods used to derive input data for the economic model are generally appropriate using published data that, for the MTC and pooled analysis of resistance, are clearly identified.

The model is appropriately structured to incorporate resistance to antiviral agents, and to maintain patients' history of resistance to agents within a given treatment strategy.

Weaknesses

The manufacturer's submission conducted a systematic search for clinical effectiveness and cost-effectiveness studies of tenofovir and comparator treatments for CHB. However, some of NICE's recommended databases were not searched, and the search is only current to August 2007. ERG replication of the searches (PubMed only) from August 2007 to December 2008 has not identified any additional tenofovir RCTs.

Whilst considered generally sound in terms of structure, the MTC suffers from certain limitations, including small numbers of studies/single studies in some networks, no quality assessment of the included studies and no discussion of potential clinical heterogeneity.

The ERG uncovered a number of errors in the submission. These include transcription errors (from the model into the written submission) and errors in calculations in the model. Where possible the ERG has corrected them and rerun the analyses. However, some of the errors would require substantial rewriting of the model. The ERG has attempted to identify where errors are likely to bias the outcome of the evaluation.

The reporting of pre-model analyses is poor, particularly in terms of searching for and critical appraisal of studies used to estimate parameter inputs. In many cases, very limited information is provided on studies contributing data to key input parameters in the model. There is generally little evidence of systematic searches for data to estimate parameters, and no critical appraisal of the scope, quality or appropriateness of included studies.

Conclusions

Tenofovir is one of a growing number of treatment options for patients with CHB. The manufacturer has provided a reasonably sound assessment of its clinical effectiveness based on two pivotal RCTs in HBeAg-positive and -negative nucleos(t)ide naive patients, albeit with some limitations.

Tenofovir was statistically significantly superior to adefovir for the primary composite outcome of HBV DNA response (400 copies/ml) and histological response. There were also statistically significant differences between the two drugs in

terms of secondary outcomes HBV DNA response (400 copies/ml) and ALT (HBeAg-positive patients only). However, there were no statistically significant differences for histology and HBeAg seroconversion. Tenofovir was generally well tolerated and adverse effects were generally similar to adefovir.

Clinical effectiveness data beyond 1 year are observational and should be interpreted with caution.

Tenofovir appears to have a favourable resistance profile based on limited data currently available. Whether this will be maintained with long-term treatment is yet to be established. These data will be important to guide decisions as to whether to initiate treatment with monotherapy or combination therapy. If resistance in the long-term is low, clinicians may decide to initiate treatment with tenofovir monotherapy, thus reserving other nucleos(t)ides as future treatment options if necessary. If resistance to tenofovir monotherapy is likely to be high then a clinically plausible combination of nucleos(t)ides (e.g. lamivudine and tenofovir) may be preferable in order to suppress the selection of resistant strains. However, there is currently a lack of RCT data for the clinical effectiveness of tenofovir in combination with other nucleos(t)ides.

There is a lack of head-to-head RCTs comparing tenofovir with other nucleos(t)ides, necessitating the production of an MTC. The results suggest that tenofovir has the highest probability of HBV DNA lower than 300 copies/ml response at 1 year of treatment. There were no statistically significant differences between the nucleos(t)ides in terms of HBeAg seroconversion.

The MTC is subject to certain methodological limitations, and it was not possible to conduct one for HBeAg-negative nucleos(t)ide naive patients, or lamivudine refractory patients.

The methods adopted for the economic evaluation were reasonable and generally appropriate. The model structure was consistent with previous economic evaluations. It was appropriately structured to incorporate resistance to antiviral agents and maintain a history of patients developing resistance to agents included in the treatment strategy. However, the reporting of pre-model analyses used to estimate parameter inputs was poor, with limited information on studies contributing data to key input parameters in the model, no evidence of systematic searches for data to estimate parameters and no critical appraisal of the scope, quality or appropriateness of included studies.

A number of errors were detected in the submission, including a serious error in the way in which QALY outcomes were discounted in the electronic model, which affected the deterministic (base-case and sensitivity/scenario analyses) and the probabilistic analyses. When possible, corrected analyses were presented by the ERG. Once the identified errors had been corrected and more appropriate estimates of uncertainty had been incorporated in the analysis, the ERG felt the model provided a reasonable characterisation of the cost-effectiveness of treatment strategies containing tenofovir, in the treatment of CHB.

Areas of uncertainty

There is a lack of head-to-head RCT evidence for the clinical effectiveness of tenofovir compared to other nucleos(t)ides. It was only possible to construct an MTC, taking into account direct and indirect RCT evidence, for HBeAg-positive treatment naive patients.

Key issues

Tenofovir monotherapy has a favourable resistance profile, based on currently available evidence. Long-term resistance data are awaited, and when available will guide decisions regarding whether monotherapy or combination therapy should be given. Further RCT data on the clinical effectiveness of nucleos(t)ide combination therapy are needed to support such decisions.

Summary of NICE guidance issued as a result of the STA

The NICE Appraisal Committee met on 11 February 2009 to discuss this topic. The guidance issued by NICE on 22 July 2009 states that:

Tenofovir disproxil, within its marketing authorisation is recommended as an option for the treatment of people with chronic HBe-Ag-positive or HBe-Ag-negative hepatitis B in whom antiviral treatment is indicated.

Key references

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