北海道大学血液内科，国立病院機構北海道がんセンター血液内科，旭川医科大学消化器・血液腫瘍制御内科，岩手医科大学血液・腫瘍内科，秋田大学第三内科，自治医科大学同血液内科，群馬大学血液内科・腫瘍センター，筑波大学血液内科，埼玉医科大学病院血液内科，埼玉医科大学国際医療センター造血器腫瘍科，埼玉医科大学総合医療センター血液内科，防衛医科大学血液内科，埼玉県立がんセンター血液内科，独協医科大学越谷病院血液内科，日本医科大学血液内科，昭和大学血液内科，東京医科大学血液内科，東京女子医科大学血液内科，武蔵野赤十字病院血液・腫瘍内科，都立駒込病院同血液内科，東京電力病院内科，東京慈恵会医科大学第三病院腫瘍・血液内科，多摩北部医療センター血液内科，国立がんセンター東病院化学療法科，千葉県立がんセンター腫瘍・血液内科，NTT東日本関東病院血液内科，北里大学血液内科，神奈川県立がんセンター化学療法科，浜松医科大学血液内科，名古屋大学血液・腫瘍科，名古屋市立大学血液・腫瘍内科，愛知医科大学血液内科，名古屋市立東部医療センター東市民病院血液内科，愛知県厚生農業協同組合連合会江南厚生病院血液・腫瘍内科，三重大学血液・腫瘍科，福井大学血液・腫瘍内科，滋賀県立成人病センター血液・腫瘍科，愛媛大学第一内科，国立病院機構九州がんセンター血液内科，佐賀大学血液・呼吸器・腫瘍内科，国立病院機構長崎医療センター血液内科，佐世保市立総合病院内科，国立病院機構熊本医療センター血液内科，熊本大学血液内科，鹿児島大学血液・膠原病内科

これらのうち，平成21年度3月末までに倫理委員会の承認が得られたのは以下の 27 診療科である。

旭川医科大学消化器・血液腫瘍制御内科，岩手医科大学血液・腫瘍内科，秋田大学第三内科，自治医科大学血液科，群馬大学血液内科，筑波大学血液内科，埼玉医科大学病院血液内科，埼玉医科大学国際医療センター造血器腫瘍科，埼玉医科大学総合医療センター血液内科，埼玉県立がんセンター血液内科，独協医科大学越谷病院血液内科，日本医科大学血液内科，武蔵野赤十字病院血液・腫瘍内科，都立駒込病院血液内科，東京電力病院内科，名古屋市立大学血液・腫瘍内科，愛知県厚生農業協同組合連合会江南厚生病院血液・腫瘍内科，国立病院機構九州がんセンター血液内科，佐賀大学血液・呼吸器・腫瘍内科，佐世保市立総合病院内科，鹿児島大学血液・膠原病内科，NTT東日本関東病院血液内科，獨協医科大学越谷病院内科，滋賀県立成人病センター血液・腫瘍内科，三重大学血液内科，福井大学血液・腫瘍内科，長崎大学第一内科，熊本大学血液内科

これら施設において，平成21年1月以降はキャリア例および既往感染例の登録が開始されている。また，平成22年3月1日には第2回目の班会議において，研究協力者も含めて症例登録の適正化，促進を図った。

D. 考察と結語

リツキシマブ以外の免疫抑制・化学療法を実施したHBVキャリアおよび既往感染例を対象に，HBV再活性化，肝炎発症の実態をprospectiveに検討する研究組織を確立した。本研究の成果に基づいてHBV-DNAを測定する症例を絞り込み，血液領域における新たなガイドラインを確立することを目指す。

E. 健康危惧情報

なし。

F. 研究発表

なし

厚生労働省科学研究費補助金（肝炎等克服緊急対策研究事業）
分担研究報告書

「免疫抑制薬，抗悪性腫瘍薬によるＢ型肝炎ウイルス再活性化の実態解明と対策法の確立」

研究分担者：鈴木　洋通
埼玉医科大学 腎臓内科 教授

研究分担者：浦　信行
手稲渓仁会病院　総合内科 部長

研究要旨：厚労科研費補助金「坪内班」と「熊田班」が合同で作成した「免疫抑制・化学療法により発症するB型肝炎対策」は，HBV再活性化の高リスク群であるリツキシマブ使用例以外でも，免役抑制薬，抗悪性腫瘍薬を投与する際には血清HBV-DNAを毎月測定することを推奨している。しかし，わが国におけるHBV既往感染例の頻度を考慮すると，これによる医療経済上の負担は莫大であり，HBV-DNAを測定する症例を絞り込むことが求められる。そこで，HBVの既往感染例およびキャリア例を対象に，リツキシマブ以外の免疫抑制・化学療法を実施した際の，HBV再活性化，肝炎発症の実態を明らかにし，ガイドラインを検証することを目的とした prospectiveな検討を開始した。平成21年度は腎臓領域における研究組織を確立し，検討の対象とする症例，治療法を決定した。平成21年度末までに 2 診療科が倫理委員会に申請を終了し，2 診療科で承認を得て，症例の登録を順次開始している。平成22年末までに既往感染150例，キャリア15例を登録し，治療終了1年後までの経過を追うことで，再活性化の頻度と治療法との関連を解析する予定である。

研究分担者：

楠本　茂	名古屋市立大学	助教
井戸 章雄	鹿児島大学	准教授
池田 健次	虎の門病院	部長

研究協力者（事務局）：

名越　澄子	埼玉医科大学	教授
中山　伸朗	埼玉医科大学	講師

A. 背景と目的

悪性リンパ腫の治療でリツキシマブと副腎皮質ステロイドを HBV 既往感染例に投与すると，ウイルス再活性化が生じて重症肝炎を発症する場合がある。その対策として厚労科研「坪内班」，「熊田班」はガイドラインを発表したが，これはリツキシマブ以外の免疫抑制薬，抗悪性腫瘍薬による治療も対象としているものの，その意義は不明である。そこで，本研究では腎臓領域で免疫抑制療法を実施する既往感染，キャリア例を対象に再活性化の実態を prospective に解明することを目指す。

B. 研究方法

平成 21 年度は腎臓領域の研究協力者による組織を確立し，対象となる症例，治療法の範囲を確定する。研究代表者，事務局の研究分担者および

4 領域の研究分担者の協議で症例の登録方法，検体の回収システム，個人情報の管理システムを確定した上で，研究協力者を含む全施設で倫理委員会に申請する。その承認を得た上で，平成 21 年度中に準じ症例の登録を開始する。症例の登録は平成 22 年度にも継続し，平成 22 年度および平成 23 年度は追跡期間とする。

C. 研究結果

(1) 腎臓領域における適応となる疾患および治療法

平成21年6月21日に開催した第1回班会議において，事務局の担当の研究分担者の合意を得て，以下のように確定した。なお，免疫抑制・化学療法に関しては，未治療例を原則とするが，再発例も当該治療が初回の場合は対象とする*。

<全診療科に共通する治療法>

副腎皮質ステロイド単独療法：プレドニゾロン換算で 0.5 mg/kg以上を2週間以上にわたって投与する症例。

＜腎臓領域＞

微小変化型ネフローゼ症候群，膜性腎症，巣状分節性糸球体硬化症，膜性増殖性糸球体腎炎，IgA 腎症，急速進行性糸球体腎炎（MPO-ANCA関連腎炎）及びその他の腎疾患（膠原病など）で副腎皮質ステロイド薬 and/or シクロスポリン，ミゾリビン，エンドキサンなどを投与する症例

(2) 研究組織の確立と倫理員会の申請，承認

第 1 回班会議において，血液およびリウマチ膠原病領域で倫理委員会の承認を得た施設の関連診療科に研究協力者として依頼することが決定した。平成21年度3月末までに倫理委員会の承認が得られて協力研究者となったのは以下の 2 診療科である。

手稲渓仁会病院総合内科，埼玉医科大学病院腎臓内科

これら施設において，平成 21 年 1 月以降はキャリア例および既往感染例の登録が開始されている。また，平成 22 年 3 月 1 日には第 2 回目の班会議において，研究協力者も含めて症例登録の適正化，促進を図った。

D. 考察と結語

リツキシマブ以外の免疫抑制・化学療法を実施した HBV キャリアおよび既往感染例を対象に，HBV 再活性化，肝炎発症の実態を prospective に検討する研究組織を確立した。本研究の成果に基づいて HBV-DNA を測定する症例を絞り込み，腎臓領域における新たなガイドラインを確立することを目指す。

E. 健康危惧情報

なし。

F. 研究発表

なし

厚生労働省科学研究費補助金（肝炎等克服緊急対策研究事業）
分担研究報告書

「免疫抑制薬，抗悪性腫瘍薬によるB型肝炎ウイルス再活性化の実態解明と対策法の確立」

研究分担者：三村　俊英
埼玉医科大学 リウマチ・膠原病科 教授

研究分担者：山本　一彦
東京大学 アレルギーリウマチ学 教授

研究要旨：厚労科研費補助金「坪内班」と「熊田班」が合同で作成した「免疫抑制・化学療法により発症するB型肝炎対策」は，HBV再活性化の高リスク群であるリツキシマブ使用例以外でも，免役抑制薬，抗悪性腫瘍薬を投与する際には血清HBV-DNAを毎月測定することを推奨している。しかし，わが国におけるHBV既往感染例の頻度を考慮すると，これによる医療経済上の負担は莫大であり，HBV-DNAを測定する症例を絞り込むことが求められる。そこで，HBVの既往感染例およびキャリア例を対象に，リツキシマブ以外の免疫抑制・化学療法を実施した際の，HBV再活性化，肝炎発症の実態を明らかにし，ガイドラインを検証することを目的とした prospectiveな検討を開始した。平成21年度はリウマチ・膠原病領域における研究組織を確立し，検討の対象とする症例，治療法を決定した。平成21年度末までに15診療科が倫理委員会に申請を終了し，9 診療科で承認を得て，症例の登録を順次開始している。平成22年末までに既往感染150例，キャリア15例を登録し，治療終了1年後までの経過を追うことで，再活性化の頻度と治療法との関連を解析する予定である。

研究分担者：

楠本　茂	名古屋市立大学	助教
井戸 章雄	鹿児島大学	准教授
池田 健次	虎の門病院	部長

研究協力者（事務局）：

名越　澄子	埼玉医科大学	教授
中山　伸朗	埼玉医科大学	講師

A. 背景と目的

悪性リンパ腫の治療でリツキシマブと副腎皮質ステロイドを HBV 既往感染例に投与すると，ウイルス再活性化が生じて重症肝炎を発症する場合がある。その対策として厚労科研「坪内班」，「熊田班」はガイドラインを発表したが，これはリツキシマブ以外の免疫抑制薬，抗悪性腫瘍薬による治療も対象としているものの，その意義は不明である。そこで，本研究ではリウマチ・膠原病領域で免疫抑制療法を実施する既往感染，キャリア例を対象に再活性化の実態を prospective に解明することを目指す。

B. 研究方法

平成 21 年度はリウマチ・膠原病領域の研究協力者による組織を確立し，対象となる症例，治療法の範囲を確定する。研究代表者，事務局の研究

分担者および4領域の研究分担者の協議で症例の登録方法，検体の回収システム，個人情報の管理システムを確定した上で，研究協力者を含む全施設で倫理委員会に申請する。その承認を得た上で，平成 21 年度中に準じ症例の登録を開始する。症例の登録は平成 22 年度にも継続し，平成 22 年度および平成 23 年度は追跡期間とする。

C. 研究結果

(1) リウマチ・膠原病領域における適応となる疾患および治療法

平成21年6月21日に開催した第1回班会議において，事務局の担当の研究分担者の合意を得て，以下のように確定した。なお，免疫抑制・化学療法に関しては，未治療例を原則とするが，再発例も当該治療が初回の場合は対象とする*。

<全診療科に共通する治療法>

副腎皮質ステロイド単独療法：プレドニゾロン換算で 0.5 mg/kg以上を2週間以上にわたって投与する症例。

<リウマチ・膠原病領域>

関節リウマチ，膠原病，膠原病類縁疾患，血管炎症候群，その他免疫抑制療法を必要とする疾患で，中等量以上の副腎皮質ステロイド，免疫抑制薬（関節リウマチに対するメトトレキサート治療を含む），抗リウマチ生物製剤（infliximab，etanercept，tocilizumab，adalimumab）を投与する症例

(2) 研究組織の確立と倫理員会の申請，承認

第 1 回班会議において，血液領域は 12 施設に，研究協力者として依頼することが決定した。先ず，これらの施設で平成21年7月末から倫理委員会の申請を開始した。平成 21 年度末までに倫理委員会の申請作業を実施しているのは以下の 15 診療科である。

北海道大学リウマチ・膠原病内科，自治医科大学リウマチ・膠原病内科，群馬大学リウマチ・膠原病内科，筑波大学リウマチ・膠原病内科，埼玉医科大学病院リウマチ・膠原病科，東京大学アレルギー・リウマチ科，東京医科歯科大学リウマチ・膠原病内科，慶応義塾大学リウマチ・膠原病内科，杏林大学リウマチ・膠原病内科，藤田保健大学リウマチ・膠原病内科，京都大学リウマチ・膠原病内科，神戸大学リウマチ・膠原病内科，産業医科大学リウマチ・膠原病内科，長崎大学リウマチ・膠原病内科，鹿児島大学血液・膠原病内科

これらのうち，平成 21 年度 3 月末までに倫理委員会の承認が得られたのは以下の 9 診療科である。

自治医科大学リウマチ・膠原病科，群馬大学リウマチ・膠原病内科，筑波大学膠原病リウマチアレルギー内科，埼玉医科大学リウマチ・膠原病科，東京医科歯科大学膠原病・リウマチ内科，神戸大学リウマチ科，産業医科大学膠原病リウマチ内科，鹿児島大学血液・膠原病内科，京都大学免疫・膠原病内科

これら施設において，平成 21 年 1 月以降はキャリア例および既往感染例の登録が開始されている。また，平成 22 年 3 月 1 日には第 2 回目の班会議において，研究協力者も含めて症例登録の適正化，促進を図った。

D. 考察と結語

リツキシマブ以外の免疫抑制・化学療法を実施した HBV キャリアおよび既往感染例を対象に，HBV 再活性化，肝炎発症の実態を prospective に検討する研究組織を確立した。本研究の成果に基づいて HBV-DNA を測定する症例を絞り込み，リウマチ・膠原病領域における新たなガイドラインを

確立することを目指す。

E. 健康危惧情報

なし。

F. 研究発表

なし

厚生労働省科学研究費補助金（肝炎等克服緊急対策研究事業）
分担研究報告書

「免疫抑制薬，抗悪性腫瘍薬によるＢ型肝炎ウイルス再活性化の実態解明と対策法の確立」

研究分担者：佐々木　康綱
埼玉医科大学国際医療センター　腫瘍内科 教授

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研究要旨：厚労科研費補助金「坪内班」と「熊田班」が合同で作成した「免疫抑制・化学療法により発症するB型肝炎対策」は，HBV再活性化の高リスク群であるリツキシマブ使用例以外でも，免役抑制薬，抗悪性腫瘍薬を投与する際には血清HBV-DNAを毎月測定することを推奨している。しかし，わが国におけるHBV既往感染例の頻度を考慮すると，これによる医療経済上の負担は莫大であり，HBV-DNAを測定する症例を絞り込むことが求められる。そこで，HBVの既往感染例およびキャリア例を対象に，リツキシマブ以外の免疫抑制・化学療法を実施した際の，HBV再活性化，肝炎発症の実態を明らかにし，ガイドラインを検証することを目的とした prospectiveな検討を開始した。平成21年度は腫瘍内科領域における研究組織を確立し，検討の対象とする症例，治療法を決定した。平成21年度末までに21診療科が倫理委員会に申請を終了し，13診療科で承認を得て，症例の登録を順次開始している。平成22年末までに既往感染150例，キャリア15例を登録し，治療終了1年後までの経過を追うことで，再活性化の頻度と治療法との関連を解析する予定である。

研究分担者：

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井戸 章雄	鹿児島大学	准教授
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研究協力者（事務局）：

名越　澄子	埼玉医科大学	教授
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A. 背景と目的

悪性リンパ腫の治療でリツキシマブと副腎皮質ステロイドを HBV 既往感染例に投与すると，ウイルス再活性化が生じて重症肝炎を発症する場合がある。その対策として厚労科研「坪内班」，「熊田班」はガイドラインを発表したが，これはリツキシマブ以外の免疫抑制薬，抗悪性腫瘍薬による治療も対象としているものの，その意義は不明である。そこで，本研究では腫瘍内科領域で化学療法を実施する既往感染，キャリア例を対象に再活性化の実態を prospective に解明することを目指す。

B. 研究方法

平成 21 年度は腫瘍内科領域の研究協力者による組織を確立し，対象となる症例，治療法の範囲を確定する。研究代表者，事務局の研究分担者お

よび4領域の研究分担者の協議で症例の登録方法，検体の回収システム，個人情報の管理システムを確定した上で，研究協力者を含む全施設で倫理委員会に申請する。その承認を得た上で，平成 21 年度中に準じ症例の登録を開始する。症例の登録は平成 22 年度にも継続し，平成 22 年度および平成 23 年度は追跡期間とする。

C. 研究結果

(1) 腫瘍内科領域における適応となる疾患および治療法

平成21年6月21日に開催した第1回班会議において，事務局の担当の研究分担者の合意を得て，以下のように確定した。なお，免疫抑制・化学療法に関しては，未治療例を原則とするが，再発例も当該治療が初回の場合は対象とする*。

<全診療科に共通する治療法>

副腎皮質ステロイド単独療法：プレドニゾロン換算で 0.5 mg/kg以上を2週間以上にわたって投与する症例。

<腫瘍内科領域>

悪性腫瘍で以下のプロトコールによる化学療法を実施する患者。

1. PaclitaxelとDocetaxelを含むregimen
2. Fluorouracilの経静脈投与を含むregimen
3. S1，S2とCisplatinまたはCapecitabin
4. Anthracycline系抗悪性腫瘍薬を含むregimen
5. Platiumを含むregimen

	対象とする	対象としない
頭頸部癌	化学放射線療法と化学療法	経口抗がん剤による化学療法
乳癌	標準的な化学療法	内分泌療法、ハーセプチン療法単独
肺癌	標準的な化学療法	分子標的薬による薬物療法
食道癌	標準的な化学療法、化学放射線療法	
胃癌	標準的な化学療法	経口抗がん剤単独での化学療法
膵癌	標準的な化学療法	経口抗がん剤単独での化学療法
大腸癌	標準的な化学療法	経口抗がん剤単独での化学療法
胚細胞腫	標準的な化学療法	

(1) 研究組織の確立と倫理員会の申請，承認

第 1 回班会議において，腫瘍内科領域は血液領域は研究協力者を依頼した 42 施設の該当診療科に依頼することが決定した。平成 21 年度末までに倫理委員会の申請作業を実施しているのは以下の 21 診療科である。

旭川医科大学消化器・血液腫瘍制御内科，岩手医科大学血液・腫瘍内科，自治医科大学臨床腫瘍科，群馬大学血液内科・腫瘍センター，埼玉医科大学国際医療センター腫瘍内科，同造血器腫瘍科，武蔵野赤十字病院血液・腫瘍内科，都立駒込病院腫瘍内科，同肝臓内科，東京慈恵会医科大学第三病院腫瘍・血液内科、国立がんセンター東病院化学療法科，千葉県立がんセンター腫瘍・血液内科，神奈川県立がんセンター化学療法科，浜松大学腫瘍センター，名古屋大学血液・腫瘍科，名古屋市立大学血液・腫瘍内科，愛知県厚生農業協同組合連合会江南厚生病院血液・腫瘍内科，三重大学血液・腫瘍科，福井大学血液・腫瘍内科，滋賀県立成人病センター血液・腫瘍科，佐賀大学血液・呼吸器・腫瘍内科

これらのうち平成 21 年度 3 月末までに倫理委員会の承認が得られたのは以下の 13 診療科である。

旭川医科大学消化器・血液腫瘍制御内科，岩手医科大学血液・腫瘍内科，自治医科大学臨床腫瘍科，群馬大学血液・腫瘍センター，埼玉医科大学国際医療センター腫瘍内科，武蔵野赤十字病院血液・腫瘍内科，都立駒込病院化学療法科，同肝臓内科，名古屋市立大学血液・腫瘍内科，愛知県厚生農業協同組合連合会江南厚生病院血液・腫瘍内科，佐賀大学血液・呼吸器・腫瘍内科，滋賀県立成人病センター血液・腫瘍内科，福井大学血液・腫瘍内科

これら施設において，平成21年1月以降はキャリア例および既往感染例の登録が開始されている。また，平成22年3月1日には第2回目の班会議において，研究協力者も含めて症例登録の適正化，促進を図った。

D. 考察と結語

リツキシマブ以外の化学療法を実施したHBVキャリアおよび既往感染例を対象に，HBV再活性化，肝炎発症の実態をprospectiveに検討する研究組織を確立した。本研究の成果に基づいてHBV-DNAを測定する症例を絞り込み，腫瘍内科領域における新たなガイドラインを確立することを目指す。

E. 健康危惧情報

なし。

F. 研究発表

なし

III. 研究成果の刊行に関する一覧表

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ORIGINAL ARTICLE

Antiviral activity, dose–response relationship, and safety of entecavir following 24-week oral dosing in nucleoside-naive Japanese adult patients with chronic hepatitis B: a randomized, double-blind, phase II clinical trial

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Abstract

Purpose A randomized, double-blind, multicenter study (ETV-047) was conducted to evaluate the dose–response relationship of entecavir and compare its antiviral activity and safety with lamivudine in Japanese patients with chronic hepatitis B (CHB).

Methods One hundred thirty-seven nucleoside-naive adult patients with CHB were randomized to once-daily oral doses of entecavir 0.01, 0.1, or 0.5 mg or lamivudine 100 mg for 24 weeks. The primary efficacy end point used to evaluate the dose–response relationship was mean change from baseline in serum hepatitis B virus (HBV) DNA level at week 22, as determined by polymerase chain reaction assay.

Results Entecavir demonstrated a clear dose–response relationship, with mean change from baseline in serum

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HBV DNA level of −3.11, −4.77, and −5.16 $\log_{10}$ copies/ml with entecavir 0.01, 0.1, and 0.5 mg, respectively. Entecavir 0.5 mg was superior to lamivudine 100 mg for the mean change in HBV DNA level (−5.16 vs. −4.29 $\log_{10}$ copies/ml; $P = 0.007$). The overall incidence of adverse events was comparable between treatment groups. Two patients discontinued treatment because of adverse events (one with liver cirrhosis [entecavir 0.5 mg] and one with grade 4 serum alanine aminotransferase (ALT) elevation, nausea, and malaise [lamivudine 100 mg]). Serum ALT flares were observed in four patients; flares were associated with 2 $\log_{10}$ reductions or more in HBV DNA level and resolved without dose interruption.

Conclusion Entecavir 0.01–0.5 mg is well tolerated and produces a dose-dependent reduction in viral load in nucleoside-naive Japanese patients with CHB. Compared with lamivudine 100 mg, entecavir 0.1 mg demonstrated noninferiority and entecavir 0.5 mg was superior in this population.

Keywords Chronic hepatitis B · Entecavir · Lamivudine · HBV DNA · ALT flare

Introduction

It is reported that more than 2 billion individuals worldwide have been infected with hepatitis B virus (HBV) and approximately 350 million people are long-term HBV carriers [1]. Chronic hepatitis B (CHB) is induced by chronic replication of HBV in the liver and has a poor prognosis, with 20–40% of infected individuals developing liver cirrhosis, noncompensated liver disorder, or hepatocellular carcinoma [2]. Treatment of CHB is aimed at sustained inhibition of HBV replication and remission of liver disease [3], ultimately preventing progression to liver cirrhosis or hepatocellular carcinoma [4].

Prior to the advent of the nucleoside analog lamivudine, interferon-α formed the mainstay of treatment, but this immunoregulatory cytokine requires parenteral administration and is poorly tolerated [5]. Lamivudine is well tolerated on oral administration and has been proven to be highly effective in the treatment of CHB, but the emergence of resistance mutations (including the YMDD motif) in the reverse-transcriptase domain of HBV polymerase frequently results in overt viral rebound and disease progression [6–9]. The novel nucleoside analog adefovir is effective against wild-type HBV and lamivudine-resistant strains and is well tolerated on long-term administration, but its clinical use is restricted by the need for renal monitoring in patients with impaired renal function [10].

Entecavir, a cyclopentylguanine-derived nucleoside analog and selective inhibitor of HBV replication, was approved by the U.S. Food and Drug Administration in 2005 for the treatment of CHB. Entecavir displays potent antiviral activity in the woodchuck and duck models of HBV infection [11, 12] and is reported to be 100- to 2,200-fold more potent than lamivudine and adefovir in inhibiting HBV replication in vitro [13, 14]. Phase II clinical trials of entecavir conducted in non-Japanese patients with CHB have demonstrated entecavir to be well tolerated and more effective than lamivudine [15, 16].

A global dose-finding study (ETV-005) conducted in lamivudine-naive patients with CHB compared three doses of entecavir (0.01, 0.1, and 0.5 mg once daily) with lamivudine 100 mg once daily over a 22-week treatment period. Entecavir showed a clear dose–response relationship and was well tolerated at all three dose levels; in addition, 0.1 and 0.5 mg of entecavir showed superior antiviral activity compared with 100 mg of lamivudine [15].

Phase I studies of single-dose (0.05–2.5 mg) and multiple-dose (0.1–1.0 mg daily) entecavir conducted in Japan have confirmed the drug's safety in healthy men. As in Caucasian populations, entecavir displayed linear plasma pharmacokinetics over a wide range of doses, including putative therapeutic doses (0.5 and 1.0 mg), in Japanese subjects; there was no evidence of significant ethnic differences in its pharmacokinetics and pharmacodynamics. Similar findings to those obtained in the global phase II clinical trials of entecavir might therefore be expected from corresponding studies conducted in Japanese patients.

To evaluate the dose–response relationship, the antiviral activity and safety of entecavir in Japanese CHB patients, we conducted a 24-week phase II study comparing entecavir (0.01, 0.1, and 0.5 mg daily) to lamivudine (100 mg daily).

Materials and methods

Study design

This randomized, double-blind, double-dummy study was conducted at 38 institutions in Japan from August 2003 to March 2005. Eligible patients comprised 20- to 75-year-old men and women with CHB who fulfilled the following criteria: (i) HBsAg-positive for 24 weeks or more or IgM HBcAb-negative with biopsy-confirmed CHB; (ii) HBeAg-positive or HBeAg-negative for 12 weeks or more; (iii) serum HBV DNA level 40 MEq/ml or more (143 pg/ml) by Quantiplex™ branched DNA hybridization method (bDNA assay) ($\geq$7.6 $\log_{10}$ genome equivalent by the transcription-mediated amplification method or $\geq 10^{7.6}$ copies/ml by Roche Amplicor™ polymerase chain reaction method [PCR assay]) measured 2 weeks or more before screening and serum HBV DNA level 40 MEq/ml or more (by bDNA assay) at screening; (iv) serum alanine

aminotransferase (ALT) level 1.25–10 times the upper limit of normal (ULN); and (v) well-compensated liver disease with prothrombin time prolongation 3 s or less or international normalized ratio 1.5 or less, serum albumin level 3.0 g/dl or more, and total bilirubin 2.5 mg/dl or less (42.75 μmol/l). After a 6-week screening period, eligible patients were stratified according to HBeAg status and study site and randomized (1:1:1:1) to oral treatment with entecavir (0.01, 0.1, or 0.5 mg plus matching placebo capsule) or lamivudine (100 mg plus matching placebo tablet) once daily for 24 weeks. All doses were administered at fixed times of the day, avoiding the 2 h before and after meals. Pregnant women were excluded from the study, as were patients with liver cirrhosis, patients with a history or evidence of variceal bleeding, patients with hepatic encephalopathy or ascites requiring diuretics, or patients with paracentesis. Patients with other liver disease (e.g., autoimmune hepatitis) were excluded from the study. In addition, patients were excluded if they had a serum creatinine level more than 1.5 × ULN, hemoglobin level less than 10.0 g/dl, platelet count less than 70,000/mm^3, granulocyte count less than <1,500/mm^3 or plasma α-fetoprotein level more than 100 ng/ml, a history of allergy induced by nucleoside analog or exposure to nucleoside analogs, a recent history (previous 24 weeks) of treatment with immunosuppressives or interferon-α/β, or current treatment of CHB.

Treatment efficacy was assessed after 22 weeks, and all eligible patients who completed 24 weeks of blinded therapy were given the option of enrolling in a separate entecavir trial. Patients who discontinued therapy prematurely were followed up for 24 weeks postdosing. Patients began anti-HBV therapy as recommended by their physician during the postdosing follow-up period.

Informed consent was obtained from all patients in writing prior to their inclusion in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and notifications were issued by the Ministry of Health and Labor.

Efficacy and safety assessment

The primary efficacy end point for the evaluation of the dose–response relationship of entecavir was the change from baseline in mean serum HBV DNA level at week 22, as determined by PCR assay. Secondary efficacy end points for the assessment of the noninferiority of entecavir at each dose to lamivudine included the change from baseline in mean serum HBV DNA level at week 22, as determined by PCR assay, the percentage of patients with a reduction in serum HBV DNA level 2 $\log_{10}$ copies/ml or more or a serum HBV DNA level below the limit of detection (400 copies/ml by PCR assay; 2.5 pg/ml or 0.7 MEq/ml by bDNA assay) at week 22, the percentage of patients with HBeAg loss, the percentage of patients with HBeAg seroconversion (HBeAg loss and appearance of HBe-antibody), the percentage of patients achieving ALT normalization (World Health Organization grade 0: <1.25 × ULN), and the percentage of patients achieving a protocol-defined response (HBV DNA level <0.7 MEq/ml by bDNA assay, HBeAg negativity and serum ALT level <1.25 × ULN for HBeAg-positive patients; HBV DNA level <0.7 MEq/ml by bDNA assay and serum ALT level <1.25 ULN for HBeAg-negative patients) at week 22. The incidence of genotypic drug resistance was also assessed in patients who had a 1 $\log_{10}$ copies/ml or more increase in HBV DNA by PCR from nadir while on study drug.

Based on the results of the global dose–response study of entecavir conducted in nucleoside-naive patients (ETV-005 study) [15], noninferiority of entecavir 0.1 or 0.5 mg compared with lamivudine (100 mg) was confirmed if the upper 95% confidence interval (CI) for the difference in mean HBV DNA levels at week 22 was 0.8 $\log_{10}$ copies/ml or less.

Assay methods

Serum HBV DNA level was determined by Roche Amplicor™ PCR assay (Roche Diagnostics K.K., Tokyo, Japan) and Quantiplex™ (Chiron) bDNA assay. Clinical laboratory tests, serum HBV DNA assays, and HBV serology were performed at the central clinical laboratory designated by the trial sponsor. Genotypic analysis of HBV isolates was performed using samples collected from patients on the first day of treatment. Genotypic analysis of HBV DNA polymerase was performed at SRL Inc. (Tokyo, Japan).

Statistical analysis

Numerical data were expressed by descriptive statistics. Serum HBV DNA level, a continuous variable, was analyzed after logarithmic transformation. For treatment group, comparisons of continuous variables, analysis of variance models, incorporating baseline HBV DNA level and HBeAg status as covariates were employed. For intertreatment comparisons of binary data, Cochran–Mantel–Haenszel tests were employed using baseline HBeAg status as a stratification factor. For analysis of dose–response relationships, Student's t test was applied to linear regression plots of serum HBV DNA level against log dose. A two-sided $P < 0.05$ was taken to indicate statistical significance. For analysis of dose–response relationships using efficacy data, a two-sided $P < 0.05/3$ was taken to

indicate statistical significance following Bonferroni adjustment.

Results

Study population and demographic characteristics

A total of 137 patients, including 20- to 73-year-old men and women, met the study eligibility criteria and were randomized to the following treatment groups: entecavir 0.01 mg ($n = 35$), entecavir 0.1 mg ($n = 34$), entecavir 0.5 mg ($n = 34$), and lamivudine 100 mg ($n = 34$). Three patients (two in the entecavir 0.5 mg group and one in the lamivudine 100 mg group) discontinued the study prematurely; the reasons for discontinuation were noncompliance (one patient in the entecavir 0.5 mg group) and adverse events (liver cirrhosis in one patient [entecavir 0.5 mg group] and grade 4 serum ALT elevation with nausea and malaise in one patient [lamivudine 100 mg group]). Accordingly, a total of 134 patients (entecavir 0.01 mg group, 35 patients; entecavir 0.1 mg group, 34 patients; entecavir 0.5 mg group, 32 patients; and lamivudine 100 mg group, 33 patients) completed 24 weeks of treatment and were included in the efficacy assessment.

The four treatment groups were matched with respect to gender, age, body weight, and proportion of HBeAg-positive patients (Table 1). Serum HBV DNA levels by PCR assay (mean ± SD) at baseline were 7.94 ± 0.87, 8.09 ± 1.05, 8.39 ± 0.73, and 7.94 ± 0.83 $\log_{10}$ copies/ml for the entecavir 0.01, 0.1, and 0.5 mg and lamivudine 100 mg groups, respectively. With regard to HBV genotype, 124 patients were genotype C, 6 patients were genotype A, 5 patients were genotype B, and 2 patients were genotype F. All patients were nucleos(t)ide-naive and none had been pretreated with interferon therapy.

Virologic response

Mean changes (from baseline) in serum HBV DNA level at week 22 were −3.11, −4.77, and −5.16 $\log_{10}$ copies/ml with entecavir 0.01, 0.1, and 0.5 mg, respectively (Fig 1; Table 2). Estimated differences in serum HBV DNA levels between the 0.1 and 0.5 mg entecavir groups and the low-dose entecavir group (0.01 mg) were determined after adjustment for baseline level and HBeAg status. Estimated intertreatment group differences (adjusted 95% CI) were −1.61 (−2.20 to −1.02) $\log_{10}$ copies/ml between the entecavir 0.01 and 0.1 mg groups and −1.95 (−2.53 to −1.37) $\log_{10}$ copies/ml between the entecavir 0.5 and 0.01 mg groups; both of these differences were statistically significant ($P < 0.0001$). In contrast, the difference in serum HBV DNA levels between the high-dose (0.5 mg) and medium-dose (0.1 mg) entecavir groups was not statistically significant (estimated difference [adjusted 95% CI] −0.23 [−0.69 to 0.23] $\log_{10}$ copies/ml). Taken together, these results demonstrate the superiority of high- and medium-dose entecavir (0.1 and 0.5 mg) compared with low-dose entecavir (0.01 mg) in terms of viral load reduction (Table 3). Linear regression analyses indicated a

Table 1 Baseline demographics and clinical characteristics of treated subjects

	ETV 0.01 mg ($n = 35$)	ETV 0.1 mg ($n = 34$)	ETV 0.5 mg ($n = 34$)	LVD 100 mg ($n = 34$)
Male, *n* (%)	25 (71.4)	23 (67.6)	23 (67.6)	28 (82.4)
Female, *n* (%)	10 (28.6)	11 (32.4)	11 (32.4)	6 (17.6)
Age (years), mean ± SD	42.0 ± 12.5	40.1 ± 9.8	39.8 ± 10.4	42.3 ± 12.6
Weight (kg), mean ± SD	66.2 ± 12.5	64.6 ± 11.9	65.3 ± 11.1	64.4 ± 9.0
Ethnicity Japanese, *n* (%)	35 (100)	34 (100)	34 (100)	34 (100)
HBV DNA ($\log_{10}$ copies/ml by PCR), mean ± SD	7.94 ± 0.87	8.09 ± 1.05	8.39 ± 0.73	7.94 ± 0.83
HBeAg positive, *n* (%)	30 (85.7)	30 (88.2)	30 (88.2)	31 (91.2)
ALT (IU/l), mean ± SD	150.1 ± 111.8	162.0 ± 127.1	142.4 ± 82.2	185.0 ± 130.8
AST (IU/l), mean ± SD	83.2 ± 40.0	114.3 ± 109.4	81.0 ± 43.0	121.6 ± 85.4
Total bilirubin (mg/dl), mean ± SD	0.65 ± 0.25	0.56 ± 0.15	0.66 ± 0.25	0.71 ± 0.28
HBV genotype (%)				
C	32 (91.4)	30 (88.2)	32 (94.1)	30 (88.2)
A	1 (2.86)	2 (5.88)	1 (2.94)	2 (5.88)
B	1 (2.86)	1 (2.94)	1 (2.94)	2 (5.88)
F	1 (2.86)	1 (2.94)	0	0

ETV entecavir; *LVD* lamivudine

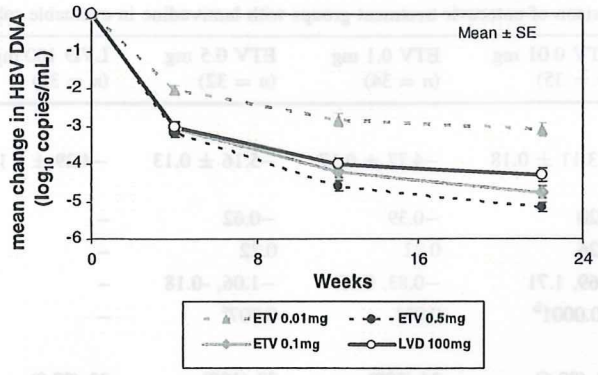

Fig. 1 Mean change from baseline in serum HBV DNA level by PCR assay through 22 weeks in patients treated with entecavir (ETV) 0.01, 0.1, and 0.5 mg and lamivudine 100 mg. Mean change in serum HBV DNA level was plotted as a function of time after the initiation of the protocol therapy (weeks). Data expressed as mean ± SE

significant dose–response relationship between $\log_{10}$ entecavir dose and reduction in $\log_{10}$ serum HBV DNA level ($P < 0.0001$).

Mean change (from baseline) in serum HBV DNA level at week 22 for the lamivudine 100 mg group was −4.29 $\log_{10}$ copies/ml (Fig. 1; Table 2). Estimated mean differences (95% CI) in serum HBV DNA level (after adjustment for baseline level and HBeAg status) were −0.39 (−0.83 to 0.05) $\log_{10}$ copies/ml between the entecavir 0.1 mg and lamivudine 100 mg groups and −0.62 (−1.06 to −0.18) $\log_{10}$ copies/ml between the entecavir 0.5 mg and lamivudine 100 mg groups, indicating the noninferiority of the entecavir 0.1 and 0.5 mg groups to the lamivudine 100 mg group and the superiority of the entecavir 0.5 mg group to the lamivudine 100 mg group ($P = 0.007$) (Table 2). In contrast, the entecavir 0.01 mg group was significantly inferior to the lamivudine 100 mg group (estimated mean difference = 1.20 [0.69–1.71]; $P < 0.0001$) (Table 2).

The secondary efficacy end point of a reduction in serum HBV DNA level 2 $\log_{10}$ copies/ml or more or HBV DNA level less than 400 copies/ml by PCR assay was achieved by 88.6% of patients in the entecavir 0.01 mg group and by 100% of patients in the entecavir 0.1 and 0.5 mg groups at week 22. Ninety-seven percent of patients in the lamivudine 100 mg group achieved this end point at week 22. HBV DNA level less than 0.7 MEq/ml by bDNA assay was achieved by 65.7%, 94.1%, and 100% of patients in the 0.01, 0.1, and 0.5 mg entecavir groups, respectively, and by 93.9% of patients in the lamivudine 100 mg treatment group.

Serologic response

Among HBeAg-positive patients, there was no significant difference between seroconversion rates at week 22 for the entecavir 0.01, 0.1, and 0.5 mg treatment groups (10.0%, 13.3%, and 3.6%, respectively) versus the lamivudine 100 mg treatment group (3.3%; Table 2). All patients who lost HBeAg also experienced HBeAg seroconversion.

Biochemical response

At baseline, elevated serum ALT levels (>1.25 × ULN) were present in more than 90% of patients in all four treatment groups. At week 22, normal serum ALT levels (World Health Organization grade 0, <1.25 × ULN) were recorded in similar proportions of patients in the entecavir 0.01, 0.1, and 0.5 mg treatment groups (75.0%, 85.3%, and 80.0% of patients, respectively) and the lamivudine treatment group (78.1% of patients), with no significant intergroup difference (Table 2).

Response

Response (HBV DNA level <0.7 MEq/ml by bDNA assay, HBeAg loss, and serum ALT level <1.25 × ULN for HBeAg-positive patients and HBV DNA level <0.7 MEq/ml by bDNA assay and serum ALT <1.25 × ULN for HBeAg-negative patients) was achieved by 14.3%, 20.6%, and 15.6% of patients in the entecavir 0.01, 0.1, and 0.5 mg

Table 2 Differences in HBV DNA levels between entecavir dose groups by PCR at week 22 in evaluable subjects

	0.1 mg ETV–0.01 mg ETV ($n = 34$, $n = 35$)	0.5 mg ETV–0.01 mg ETV ($n = 32$, $n = 35$)	0.5 mg ETV–0.1 mg ETV ($n = 32$, $n = 34$)
Estimated difference[a] ($\log_{10}$ copies/ml)	−1.61	−1.95	−0.23
Standard error	0.24	0.24	0.19
95% Confidence interval[b]	−2.20, −1.02	−2.53, −1.37	−0.69, 0.23
P-value	<0.0001	<0.0001	0.227

[a] Estimated differences are regression-adjusted for baseline serum HBV DNA and HBeAg status

[b] 95% Confidence interval is adjusted by modified Bonferroni procedures

ETV entecavir

Table 3 Virology and biochemical responses at week 22 and comparison of entecavir treatment groups with lamivudine in evaluable subjects

Response	ETV 0.01 mg ($n = 35$)	ETV 0.1 mg ($n = 34$)	ETV 0.5 mg ($n = 32$)	LVD 100 mg ($n = 33$)
HBV DNA by PCR assay				
Reduction from baseline at week 22 (log_{10} copies/ml), mean ± S.E.	−3.11 ± 0.18	−4.77 ± 0.17	−5.16 ± 0.13	−4.29 ± 0.18
HBV DNA estimated difference[a] (vs. LVD) (log_{10} copies/ml)	1.20	−0.39	−0.62	–
Standard error	0.26	0.22	0.22	–
95% Confidence interval	0.69, 1.71	−0.83, 0.05	−1.06, -0.18	–
P-value	<0.0001[b]	0.081	0.007[c]	–
HBV DNA by Roche Amplicor™ PCR assay				
Change in log_{10} HBV DNA reduction >2 or HBV DNA <400 copies/ml at week 22, *n* (%)	31 (88.6)	34 (100)	32 (100)	32 (97.0)
P-value (vs. LVD)	0.206	NR[d]	NR[d]	–
HBV DNA by Quantiplex assay				
HBV DNA <0.7 MEq/ml (2.5 pg/ml) at week 22, *n* (%)	23 (65.7)	32 (94.1)	32 (100)	31 (93.9)
P-value (vs. LVD)	0.002	1.000	NR[d]	–
Normalization of ALT levels[e]				
At week 22, *n*/*n* with abnormal baseline (%)	24/32 (75.0)	29/34 (85.3)	24/30 (80.0)	25/32 (78.1)
P-value (vs. LVD)	0.842	0.439	0.880	–
Loss of HBeAg and seroconversion at week 48[f]				
HBeAg loss, n/n HBeAg positive at baseline (%)	3/30 (10.0)	4/30 (13.3)	1/28 (3.6)	1/30 (3.3)
HBeAg seroconversion	3/30 (10.0)	4/30 (13.3)	1/28 (3.6)	1/30 (3.3)
P-value (vs. LVD)	0.605	0.350	1.000	–
Response[g] at week 22, *n* (%)	5 (14.3)	7 (20.6)	5 (15.6)	3 (9.1)
P-value (vs. LVD)	0.735	0.190	0.480	–

[a] Estimated differences are regression-adjusted for baseline HBV DNA and HBeAg status

[b] Two-sided test indicates inferiority of the entecavir 0.01 mg dose

[c] Two-sided test indicates superiority of the entecavir dose

[d] Not reported because expected counts <5

[e] WHO grade 0, ALT <1.25 × upper limit of normal

[f] Seroconversion was defined as disappearance of HBe-antigen and appearance of HBe-antibody

[g] Response was defined as HBV DNA levels <0.7 MEq/ml, HBeAg negativity and ALT <1.25 × ULN for HBeAg-positive patients and HBV DNA levels <0.7 MEq/ml and ALT <1.25 × ULN for HBeAg-negative patients

ETV entecavir

LVD lamivudine

treatment groups, respectively, and by 9.1% of patients in the lamivudine treatment group at week 22, and there were no significant differences in the rates of response between the four treatment groups (Table 2).

Resistance analysis

During the treatment period, serum HBV DNA level increased by 1 log_{10} copies/ml or more from its nadir in one patient in the entecavir 0.01 mg group and one patient in the lamivudine 100 mg group. Nucleotide sequence analysis of the DNA polymerase coding region, using viral samples collected from these two patients at day 1 and at week 22, revealed no lamivudine-resistance substitutions (rt180 and rt204 amino acid residues) [17, 18] or entecavir-resistance substitutions (rt184, rt202, and rt250 amino acid residues) [19].

Safety

During the study, adverse events were experienced by similar proportions of patients in the entecavir 0.01, 0.1, and 0.5 mg groups and the lamivudine 100 mg treatment group (97.1%, 97.1%, 91.2%, and 100.0%, respectively). Most adverse events were of mild or moderate intensity (grade 1/2) and transient. The most frequently reported adverse events (affecting ≥ 10% of patients in any one treatment group) included nasopharyngitis, headache, and

Table 4 Summary of adverse events and laboratory abnormalities during the 24-week blinded treatment phase

	ETV 0.01 mg ($n = 35$)	ETV 0.1 mg ($n = 34$)	ETV 0.5 mg ($n = 34$)	LVD 100 mg ($n = 34$)
Any adverse events	34 (97)	33 (97)	31 (91)	34 (100)
Most frequent clinical adverse events,[a] *n* (%)				
Nasopharyngitis	9 (25.7)	10 (29.4)	11 (32.4)	10 (29.4)
Headache	6 (17.1)	7 (20.6)	2 (5.9)	7 (20.6)
Diarrhea	1 (2.9)	1 (2.9)	4 (11.8)	4 (11.8)
Grade 3/4 clinical adverse events, *n* (%)	0	0	1 (2.9)	1 (2.9)
Grade 3/4 laboratory adverse events, *n* (%)	2 (5.7)	4 (11.8)	2 (5.9)	4 (11.8)
Any serious adverse events, *n* (%)	0	1 (2.9)	2 (5.9)	1 (2.9)
Discontinuations due to adverse events,[b] *n* (%)	0	0	1 (2.9)	1 (2.9)
ALT flares,[c] *n* (%)	0	1 (2.9)	1 (2.9)	2 (5.9)
Death, *n* (%)	0	0	0	0

[a] Occurring in at least 10% of patients

[b] One patient treated with ETV 0.5 mg discontinued the study drug due to hepatic cirrhosis. One patient treated with lamivudine discontinued due to increased ALT

[c] ALT flare defined ALT >2 × baseline and 10 × ULN

ETV entecavir

LVD lamivudine

diarrhea (Table 4). Grade 3/4 clinical adverse events occurred in one patient in the entecavir 0.5 mg group (colon carcinoma) and one patient in the lamivudine group (anal ulcer); neither of these events was considered to be related to the study drug. Serious adverse events were limited to the above-mentioned case of colon carcinoma, serum ALT elevation (entecavir 0.1 mg group [$n = 1$], entecavir 0.5 mg group [$n = 1$]), and serum aspartate aminotransferase (AST)/ALT elevation (lamivudine 100 mg group [$n = 1$]), but these were not considered to be causally related to the study drug and did not necessitate treatment discontinuation. Transient ALT flares (serum ALT >2 × baseline level and >10 × ULN) occurred in four patients (entecavir 0.1 mg group [$n = 1$], entecavir 0.5 mg group [$n = 1$], and lamivudine 100 mg group [$n = 2$]) and were associated with HBV DNA level decreases of 2 $\log_{10}$ copies/ml or more. None of the ALT flares were associated with hepatic decompensation and serum ALT and AST levels recovered to less than 1.25 × baseline level on continuation of the study treatment.

Discussion

The global ETV-005 study reported that entecavir was superior to lamivudine at reducing viral load in nucleoside-naive patients with CHB infection [15]. We conducted the present study, using an identical design to the ETV-005 study, to determine whether the findings from this earlier study are applicable to Japanese patients. In keeping with the previous findings, our results indicate that entecavir produces a dose-related reduction in serum HBV DNA level ($0.01 < 0.1 \leq 0.5$ mg) in nucleoside-naive Japanese patients with CHB; the log dose–response curves for the reduction in serum HBV DNA level with entecavir in the two studies were similar, with estimated regression curve slopes of –1.24 (Japanese study) and –1.32 (global study). In addition, both studies demonstrated the noninferiority of the entecavir 0.1 mg group compared with the lamivudine 100 mg group and the superiority of the entecavir 0.5 mg group compared with the lamivudine 100 mg group. The demonstration of a dose–response relationship for entecavir and the superiority of the entecavir 0.5 mg dose over lamivudine confirm that the antiviral activity of entecavir in Japanese patients is similar to that observed in study ETV-005. In a previous study, Ono et al. [14] demonstrated that the in vitro potency of entecavir was up to 2,200 times greater than that of lamivudine. The results presented here substantiate these earlier in vitro data and confirm the greater potency of entecavir over lamivudine in patients with CHB.

Serum ALT normalization rates with entecavir 0.5 mg and lamivudine 100 mg (~80%) were higher in the present study than those reported in the ETV-005 study (entecavir 0.5 mg, 69.0%; lamivudine 100 mg, 59.1%) [15]. In keeping with previous findings [20, 21], the incidence of entecavir-associated serum ALT flares in Japanese patients was low. The serum ALT flares occurred against a background of 2 $\log_{10}$ copies/ml or more reductions in serum

HBV DNA level, and serum ALT levels subsequently normalized without discontinuation of entecavir. Therefore, the serum ALT flare noted here may indicate recovery of the host's immune response arising from the reduction in HBV viral titer [22, 23]. ALT flares have been reported after the discontinuation of entecavir therapy [15, 16], thus necessitating long-term follow-up to identify possible posttreatment viral rebound.

In conclusion, the results of this dose-ranging study demonstrate a clear dose–response relationship for entecavir in terms of mean HBV DNA level reduction at week 22. Entecavir 0.5 mg was significantly more effective than lamivudine 100 mg in reducing HBV DNA levels in nucleoside-naive Japanese adult patients with CHB. At this dose level, entecavir treatment resulted in serum HBV DNA levels of less than 400 copies/ml in 100% of patients and normalization of serum ALT levels in 80% of patients after 22 weeks. Moreover, entecavir 0.5 mg once daily was well tolerated and showed a comparable safety profile to lamivudine.

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Original Article

Case–control study for the identification of virological factors associated with fulminant hepatitis B

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Background: Host and viral factors can promote the development of fulminant hepatitis B (FHB), but there have been no case–control studies for figuring out virological parameters that can distinguish FHB.

Methods: In a case–control study, virological factors associated with the development of FHB were sought in 50 patients with FH developed by transient hepatitis B virus (HBV) infection (FH-T) and 50 with acute self-limited hepatitis B (AHB) who were matched for sex and age. In addition, 12 patients with FH developed by acute exacerbation (AE) of asymptomatic HBV carrier (ASC) (FH-C) were also compared with 12 patients without FH by AE of chronic hepatitis B (AE-C).

Results: Higher HBV DNA levels, subgenotype B1/Bj, A1762T/G1764A, G1896A, G1899A and A2339G mutation were significantly more frequent ($P < 0.05$), while hepatitis B e-antigen was less frequent in the FH-T patients than AHB. In multivariate analysis, G1896A mutation (odds ratio [OR], 13.53; 95% confidence interval [CI], 2.75–66.64), serum HBV DNA more than 5.23 log copies/mL (OR, 5.14; 95% CI, 1.10–24.15) and total bilirubin more than 10.35 mg/mL (OR, 7.81; 95% CI, 1.77–34.51) were independently associated with a fulminant outcome by transient HBV infection. On the other hand, in comparison with the patients between FH-C and AE-C groups, there was no significant difference of virological factors associated with the development of FHB.

Conclusion: A number of virological factors have been defined that may distinguish FH-T from AHB in a case–control study. The pathogenic mechanism of FHB between transient HBV infection and AE of ASC would be different.

Key words: acute exacerbation of asymptomatic hepatitis B virus carrier, fulminant hepatitis, genotypes, transient hepatitis B virus infection

INTRODUCTION

IN JAPAN, 634 patients with fulminant hepatitis (FH) were registered from 1998–2003. Of them, 41.8% were infected with hepatitis B virus (HBV) that is the most frequent cause of FH there.[1] HBV is classified into eight genotypes (A–H) based on a sequence divergence of more than 8% in the entire genome of approximately

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