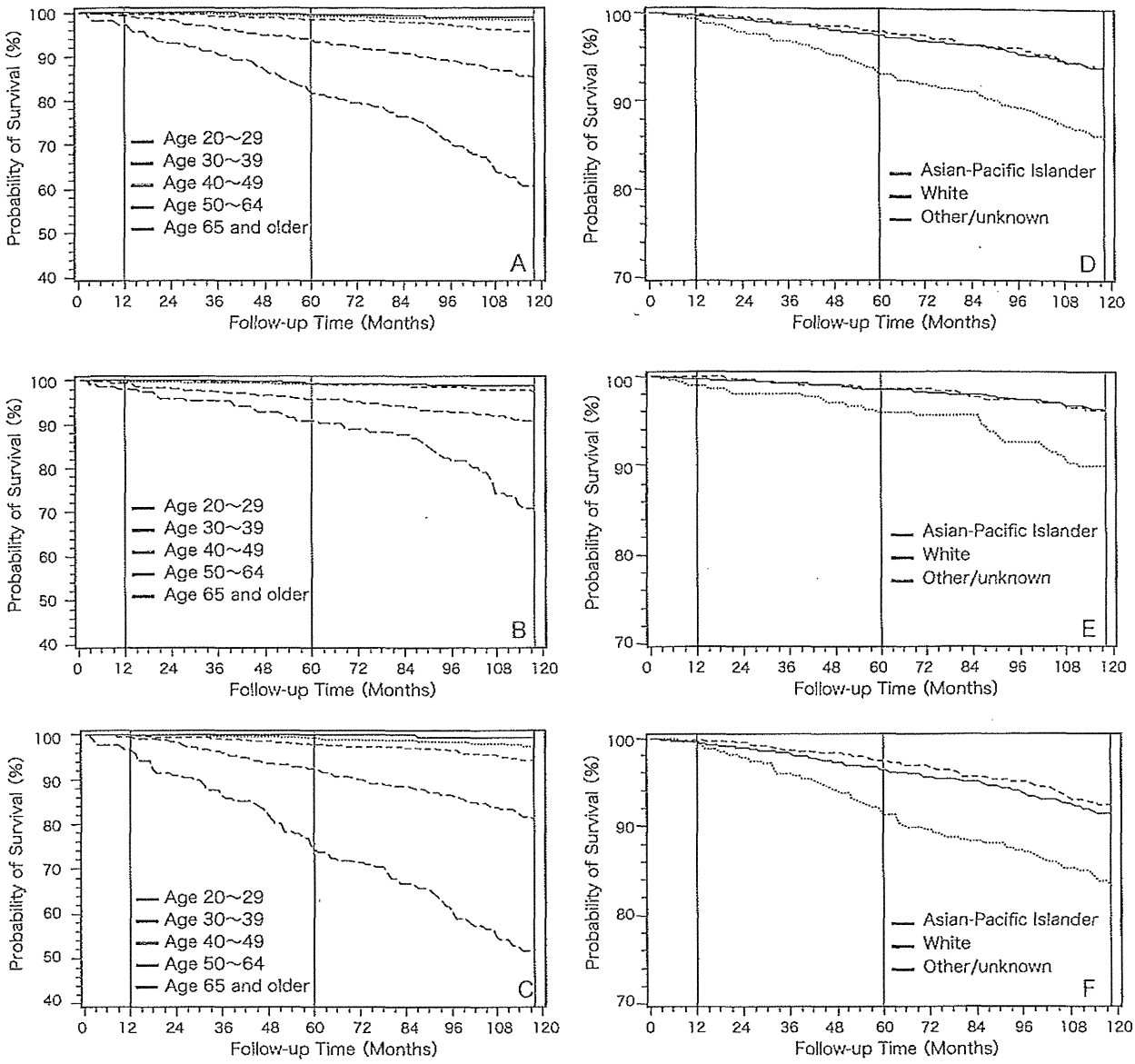

図3　性別・年齢別HBV関連生存率

死亡率は年齢に伴い増加し，特に女性に比し男性で死亡率が高い．またHBV関連死亡率はアジア太平洋家系のほうが白人よりも高い．（文献12より引用）

見と思われる．

3　米国におけるB型肝炎自然予後

欧米の論文では無治療の住民を対象としたB型肝炎予後に関する報告は少ないが，米国では，HBs抗原陽性であった一過性感染例を除く未治療の6,689人を対象にした10年間の追跡で，HBV関連死を含む総死因調査を行っている[12]．人種の内訳は，68.3％はアジア太平洋出身，11.8％は白人であった．10年間の総死亡率は男性(8.9％)が女性(4.1％)より高く，またHBV関連死も女性(1.2％)に比し男性(4.8％)で高率であった(図3)．死亡率は年齢とともに高くなり，40歳以上の総死亡のうち40％はHBV関連死であった．多変量解析ではHBV関連死に最も影響する因子は男女ともに年齢であった(表5)．米国においてもB型肝炎はHBV感染者の死因の40％を占めていることが明らかとなり，年齢とともにそのリスクが高くなることから，HBVキャリアの囲い込みを今後どうしていくのか注目される．

表5　HBV関連死予測因子（多変量解析）（文献12より一部改変）

予測因子	全体(6,657)			女性(3,237)			男性(3,420)		
	死亡数	HR（95％CI）	P	死亡数	HR（95％CI）	P	死亡数	HR（95％CI）	P
	37	0.3（0.2～0.4）	<0.01	N/A			N/A		
女性									
初診年齢									
0～39歳	11	referent		2	referent		9	referent	
40～64歳	129	8.5（4.6～15.8）	<0.01	24	11.4（2.7～48.5）	<0.01	105	7.8（3.9-15.5）	<0.01
65歳以上	48	36.7（18.7～71.9）	<0.01	11	50（10.7～233.7）	<0.01	37	34.4（16.3-72.6）	<0.01
人種									
アジア太平洋	127	0.9（0.6～1.4）	0.72	30	3.2（0.8～13.5）	0.12	97	0.8（0.5-1.2）	0.23
白人	36	referent		2	referent		34	referent	
その他	25	0.8（0.5～1.3）	0.31	5	2.2（0.4～11.1）	0.36	20	0.7（0.4-1.2）	0.17

4　Community-based cohortからみたB型肝炎の長期予後の検討（上五島コホート）

本邦には，地域住民を対象としたB型肝炎コホート研究が現在も行われている地域がある．長崎県上五島は，長崎県の西方にある五島列島の北部に位置し，離島という閉鎖的な環境により住民の異動が比較的少なく最終転帰が把握しやすいこと，また人口がおよそ2.5万人と，コホート研究として比較的取り扱いやすい地域である．

上五島病院の白濱，国立長崎医療センター・臨床研究センターの山崎，八橋らは，1978年より上五島地区全住民を対象にHBs抗原スクリーニングを行っており，これまでにB型肝炎の長期予後に関するさまざまな検討を行っている．これらは本稿のテーマにふさわしい疫学研究と考えられるので，著者の許可をいただき，ここでその概要について，①肝硬変・肝癌罹患，②HBe抗体と肝機能からみた臨床的治癒率，③HBs抗原自然消失，そして④同地区一般住民と比較したHBV感染住民の生命予後，に関する研究成果を紹介させていただく（personal communication）[13]．

1．上五島の感染予防対策

上五島地区の平成10年～14年の肝癌標準化死亡比は男215，女149と極めて高く，HBs抗原は1978年から，HCV抗体は1990年からスクリーニングが開始された．

B型肝炎に対してはHBVキャリアの撲滅をめざし，1978年スクリーニングと同時に母児間感染ブロックも開始した．当初はHBVグロブリン，1980年からはHBVワクチンを導入した．その結果1980年代出生者のHBs抗原陽性率は0.5％と激減し，1990年以降の出生者からHBs抗原陽性者はいまだ確

認されず，ほぼ撲滅状態となった．

2. 肝硬変・肝癌罹患ハザード比

2008年までに延べ34,517名が受診し，HBs抗原陽性1,474名(4.3％；genotype C＝92％)のうち，解析可能であったHBs抗原陽性持続感染者1,045例を最終対象としている．平均観察期間は18.5年(最長で33.8年)，男性605例(58％)，年齢中央値44歳(0.6～95歳)であった．

一般住民をコントロールとしたB型関連肝疾患ハザード比をみると，HBe抗原陽性肝硬変(LC)：0.138 (95％CI 0.089-0.215)，HBe抗原陰性LC：0.249 (95％ CI 0.152-0.408)，HBe抗原陽性慢性肝炎(CH)：0.378 (95％ CI 0.214-0.668)，HBe抗原陽性ASC：0.372 (95％ CI 0.147-0.943)，HBe抗原陰性CH：0.393 (95％ CI 0.213-0.726)，HBe抗原陰性ASC：0.827 (95％ CI 0.669-1.021)であった．

3. HBe抗体と肝機能からみた臨床的治癒

HBe抗体陽転・肝機能正常に至る臨床的治癒率を検討したところ，観察開始時20歳未満群では年率4％であったが，35歳までに累積100％の治癒となった．またこれら臨床的治癒例におけるHBs抗原自然消失率は年率1％であった．一方，35歳時HBe抗原陽性群では臨床的治癒率は年率1％であり，また治癒に至ってもその半数が肝硬変に進展していた．このことから20歳未満HBe抗原陽性キャリアへの治療介入は不要であるものの，35歳以上でHBe抗原陽性例では積極的な治療介入の必要性が示唆される結果となった．

4. HBs抗原自然消失と肝発癌

一方，初診時HBe抗原陰性ASC群において，観察開始から20年ほど経過すると136例(22.6％)にHBs抗原消失を認め，この群におけるHBs抗原累積消失率は20年で27.2％であった．HBs抗原が自然消失した全175例における平均10年間の肝発癌は3例に認め，うち2例はHCV重感染例であり，HBV単独感染例は1例であった．

5. 一般住民と比較したHBVキャリアの生命予後

興味深いことに，HBe抗原陰性ASCの生存率は一般住民に比し観察開始から20年までは低いものの，それ以降はキャリアと一般住民の間で差がなかった．また肝疾患関連死の割合は一般住民群1.1％に対し，HBV持続感染群では33.8％と有意に高かった．

さらに，HBs抗原消失175例の累積生存率を算出し一般住民に対するハザード比を求めると，注目すべきことに死亡リスク比は同等であった．このことから，地域住民コホートからみると，B型肝炎は非活動期の無症候性キャリアに至っても一般住民より生命予後は不良だが，HBs抗原が消失した場合，一般住民の生命予後と同等にまで改善することがわかった．

このコホートは本邦におけるB型肝炎自然史を知り得る極めて貴重なものであり，B型肝炎の目指すべき治療目標はHBs抗原消失であることを示唆するものである．さらなる追跡結果の集積が日本の医療施策に反映されることを期待している．

5 C型肝炎多発地域におけるHBV，HCV感染状況

一方，本邦には地域住民のHCV抗体陽性率が10％を超える，いわゆるHCV感染高浸淫地域がいくつか知られている．このような地域でHBVとHCV感染状況を比較することは，双方の感染経路の違いを考えるうえで重要なことである．

新澤らは[14] 1991年～1993年の3年間に就学年齢以上の住民7,292人に対し行ったHCV

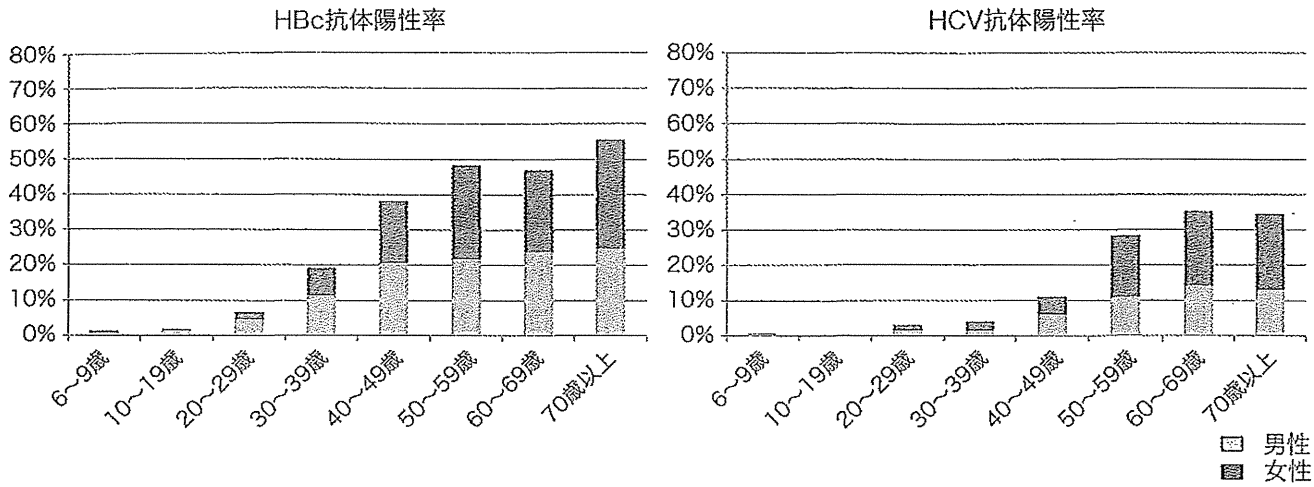

図4　性別・年齢階層別HBc抗体・HCV抗体陽性率(文献14より改変)

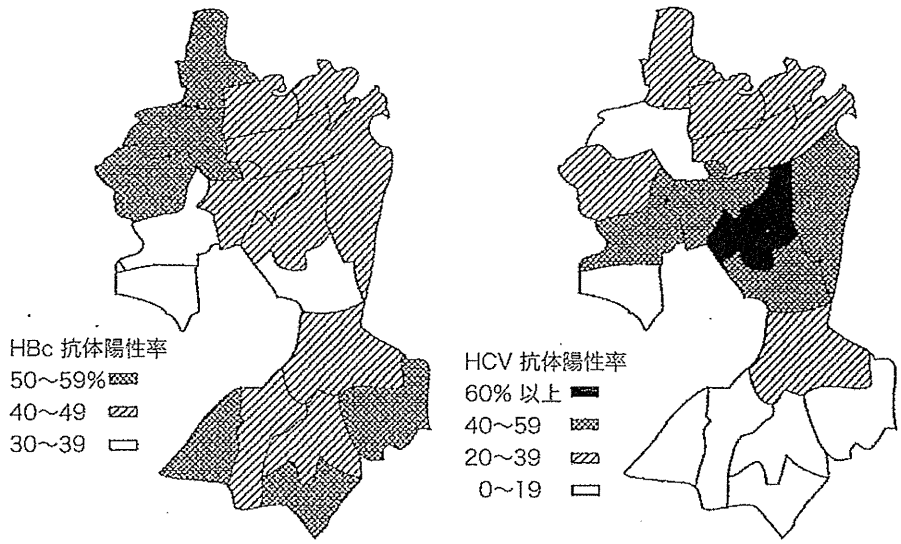

図5　地域別HBc抗体，HCV抗体陽性率(文献14より引用)

高浸淫地域における住民検診で，検診に応じた4,425人(受診率60.7%)を対象に，HBV，HCV感染状況を比較検討した．なお住民検診の性格上，現在あるいは過去のHBV感染を問わず，HBc抗体陽性者をHBV感染者としている．

性別・年齢階層別にHBs抗原，HBc抗体陽性率をみてみると，ともに男性で陽性率が高かったが，HCV抗体陽性率は女性で高かった．HBs抗原陽性率は6～9歳で0.4%，10～19歳で0.6%，20～29歳で0.5%，30～39歳で2.7%，40～49歳で2.9%，50～59歳で2.9%，60～69歳で2.8%，70歳以上で2.5%であった．すなわち20歳代までの若年では0.5%前後であったが，30歳代以上では2.5%以上の陽性率であった．またHBc抗体陽性率は20歳代まで緩やかに上昇し，30歳代からは急峻な上昇を示す一方，HCV抗体陽性率は30歳代まで段階的にわずかに上昇し，40歳代以降，急峻な上昇を示した(図4)．以上より，HBV感染者のピークはHCV感染者よりも10歳若年であり，男性に感染者が多いことが明らかとなった．

本地域集落別のHCV感染率(HCV抗体陽

性)とHBV感染率(HBc抗体陽性)を調べると(図5)，HCV抗体陽性率は同心円状に陽性率の推移を認め，明らかな集積性がみられたのに対し，HBc抗体陽性率はそのような集積性はみられなかった．この地域はHCV抗体陽性率が18.7%，HBc抗体陽性率は33.4%であるが，地域内陽性率の比較からは，HBVとHCV感染が共通の感染経路によるものではない可能性が示唆された．

6 おわりに

B型肝炎自然予後に関し，国内外の住民コホートから得られた知見の一部を紹介した．無治療キャリアからの肝発癌，HBs抗原自然消失，そして生命予後に与える影響など，その機序を含め今後明らかにしなければならない点は多いが，そのためにも自然史を理解するためのさらなるエビデンスの集積が欠かせないと思われる．ここで紹介した自然予後に関わる知見はいずれもウイルス側あるいは疾患因子であるが，今後住民コホートを用いたHBVキャリアのGWASあるいは次世代シークエンサーによる宿主因子解析が進められれば，患者コホートデータとあわせ，B型肝炎自然史に影響するkey molecule (s)がみいだされることが大いに期待される．

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消化器疾患最新の治療

2013-2014

編集

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オンラインアクセス権付き

注目トピックス

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3. 慢性便秘の病態と薬剤開発
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10. NASH と遺伝子多型

南江堂

4 B型慢性肝炎

鈴木文孝，熊田博光

♣ 患者への説明のポイント

- B型慢性肝炎の治療は，インターフェロン（IFN）と核酸アナログ製剤が中心である．
- IFN療法は，35歳未満の症例，genotype AまたはBの症例で効果が高い．
- IFNには，発熱（90%），全身倦怠感（80%），頭痛（50%），うつ病（5%未満），間質性肺炎（0.1%未満）などの副作用がある．
- 核酸アナログ製剤は，35歳以上の症例，肝炎重症化例，肝組織像が進行した症例で適応になる．
- 核酸アナログ製剤には副作用はほとんどないが，長期投与にて耐性ウイルス出現のリスクがある．
- B型慢性肝炎の治療のガイドラインが示されている．

疾患の解説

日本には，100〜150万人のHBVキャリアが存在すると推定されている．日本のHBVキャリアの多くは生後3年以内の免疫能の未熟な時期に感染したものであり，出産時HBVキャリアの母親から感染することが多かった．現在は母親がHBVキャリアである場合，γグロブリンとワクチン接種が行われており25歳以下のキャリア数は減少している．一方，HBVのgenotype Aの感染例では成人でも慢性化する可能性があり，現在感染症例の増加が認められている[1]．

HBVキャリアの自然経過は，若年時HBe抗原陽性でウイルス量が多いにもかかわらずALT値正常の時期（immune tolerance期）から始まる．その後宿主の免疫応答（細胞性免疫によるHBV感染細胞の破壊）によって肝炎が起こりHBe抗体へとseroconversionを認め（immune clearance期），最終的にはALT値正常，ウイルス量の低下したHBe抗体陽性の無症候性キャリアになる（low replicative期）．さらにHBs抗原が消失する症例も認められる（recovery期）．seroconversionの時期は10〜30歳代に認められることが多く，この時期に一時的な肝炎の発症が認められる．しかし一部の症例では肝炎が持続し慢性肝炎，肝硬変症へと進行する．またlow replicative期に移行した後にHBVが再増殖しALT値が変動する症例もある（reactivation期）．

治療の対象となるのは，immune clearance期およびreactivation期の両者で，トランスアミナーゼが変動し，肝病変が活動性で進行性を示す症例である．さらにHBVキャリアの場合無症候性キャリアとなっていても肝発癌の可能性はあり，定期的な経過観察は必ず必要である．

診断と検査

HBVキャリアの病態を把握するうえで，HBV DNA量，HBe抗原の測定，肝機能検査は定期的に必要である．また，genotypeによって治療成績が異なるため，初回検査時にはHBV genotypeを一度測定しておくことが望ましい．

治療の目標は，HBe抗原の陰性化，ALT値の正常化，HBV DNA量が4〜5 log copies/mL以下を持続することである．最終的には，HBs抗原の陰性化が得られるとその後の肝炎の再燃はほとんど認められなくなり，発癌のリスクも低下する[2]．しかし日本においてはHBVキャリアからのHBs抗原の陰性化例は少ない．

治療の一般方針

1 治療方針の立て方

B型慢性肝炎の治療に対しては，厚生労働科学研究費補助金肝炎等克服緊急対策研究事業（肝炎分野）における「ウイルス性肝炎における最新の治療法の標準化を目指す研究」班においてB型慢性肝炎治療のガイドラインを作成している[3]．このガイドラインでは，治療対象をALT≧31 IU/LでHBe抗原陽性例はHBV DNA量5 log copies/mL以上，HBe抗原陰性例は4 log copies/mL以上，肝硬変症例では3 log copies/mL以上としている．また年齢，HBe抗原の有無，ウイルス量によって分類し治療法を提示している（表1，2）．

若年症例（35歳未満）は自己の免疫力によってHBe抗原の陰性化や肝炎の収束が期待されるため核酸アナログ製剤の長期投与ではなくIFN長期間歇を基本治療としている．中高年では，核酸アナログ製剤の長期投与を基本治療としている．

2 薬物療法

a. インターフェロン（IFN）療法

日本では，従来のIFN（スミフェロン，フエロンなど）はHBe抗原の慢性肝炎に対して6ヵ月間投与が保険にて認められている．さらに2011年9月よりペグインターフェロン（PEG-IFN，ペガシス）がHBe抗原陽性例，陰性例のB型慢性肝炎症例で保険適用になった．HBe抗原陽性例のIFN療法の治療成績（治療6ヵ月後の時点）は約

表1 35歳未満B型慢性肝炎の治療ガイドライン

HBe抗原＼HBV DNA量	≧7 log copies/mL	<7 log copies/mL
e抗原陽性	①PEG-IFNα-2a（48週）またはIFN長期投与（24～48週） ②sequential療法 ③エンテカビル	①PEG-IFNα-2a（48週）またはIFN長期投与（24～48週） ②エンテカビル
e抗原陰性	①sequential療法 ②エンテカビル	①経過観察またはエンテカビル ②PEG-IFNα-2a（48週）

治療対象は，ALT ≧ 31IU/Lで：
HBe抗原陽性例は，HBV DNA量5 log copies/mL以上
HBe抗原陰性例は，4 log copies/mL以上
肝硬変では，3 log copies/mL以上
血小板15万未満またはF2以上の進行例には最初からエンテカビル．
（熊田博光：厚生労働科学研究費補助金，肝炎等克服緊急対策研究事業（肝炎分野），ウイルス性肝炎における最新の治療法の標準化を目指す研究，平成23年度総括・分担研究報告書，2012）

表2 35歳以上B型慢性肝炎の治療ガイドライン

HBe抗原＼HBV DNA量	≧7 log copies/mL	<7 log copies/mL
e抗原陽性	①エンテカビル ②sequential療法	①エンテカビル ②PEG-IFNα-2a(48週)またはIFN長期投与(24～48週)
e抗原陰性	①エンテカビル ②PEG-IFNα-2a（48週）	①エンテカビル ②PEG-IFNα-2a（48週）

治療対象は，ALT≧31 IU/Lで：
HBe抗原陽性例は，HBV DNA量5 log copies/mL以上，
HBe抗原陰性例は，4 log copies/mL以上
肝硬変では，3 log copies/mL以上
（熊田博光：厚生労働科学研究費補助金，肝炎等克服緊急対策研究事業（肝炎分野），ウイルス性肝炎における最新の治療法の標準化を目指す研究，平成23年度総括・分担研究報告書，2012）

20%が著効となると報告されている[4]．著効になる症例は年齢が35歳未満，治療開始時ALT値が高い例，ウイルス量が低い症例であった．このことから，ガイドラインにおいても35歳未満のHBe抗原陽性症例では，IFN療法が推奨されている．また，genotype AまたはB型の場合は，35歳以上でもIFN療法の効果が高いため，IFN療法が推奨されている．

処 方 例

- ペガシス　週1回90 μg　皮下注
  48週間投与
  180 μgも投与も可能であるが，血液学的副作用に注意が必要．

- スミフェロン　1日1回300万～600万単位
  皮下または筋注　2～4週間連日，その後週3回合計24週間投与

- オーアイエフ　1日1回250万～500万単位
  皮下または筋注　2～4週間連日，その後週3回合計24週間投与

- イントロンA　1日目　1回300万～600万単位　1週目1日1回600万～1,000万単位
  2週目　～600万単位　筋注　2～4週連日，その後週3回合計24週間

- フェロン　初日300万単位　点滴静注または静注　以後6日間1日1～2回，2週以降1日1回　点滴静注または静注

b. 核酸アナログ製剤（ラミブジン，アデホビル，エンテカビル）

核酸アナログ製剤であるラミブジンは，逆転写酵素阻害作用を有しウイルスのDNAポリメラーゼに選択的に作用する．ラミブジンは1日100 mg（ゼフィックス1錠）を経口投与する．ラミブジンには副作用がほとんど認められず，また強力なウイルス増殖抑制作用があり2000年の保険適用以来多くの症例で使用されてきた．しかしラミブジンは投与中止により多くの症例で肝炎の再燃を認めることと，長期投与によって耐性ウイルスが高率に出現するという問題点がある．このため現在ではより耐性ウイルスの出現率が低いエンテカビル（バラクルード）の使用が奨励されている．

ラミブジン耐性ウイルス出現例の対処としては，アデホビル（ヘプセラ）またはエンテカビルの使用が可能である．この場合アデホビルの使用が奨励されている．アデホビルはエンテカビルと比較して，HBV DNAの減少率で上回り，またラミブジンとの併用で両剤への耐性ウイルスの出現率が低率であることが報告されている．

一方，エンテカビルの場合は，ラミブジン耐性ウイルスが存在しウイルス量が2.1 log copies/mL以上の症例ではエンテカビル耐性ウイルスの出現の可能性があるため，その使用には慎重でなくてはならない．

処 方 例

- ヘプセラ（10 mg）　1錠　分1　経口投与
  ラミブジン耐性ウイルス出現時にラミブジン100 mgと併用投与．

エンテカビルは2006年9月に保険適用となった新たな核酸アナログ製剤である．エンテカビルは，ラミブジンと比較してHBV DNAの減少率で有意に上回っていること，また核酸アナログ未使用症例（naïve症例）においては耐性ウイルスの出現率が低率であることが報告されている．このことからガイドラインではnaïve症例における第一選択薬となっている．

処 方 例

- バラクルード（0.5 mg）　1錠　分1　経口投与
  内服前後で2時間は食事摂取を避ける必要があるため眠前に投与することが多い．

ラミブジンを使用していた症例での核酸アナログ製剤使用の方法についてもガイドラインは提示している（表3）．HBV DNA量が2.1 log copies/mL以上でviral breakthrough（HBV DNA量が最低値より1 log copy/mL以上の上昇）を認めた症例はラミブジンとアデホビル併用，viral breakthroughを認めていない症例ではエンテカビルに切り替え可能である．HBV DNA量が2.1 log copies/mL未満が6ヵ月以上続いている症例ではエンテカビルに切り替えを奨励している．

c. sequential療法

sequential療法は，核酸アナログ製剤を先行投与した後にIFNと核酸アナログ製剤の併用投与

表3 ラミブジン投与中B型慢性肝炎患者に対する核酸アナログ製剤治療ガイドライン

HBV DNA量	治療法	
<2.1 log copies/mL[*1] 持続	原則エンテカビル0.5 mg/日に切り替え	
≧2.1 log copies/mL	VBT[*2] なし	エンテカビル 0.5 mg/日に切り替え可
	VBT あり	アデホビル 10 mg/日併用

[*1] 持続期間は，6カ月を目安とする
[*2] VBT: viral breakthrough（HBV DNA量が最低値より1 log copy/mL以上の上昇）
（熊田博光：厚生労働科学研究費補助金，肝炎等克服緊急対策研究事業（肝炎分野），ウイルス性肝炎における最新の治療法の標準化を目指す研究，平成23年度総括・分担研究報告書，2012）

を4週間行いさらにIFN療法を単独で20週間使用する方法である．核酸アナログ製剤を中止したい場合の治療法のひとつである．sequential療法を行う場合は，核酸アナログ治療でHBe抗原が陰性化（または陰性）症例で核酸アナログを投与後ウイルスの陰性化期間が1年以上経過し，コア関連抗原（HBcrAg）が3.0 log U/mL以下，HBsAg 1,000 IU/mL以下の症例に行うのが望ましい．

処方例

- バラクルード（0.5 mg） 1錠 分1 経口投与
- スミフェロン 1日1回300万～600万単位 皮下または筋注 週3回合計24週間投与
  IFNを4週間併用したのちエンテカビルを中止する．

- バラクルード（0.5 mg） 1錠 分1 経口投与
- ペガシス 週1回90 μg 皮下注 24週間投与
  IFNを4週間併用したのちエンテカビルを中止する．

3 その他

ガイドラインの補足として，治療に対する基本的な考え方が提示されている．抗ウイルス療法は，ALT値が≧31 IU/Lの場合に考慮するが，35歳以上でF2以上の進行例にはALT値<31 IU/Lでもウイルス増殖が持続する場合は抗ウイルス療法の対象となる．しかし，高齢者やHBe抗原陰性例，抗ウイルス薬の投与が難しい例では肝庇護療法（SNMC，UDCA等）で経過をみることも可能である．

ラミブジンおよびエンテカビル耐性株に対しては，ラミブジン＋アデホビル併用療法を基本とする．しかし，ラミブジン＋アデホビル併用療法を行って3年以上経過してもHBV DNAが4 log copies/mL以上でかつALT値≧31 IU/Lの症例はエンテカビル＋アデホビル併用療法も選択肢のひとつとなる．ラミブジン，アデホビル，エンテカビルのいずれの薬剤にも耐性株が出現した症例に対しては，エンテカビル＋アデホビル併用療法あるいはテノホビルも選択肢のひとつとなる．

治療のご法度

①HIV合併症例は，エンテカビルの使用によりHIV耐性ウイルスが出現する可能性がある．このためエンテカビルは原則として使用すべきでない．エンテカビル開始前にはHIVの測定を行うことが望ましい．

②核酸アナログ製剤では，催奇形性の問題は解決していない．挙児希望がある場合は，慎重に適応を決定する必要がある．

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Research Article

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Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options

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See Editorial, pages 643–645

Background & Aims: Improved therapeutic options for chronic hepatitis C virus (HCV) infection are needed for patients who are poor candidates for treatment with current regimens due to anticipated intolerability or low likelihood of response.

Methods: In this open-label, phase 2a study of Japanese patients with chronic HCV genotype 1b infection, 21 null responders (<2 $\log_{10}$ HCV RNA reduction after 12 weeks of peginterferon/ribavirin) and 22 patients intolerant to or medically ineligible for peginterferon/ribavirin therapy received dual oral treatment for 24 weeks with the NS5A replication complex inhibitor daclatasvir (DCV) and the NS3 protease inhibitor asunaprevir (ASV). The primary efficacy end point was sustained virologic response at 12 weeks post-treatment (SVR_{12}).

Results: Thirty-six of 43 enrolled patients completed 24 weeks of therapy. Serum HCV RNA levels declined rapidly, becoming undetectable in all patients on therapy by week 8. Overall, 76.7% of patients achieved SVR_{12} and SVR_{24}, including 90.5% of null responders and 63.6% of ineligible/intolerant patients. There were no virologic failures among null responders. Three ineligible/intolerant patients experienced viral breakthrough and four relapsed post-treatment. Diarrhea, nasopharyngitis, headache, and ALT/AST increases, generally mild, were the most common adverse events; three discontinuations before week 24 were due to adverse events that included hyperbilirubinemia and transaminase elevations (two patients).

Conclusions: Dual therapy with daclatasvir and asunaprevir, without peginterferon/ribavirin, was well tolerated and achieved high SVR rates in two groups of difficult-to-treat patients with hepatitis C virus genotype 1b infection.

Keywords: Daclatasvir; Asunaprevir; Hepatitis C; Antiviral.

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Abbreviations: HCV, hepatitis C virus; DAA, direct-acting antiviral; PegIFN-α/RBV, peginterferon alfa and ribavirin; SVR, sustained virologic response; HIV, human immunodeficiency virus; NS5A, non-structural protein 5A; NS3, non-structural protein 3; ALT, alanine aminotransferase; ULN, upper limit of the normal reference range; INR, international normalized ratio; CYP3A4, cytochrome P450 3A4.

Introduction

Therapies for chronic hepatitis C virus (HCV) infection have improved markedly over the past decade. The recent approval of the first direct-acting antivirals (DAAs) was an important milestone in the evolution of HCV therapy, establishing that DAAs can enhance regimen efficacy and provide durable viral clearance. These new agents in combination with peginterferon and ribavirin (PegIFN-α/RBV) achieve overall sustained virologic response (SVR) rates of approximately 70% in treatment-naïve patients with HCV genotype 1 infection [1,2].

Despite these advances, current treatment options remain inadequate for some patients. Patients with prior null response to PegIFN-α/RBV (<2 $\log_{10}$ decline in HCV RNA after 12 weeks) have a particularly acute need for further therapeutic improvements. Null responders generally respond poorly to retreatment with PegIFN-α/RBV; fewer than 10% achieve SVR [3]. Retreatment of null responders with PegIFN-α/RBV combined with telaprevir or boceprevir increases SVR rates to approximately 30–38%, suggesting that addition of a DAA to PegIFN-α/RBV increases efficacy, but that more potent regimens are still urgently needed [4,5]. There are also many patients who cannot be treated with current therapies; this group includes patients with prior intolerance to PegIFN-α/RBV and patients who are ineligible for PegIFN-α/RBV -containing therapy for medical reasons.

There is precedence for use of combination antiviral regimens to treat human immunodeficiency virus (HIV) infections;

Research Article

evidence is mounting that DAA regimens can also provide durable clearance of HCV infections. Thus, there is a strong rationale for exploration of dual DAA regimens, without PegIFN-α/RBV. In combination, DAAs with different molecular targets can increase regimen potency and raise the barrier to resistance, potentially eliminating the need for PegIFN-α/RBV and providing a viable therapy for patients who are anticipated to be poorly responsive or intolerant to current PegIFN-α/RBV-containing regimens. The improved tolerability and convenience that can be anticipated with dual DAA regimens suggests that they may also benefit treatment-naïve patients and other groups. Previous studies of DAA-only regimens, or DAAs combined with RBV, have demonstrated marked antiviral effects in treatment-naïve and experienced patients, including null responders, supporting the further evaluation of dual DAA therapy reported here [6–10].

Daclatasvir (DCV; BMS-790052) is a first-in-class, highly selective NS5A replication complex inhibitor with picomolar potency and broad genotypic coverage; asunaprevir (ASV; BMS-650032) is a potent NS3 protease inhibitor active against genotypes 1 and 4. Daclatasvir and asunaprevir have different modes of action and resistance-associated variants, and in combination show increased antiviral potency *in vitro* and a high genetic barrier to resistance [11,12]. Daclatasvir and asunaprevir had no clinically meaningful pharmacokinetic interaction in healthy volunteers [13]. Initial efficacy evaluations of daclatasvir and asunaprevir (DUAL therapy) showed potent antiviral effects and SVR rates ⩾90% in Japanese and US/European null responders with HCV genotype 1b infection [7,8].

We present final results of an open-label trial evaluating DUAL oral therapy with daclatasvir and asunaprevir in Japanese patients with chronic HCV genotype 1b infection. Initial results from a sentinel cohort of 10 patients with prior null response to PegIFN-α/RBV have been reported [7]. The present report combines these data with results for 11 additional null responders, together with results for 22 patients with prior intolerance to PegIFN-α/RBV or who were medically ineligible for PegIFN-α/RBV-containing therapy.

Materials and methods

Study design

This open label, phase 2a study (AI447-017; clinicaltrials.gov identifier NCT01051414) was conducted in two populations of patients with HCV genotype 1 infection, including null responders (<2 $\log_{10}$ decline of serum HCV RNA levels after 12 weeks of prior PegIFN-α/RBV), and PegIFN-α/RBV ineligible/intolerant patients. The latter group discontinued prior therapy with PegIFN-α/RBV due to intolerance after <12 weeks, or patients were treatment-naïve but poor candidates for PegIFN-α/RBV for medical reasons such as advanced age or complications of depression, anemia, myelosuppression, diabetes, or cardiovascular or renal dysfunction.

Patients were enrolled in two cohorts of null responders and two cohorts of PegIFN-α/RBV ineligible/intolerant patients. One cohort of each population included intensive sampling for pharmacokinetic analyses; both cohorts of each population were combined for efficacy and safety assessments. The sentinel cohort of null responders, reported previously, provided 4-week safety data for review by the study Safety Committee, prior to initiation of the other cohorts [7]. The primary efficacy end point was the proportion of patients with undetectable HCV RNA at 12 weeks post-treatment (SVR_{12}). Key secondary end points included the proportions of patients with HCV RNA undetectable at week 4, week 12, the end of treatment, and post-treatment week 24 (SVR_{24}).

Written informed consent was obtained from all patients. The study was approved by institutional review boards at each site and was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and local regulatory requirements.

Patients

Eligible patients were men and women aged 20–75 years with HCV genotype 1 infection ⩾6 months and HCV RNA ⩾10^5 IU/ml. Women of childbearing potential were using adequate contraception. Patients were excluded if they had evidence of liver cirrhosis within 24 months of screening by laparoscopy, imaging studies, or liver biopsy; a history of hepatocellular carcinoma, other chronic liver disease, variceal bleeding, hepatic encephalopathy, or ascites requiring diuretics or paracentesis; co-infection with hepatitis B virus or HIV; other clinically significant medical conditions; exposure to any investigational drug or placebo within 4 weeks, or any previous exposure to NS5A or NS3 protease inhibitors.

Exclusionary laboratory findings included alanine aminotransferase (ALT) >5× upper limit of normal (ULN), total bilirubin ⩾2 mg/dl, direct bilirubin >1.5× ULN, international normalized ratio (INR) ⩾1.7, albumin ⩽3.5 g/dl, hemoglobin <9.0 g/dl, white blood cells <1500/mm^3, absolute neutrophils <750/mm^3, platelets <50,000/mm^3, and creatinine >1.8× ULN. Prohibited concomitant medications included CYP3A4 inducers or moderate/strong CYP3A4 inhibitors, non-study medications with anti-HCV activity, prescription or herbal products not prescribed for treatment of a specific condition, proton pump inhibitors, and erythropoiesis-stimulating agents. Prescribed H2 receptor antagonists were administered ⩾2 h after and ⩾10 h prior to daclatasvir; other acid modifying agents were administered ⩾2 h prior and ⩾2 h after daclatasvir.

Study drug dosing

Patients received 24 weeks of treatment with daclatasvir 60 mg once daily (two 30 mg tablets), combined with asunaprevir 200 mg twice daily, with 24 weeks of post-treatment follow-up. In the sentinel cohort of null responders, asunaprevir was initially administered as three 200 mg tablets twice daily (600 mg BID), subsequently reduced to 200 mg BID during treatment following reports from another study of greater and more frequent aminotransferase elevations with the higher dose [14].

Patients with HCV RNA <15 IU/ml on or after week 4 continued treatment to week 24; patients discontinued treatment if HCV RNA decreased <2 $\log_{10}$ IU/ml from baseline on or after week 2. Patients with viral breakthrough on or after week 2, or quantifiable HCV RNA (⩾15 IU/ml) on or after week 4, either discontinued treatment or weight-based PegIFN-α/RBV was added (null responders only), for up to 48 additional weeks, at the discretion of the investigator based on anticipated tolerability. Viral breakthrough was defined as confirmed ⩾1 $\log_{10}$ IU/ml increase from nadir of HCV RNA, or HCV RNA ⩾15 IU/ml after confirmed undetectable. Post-treatment relapse was defined as confirmed HCV RNA ⩾15 IU/ml during follow-up in patients with undetectable HCV RNA at the end of treatment.

Safety and efficacy assessments

HCV RNA, physical examinations, adverse events, laboratory parameters, and concomitant medications were assessed at screening, study days 1 (baseline), weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24, and post-treatment weeks 4, 8, 12, and 24. Twelve-lead electrocardiograms were recorded at all visits except weeks 3 and 6.

Serum HCV RNA levels were determined at a central laboratory using the Roche COBAS® TaqMan® HCV Auto assay, (Roche Diagnostics KK, Tokyo, Japan), lower limit of quantitation 15 IU/ml. HCV genotype and subtype and *IL28B* genotype (rs12979860) were determined by PCR amplification and sequencing. Baseline liver fibrosis was assessed by serum blood markers (APRI; AST and Platelet Ratio Index) [15]. HCV resistance-associated polymorphisms were analyzed in stored baseline samples from all patients and post-failure samples from patients with viral breakthrough or post-treatment relapse. Polymorphisms were analyzed by PCR amplification and population sequencing of the HCV NS3 protease and NS5A domains.

Statistical analysis

Categorical variables were summarized using counts and percents; continuous variables were summarized with univariate statistics.

Table 1. Baseline demographic and disease characteristics.

Parameter		Null responders n = 21	Ineligible/intolerant n = 22
Age, median yr (range)		61 (31-70)	68 (47-75)
Male, n (%)		8 (38.1)	6 (27.3)
HCV genotype 1b, n (%)		21 (100)	22 (100)
IL28B genotype, n (%)			
(rs12979860)	CT	18 (85.7)	6 (27.3)
	CC	3 (14.3)	16 (72.7)
HCV RNA, mean log_{10} IU/ml (SD)		6.8 (0.47)	6.6 (0.64)
ALT, mean U/L (SD)		57.9 (24.86)	45.7 (25.79)
APRI score			
	Score >2, n (%)	3 (14.3)	1 (4.5)
	Median (range)	0.96 (0.24-3.41)	0.57 (0.40-2.79)
PegIFN-α/RBV ineligible, n (%)		n.a.	18 (81.8)
PegIFN-α/RBV intolerant, n (%)		n.a.	4 (18.2)

n.a., Not available.

Results

Patient characteristics and disposition

Forty-nine patients were screened of which six failed to meet entry criteria; 21 null responders and 22 ineligible/intolerant patients were enrolled and treated (Table 1). The enrolled population was generally older (median 62 years), consistent with HCV epidemiology in Japan, and primarily female (67%); all patients were Japanese. No patient had prior exposure to HCV DAAs. Although any HCV genotype 1 subtype was permitted, all enrolled patients had genotype 1b infection, reflecting the high proportion of this subtype in Japan [16]. Null responders were primarily *IL28B* genotype CT (rs12979860) as expected [17]; ineligible/intolerant patients were primarily genotype CC, consistent with the distribution of *IL28B* genotypes in Japan [18]. Eighteen ineligible/intolerant patients were treatment-naïve and considered ineligible for PegIFN-α/RBV due to anticipated difficulty in completing therapy due to advanced age (≥70 years) (seven patients), cytopenia (two), depression (two), hypertension (one), or other reasons (six), consistent with common clinical practice in Japan. Four patients had prior PegIFN-α/RBV intolerance due to cytopenia (two patients), depression (one), or other reasons (one). Baseline HCV RNA and ALT levels were similar across patient groups. Although patients with cirrhosis by imaging criteria were excluded, four enrolled patients had APRI scores >2 at baseline, indicating probable cirrhosis [15].

Thirty-six of 43 enrolled patients completed 24 weeks of therapy (Fig. 1). Two null responders discontinued study medication due to hyperbilirubinemia (week 2) and aminotransferase elevation (week 12), respectively. One null responder achieved very low HCV RNA (50 IU/ml) at week 4; however, stringent protocol-defined rules required discontinuation from DAA-only therapy and addition of PegIFN-α/RBV to the dual DAA regimen at week 6. Study drugs were discontinued in four ineligible/intolerant patients due to aminotransferase elevation (week 16), viral breakthrough (week 16), or patient request (weeks 8 and 16); all four patients remained on study for assessment of SVR.

Virologic response

High rates of virologic response were seen at all time points in both study populations (Table 2). Overall, 77% of patients achieved SVR_{12} and SVR_{24}. HCV RNA was undetectable in more ineligible/intolerant patients than null responders at week 4, suggesting a more rapid initial antiviral effect, but HCV RNA was undetectable in similar proportions of both populations at week 12 and the end of treatment. Rates of SVR_{24} were higher in null responders (91%) than in ineligible/intolerant patients (64%) due to virologic failures in the latter group (3 breakthroughs and 4 relapses). Assessment of virologic response by *IL28B* genotype (rs12979860) showed slightly greater responses at weeks 2, 3, and 4 in patients with genotype CC; however, similar proportions of patients with genotypes CC and CT achieved SVR_{24} (Fig. 2). All four patients with possible cirrhosis based on APRI score achieved SVR_{24}.

HCV RNA declined rapidly after initiation of therapy in all patients (Fig. 3). Mean reductions of HCV RNA from baseline at week 4 were 5.6 and 5.4 log_{10} IU/ml in null responders and ineligible/intolerant patients, respectively; HCV RNA was undetectable by week 8 in all patients on therapy. In the ineligible/intolerant group, initial virologic response in the four intolerant patients was similar to that of the cohort overall; three of these patients subsequently achieved SVR_{24} and one relapsed. The null responder who discontinued at week 2 with hyperbilirubinemia had low-level HCV RNA at discontinuation and undetectable HCV RNA at all post-treatment assessments. The null responder who added PegIFN-α/RBV at week 6 received 46 weeks of quadruple therapy and HCV RNA remained undetectable 24 weeks post-treatment. Among the four ineligible/intolerant patients who discontinued study drugs before week 24, HCV RNA was undetectable at discontinuation (weeks 8 or 16) in three patients and remained undetectable in the two patients who completed post-treatment follow-up.

Viral breakthrough and relapse

No null responders experienced virologic breakthrough or relapse (Table 2). Three ineligible/intolerant patients experienced viral breakthrough at weeks 10 or 16 after ≥4 weeks with undetectable

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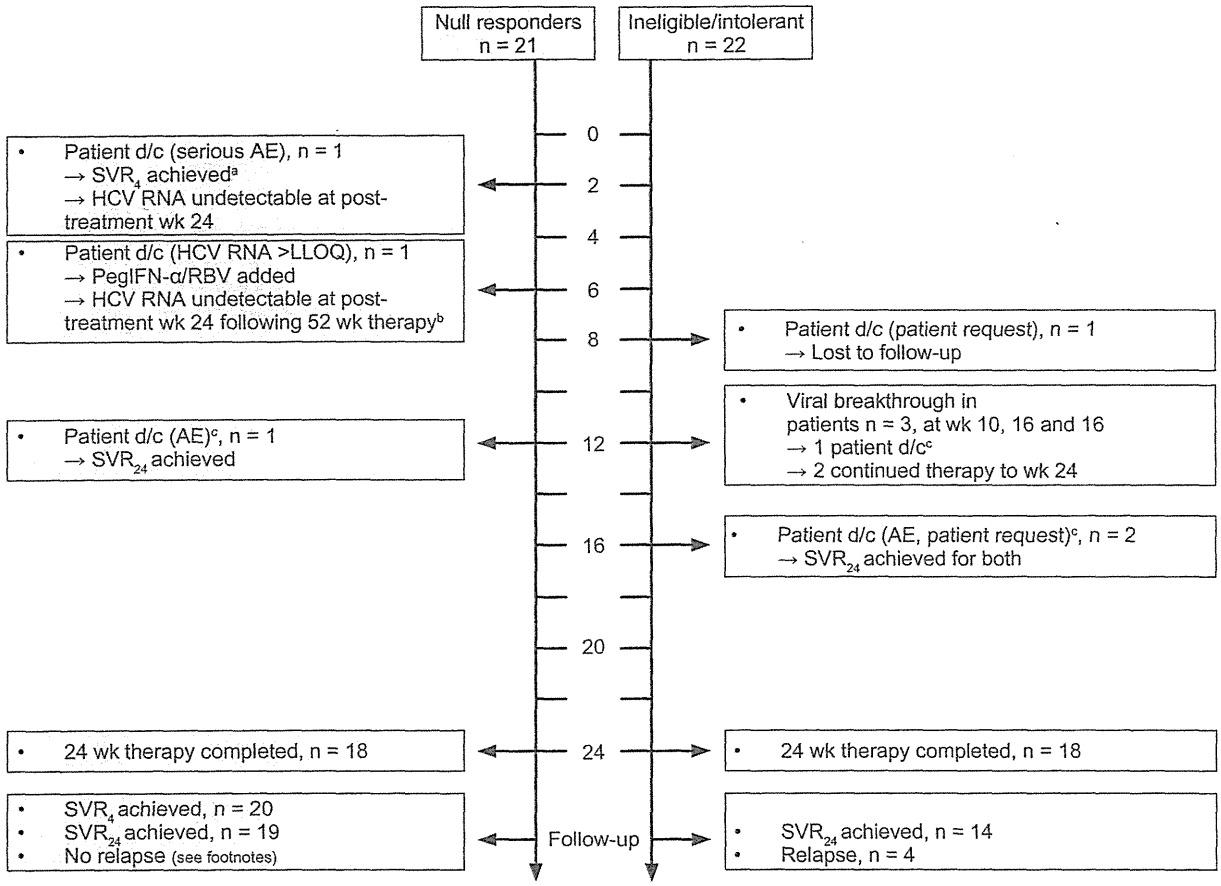

Fig. 1. Patient disposition. Patient flow through treatment and follow-up is shown. d/c, Discontinuation of study medication; SVR_4, SVR_{12} and SVR_{24}, sustained virologic response 4, 12 or 24 weeks post-treatment. [a]On-study follow-up continued to post-treatment week 4; HCV RNA remained undetectable at post-treatment week 24 after study discontinuation, reported as failure for SVR_{24} per statistical protocol requirements; [b]HCV RNA was undetectable at post-treatment week 24 after study discontinuation due to addition of PegIFN-α/RBV, reported as failure for SVR per statistical protocol requirements; [c]on-study follow-up to assess SVR continued after discontinuation of study drugs.

Table 2. Virologic outcomes.

n (%)	Null responders, n = 21	Ineligible/intolerant, n = 22
HCV undetectable		
Wk 4 (RVR)	11 (52.3)	19 (86.4)
Wk 12 (cEVR)	19 (90.5)	20 (90.9)
End of treatment	19 (90.5)	19 (86.4)
SVR_4	20 (95.2)[1]	15 (68.2)[2]
SVR_{12}	19 (90.5)[1]	14 (63.6)[2]
SVR_{24}	19 (90.5)[1]	14 (63.6)[2]
Viral breakthrough	0	3 (13.6)
Post-treatment relapse	0	4 (18.2)

Intention to treat (missing = failure) analysis. End of treatment is week 24 or last on-treatment visit for patients who discontinued early.
RVR, rapid virologic response; cEVR, complete early virologic response; SVR_4, SVR_{12}, and SVR_{24}, sustained virologic response 4, 12 or 24 weeks post-treatment.
[1]Two patients discontinued from the study before completion of follow-up. One patient received added PegIFN-α/RBV per protocol criteria and is counted as failure for SVR_4, SVR_{12}, and SVR_{24} for DAA only therapy; one patient had missing HCV RNA data for follow-up weeks 12 and 24 and is counted as failure for SVR_{12} and SVR_{24} per statistical protocol.
[2]One patient was lost to follow-up for assessment of SVR_{12} and SVR_{24}.

serum HCV RNA, and four patients relapsed at post-treatment week 4 (three patients) or 12 (one patient) after ⩾18 weeks with undetectable HCV RNA. All three patients with viral breakthrough were *IL28B* genotype CT (rs12979860), compared with 6/22 ineligible/intolerant patients overall. Three patients who relapsed were *IL28B* genotype CC; one was genotype CT.

Resistance-associated polymorphisms in NS5A and/or NS3 protease were found pretreatment in 33/43 patients overall, most of whom achieved SVR. Daclatasvir and asunaprevir resistance-associated variants were detected post-failure in all seven patients with virologic failure (Table 3). The NS5A-Y93H variant pre-existed in 10/43 study patients, of which five (50%) experienced virologic failure and five (50%) achieved SVR. NS5A-L31 and NS3-D168 substitutions emerged in all failures, but were not detected pretreatment except for NS5A-L31M in one patient.

In general, patients with virologic failure had concurrent asunaprevir and daclatasvir trough concentrations below median values, but within the expected range (Fig. 4). Notably, most patients with trough concentrations below median values achieved SVR. There were no strong associations between virologic failure and pretreatment parameters that included gender, age, baseline HCV RNA level, *IL28B* genotype, reason for PegIFN-

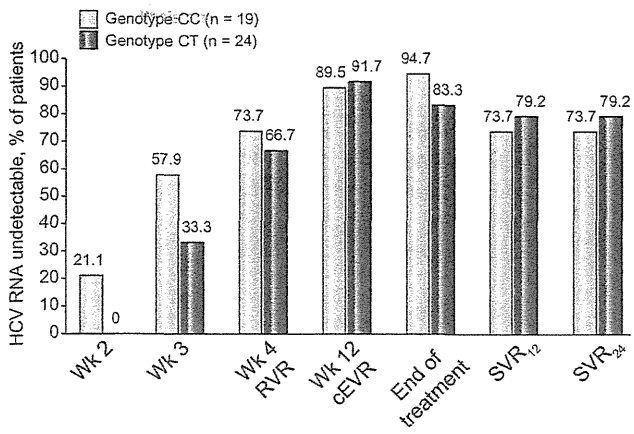

Fig. 2. Outcomes by *IL28B* genotype. Virologic outcomes at milestone time points are shown for the overall population by *IL28B* (rs12979860) genotype. End of treatment is week 24 or the last on-treatment visit for patients who discontinued early. RVR, rapid virologic response; cEVR, complete early virologic response; SVR_{12} and SVR_{24}, sustained virologic response 12 or 24 weeks post-treatment.

α/RBV ineligibility, and fibrosis stage. Adherence to treatment, assessed by pill counts at study visits, was high in six of the seven patients with virologic failure.

Safety

The most frequently reported adverse events were generally mild headache, nasopharyngitis, aminotransferase elevations, and diarrhea (Table 4). The most frequent grade 3 or 4 laboratory abnormalities were serum aminotransferase elevations. There were six serious adverse events in five patients, including grade 2/3 pyrexia (three patients), grade 2 exacerbation of hypochondriasis, and grade 2 gastroenteritis (unrelated to study drugs) with grade 4 hyperbilirubinemia (described in detail previously)

Table 3. Resistance-associated polymorphisms in patients with virologic failure.

	Patient		NS5A				NS3	
			L31	Q54	P58	Y93	Q80	D168
Viral breakthrough	1	Baseline	L/M			Y/H		
		Post-VBT	M		A	H		A
	2	Baseline		Y		Y/H	L	
		Post-VBT	M	Y		H		V
	3	Baseline		Y		H		
		Post-VBT	M	Y		H		V
Post-treatment relapse	4	Baseline			P/S	Y/H		
		Post-relapse	M			H		A
	5	Baseline			L			
		Post-relapse	M		L	H		V/D
	6	Baseline						
		Post-relapse	V			H		V
	7	Baseline				H		
		Post-relapse	V/M			H		V

[7]. All three pyrexia events resolved after 4–10 days with continued study treatment; the hypochondriasis persisted for approximately six months and resolved after completion of study treatment. In the patient who discontinued with hyperbilirubinemia, bilirubin normalized four weeks post-treatment [7]. Serum aminotransferases normalized by four weeks post-treatment in the two patients who discontinued for elevations.

Discussion

High rates of SVR_{24} were achieved after 24 weeks of dual oral DAA therapy in null responders and PegIFN-α/RBV ineligible or

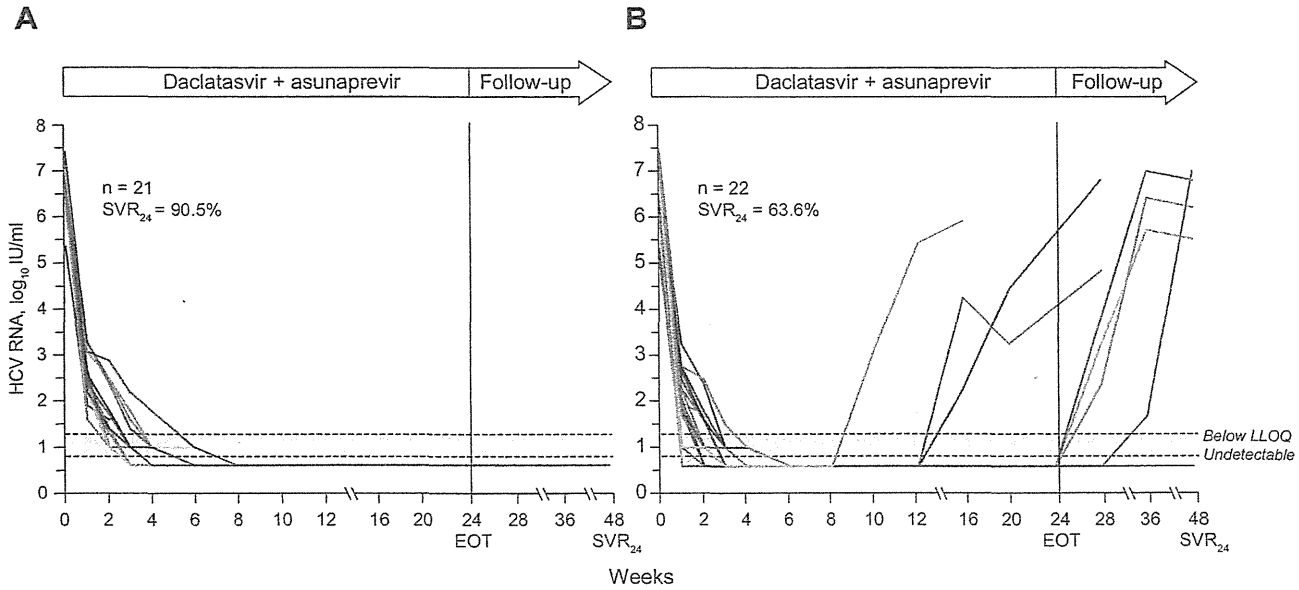

Fig. 3. HCV RNA levels, individual patients. Serum HCV RNA levels over time are shown for each patient. (A) Null responders; (B) ineligible/intolerant patients. EOT, end of treatment; SVR_{24}, sustained virologic response 24 weeks post-treatment; LLOQ, lower limit of quantitation = 15 IU/ml.

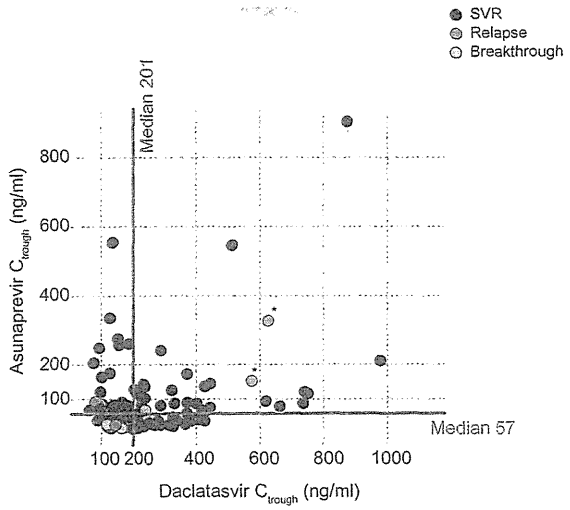

Fig. 4. Daclatasvir and asunaprevir trough plasma concentrations. Available trough plasma concentrations of asunaprevir and daclatasvir for individual patients are plotted and color-coded according to each patient's virologic outcome. Multiple determinations are shown for some patients. *Indicates values from a single patient with documented non-compliance.

Table 4. Most frequent adverse events and laboratory abnormalities.

Event, n (%)		Null responders (n = 21)	Ineligible/ intolerant (n = 22)
Adverse events occurring in ≥3 patients in either group	Headache	8 (38)	6 (27)
	Nasopharyngitis	6 (29)	8 (36)
	ALT increase	6 (29)	6 (27)
	Diarrhea	9 (43)	2 (9)
	AST increase	6 (29)	4 (18)
	Pyrexia	3 (14)	5 (23)
	Eosinophilia	1 (5)	4 (18)
	Abdominal discomfort	3 (14)	2 (9)
	Malaise	2 (10)	3 (14)
	Constipation	2 (10)	3 (14)
	Back pain	3 (14)	1 (5)
	Decreased appetite	0	3 (14)
Grade 3 or 4 lab abnormalities	ALT	2 (10)	2 (9)
	AST	1 (5)	2 (9)
	Lymphocytes	2 (10)	1 (5)
	Phosphorus	1 (5)	1 (5)
	Bilirubin, total	1 (5)	0
	Leukocytes	1 (5)	0

intolerant patients, representing two populations that are particularly difficult to treat due to limited therapeutic options. SVR rates were comparable at post-treatment weeks 4, 12, and 24; only one relapse occurred more than 4 weeks post-treatment. The 90.5% SVR rate in null responders is substantially higher than the generally poor response to PegIFN-α/RBV retreatment and the 37% SVR rate reported for genotype 1b null responders treated with PegIFN-α/RBV and telaprevir [4,19]. Therefore, therapy of this population with daclatasvir and asunaprevir appeared to overcome the poor interferon responsiveness, which may be less relevant to the efficacy of this DAA-only regimen. The SVR rate of 63.6% in ineligible/intolerant patients, although lower than results in null responders, is the first demonstration of a potentially effective treatment for these patients who currently have no therapeutic options. High SVR rates in both populations were achieved despite multiple adverse predictors of response to PegIFN-α/RBV therapy, including older age, high viral load, and a high proportion of *IL28B* genotype CT in the null responders.

Detectable HCV RNA was cleared rapidly; viral suppression was greater at all time points compared to reported results with PegIFN-α/RBV combined with telaprevir or TMC435 in genotype 1 null responders [4,20]. The slightly greater early viral suppression in ineligible/intolerant patients may reflect the higher frequency of *IL28B* CC genotype in this group. In the overall population, early virologic response was greater in patients with CC genotype, although this difference disappeared by week 12. Potentially, CC genotype may increase early viral suppression by increasing responsiveness to endogenous interferons that are released as a result of the rapid antiviral activity of the dual DAA therapy, allowing reversal of HCV-induced immunosuppression [21].

These results in patients with HCV genotype 1b differ from those reported for genotype 1a. In a similar study of US/European null responders, 2/9 patients with genotype 1a achieved SVR with daclatasvir + asunaprevir dual therapy, compared with 10/10 patients with genotype 1a who received quadruple therapy combining daclatasvir and asunaprevir with PegIFN-α/RBV [8]. This difference suggests that viral genotype can influence responses to DAA regimens, and outcomes can be optimized by individualized therapy that considers viral genotype.

The two populations included in this study represent substantial numbers of patients worldwide. Approximately 10% of HCV genotype 1-infected patients receiving PegIFN-α/RBV have a null response [22]. The cumulative prevalence of PegIFN-α/RBV null responders and the frequent failure of retreatment with current regimens, together suggest that a large population of null responders is awaiting improved therapies. The population of PegIFN-α/RBV ineligible or intolerant patients has not been extensively studied but may be substantial. In the IDEAL study, 23.2% of the 4469 patients screened were considered ineligible for PegIFN-α/RBV therapy; of these, 30.3% had hematologic or psychiatric conditions that may not preclude DAA-only regimens [23]. In registration trials, 9.7–14% of patients receiving PegIFN-α/RBV discontinued study treatment due to intolerance [24,25]. Moreover, these clinical trial data are likely to underestimate the true size of the ineligible and intolerant populations in community practice.

Virologic failures occurred relatively late in therapy after extended periods with undetectable HCV RNA. All seven patients with virologic failure had emergent NS5A and NS3 mutations that together confer high-level resistance to both daclatasvir and asunaprevir *in vitro* [11,12]. Pretreatment, NS5A-Y93H was detected in five of the seven patients with virologic failure and in five additional patients who achieved SVR, suggesting that pre-existing Y93H is loosely associated with virologic failure but is not an absolute predictor. Pharmacokinetics may also have contributed; nearly all patients with virologic failure had trough plasma concentrations of daclatasvir and asunaprevir below their respective median values. However, SVR was achieved by most patients with trough drug levels below the median, and by

several patients who discontinued study treatment after 2–16 weeks. Thus, the relationship of drug exposure to virologic outcome remains uncertain; further study is needed to define on-treatment predictors of outcome and the optimal duration of therapy.

Current data do not fully explain the observed differences in rates of virologic failure and SVR, between the two study populations. *IL28B* genotype was the primary difference between the two populations pretreatment. All three breakthroughs occurred in ineligible/intolerant patients with the unfavorable *IL28B* CT genotype; however, null responders had no breakthroughs, despite a much higher frequency of this genotype. Differing proportions of patients with concurrent pre-existing resistance-associated polymorphisms and low plasma drug concentrations may have contributed to differing rates of virologic failure between the two populations. Analysis of baseline parameters failed to identify other factors that may have influenced outcomes. However, these analyses were limited by the relatively small study population and may have been confounded by unreported non-adherence or baseline parameters not quantified absolutely, such as the stage of liver fibrosis. This issue requires further study in larger populations to confirm the apparent difference in outcomes and to identify factors predictive of virologic failure.

The adverse event profile of the study regimen was generally more favorable than that typically observed with PegIFN-α/RBV-containing regimens [26]. There were no significant hematologic or psychiatric abnormalities; the most common adverse events were non-specific in nature and generally mild to moderate in intensity. Mild diarrhea was experienced by 26% of study patients, consistent with previous studies of asunaprevir and other drugs of this class [4,6,14]. The four observed grade 3/4 ALT elevations resolved with continued therapy or after discontinuation and were not associated with significant clinical events. A role for study drugs in the reported serious adverse events cannot be ruled out except for gastroenteritis; however, four of the six events resolved spontaneously with continued treatment. The case of hyperbilirubinemia with gastroenteritis was complicated by multiple confounding factors, and the contribution of study drugs is uncertain [7].

In conclusion, dual oral therapy with daclatasvir and asunaprevir elicited rapid clearance of detectable HCV RNA and achieved high rates of SVR in two difficult-to-treat patient populations. These results confirm initial findings that HCV genotype 1b infections can be cured with daclatasvir combined with asunaprevir, without PegIFN-α/RBV [7,8]. Thus, this regimen has potential to offer effective treatment to null responders who have previously shown little or no response to PegIFN-α/RBV, and to PegIFN-α/RBV ineligible/intolerant patients who have no current treatment options. Further research will assess the benefits of this and other DAA combinations in larger and more diverse patient populations, but the promise of all oral and well-tolerated HCV therapy is on the horizon.

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Conflicts of interest

K Chayama has received research grants and consulting fees from Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Toray Industries, Otsuka Pharmaceutical Company, and GlaxoSmithKline KK. Hiroki Ishikawa, Hideaki Watanabe, Wenhua Hu, Timothy Eley, Fiona McPhee, and Eric Hughes are employees of Bristol-Myers Squibb. All other authors have no conflicts to report.

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Virological response and safety of 24-week telaprevir alone in Japanese patients infected with hepatitis C virus subtype 1b

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SUMMARY. Hepatitis C virus (HCV) subtype 1b, which infects approximately 70% of Japanese carriers, is likely to be more eradicable by a telaprevir regimen than subtype 1a because of the higher genetic barrier of Val^{36} and Arg^{155} substitutions. The aims of this exploratory study were to evaluate the virological response and safety of 24-week oral administration of telaprevir alone in chronic HCV subtype 1b infection. Fifteen treatment-naïve patients were treated with telaprevir 750 mg every 8 h for 24 weeks. All patients were Japanese whose median age was 58.0 years (range: 45–68), and six patients (40%) were men. Median baseline HCV RNA level was 6.80 $\log_{10}$ IU/mL (range: 3.55–7.10). The HCV RNA levels decreased to undetectable in five patients (33%) within 8 weeks. Three patients (20%) with negative HCV RNA by Week 4 achieved end of treatment response. One patient (7%) who achieved sustained virological response had a low baseline viraemia of 3.55 $\log_{10}$ IU/mL. Most of the adverse events including anaemia and skin disorders were mild to moderate. Developed variants were T54A and A156V/T/F/Y with or without secondary substitutions rather than V36M ± R155K. Telaprevir alone for 24 weeks in Japanese patients with HCV subtype 1b resulted in an sustained viral response rate of 7% (1/15) and was well tolerated for 24 weeks. These results will support the implementation of further studies on oral combination of telaprevir with other direct-acting antiviral agents in patients infected with HCV subtype 1b.

Keywords: hepatitis C virus, monotherapy, subtype 1b, telaprevir.

INTRODUCTION

The World Health Organization (WHO) estimates that approximately 170 million people are infected with hepatitis C virus (HCV) [1]. In Japan, it is estimated that more than 1.5 million people are chronically infected with hepatitis C.

Telaprevir is a novel peptidemimetic HCV NS3-4A protease inhibitor. The mechanism of inhibition involves the formation of a stable, reversible, covalent bond between the ketocarbonyl of telaprevir and the active site serine of NS3 protease. Recently, telaprevir was approved for patients with HCV genotype 1 infection in the United States (US), Canada, European Union (EU) and Japan. The Phase 3 studies showed that patients who received telaprevir in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV) achieved significantly higher rates of sustained viral response (SVR) compared to those who received PEG-IFN and RBV alone, regardless of their prior treatment experience [2–4]. The Japanese Phase 3 studies of the telaprevir-based triple regimen also showed high SVR rates [5,6]. The most common side effects in the telaprevir-based triple regimen were anaemia, rash and IFN-induced systemic symptoms.

The epidemiology of HCV in Japan takes on a different aspect from US and EU; that is, the majority of patients are aged more than 55 years [7]. Accordingly, the RBV dose reduction rate and the frequency of discontinuation of telaprevir treatment in Japan are higher than those in US and EU [2–6]. Taking such problems with telaprevir in combination with PEG-IFN and RBV into consideration, IFN-free

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral agent; EU, European Union; HCV, Hepatitis C virus; LDL, low-density lipoprotein; LOQ, lower limit of quantification; PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained viral response; T-bil, total bilirubin.

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regimens may become very useful options and satisfy important unmet medical needs especially for intolerant patients with IFN-based regimens. Clinical trials of IFN-free therapy for patients with chronic hepatitis C would provide us with meaningful knowledge for the future development of HCV therapy. Interestingly, HCV subtype 1b, which infects approximately 70% of Japanese HCV carriers [8], is likely to be more eradicable by telaprevir regimens than subtype 1a because of the higher genetic barrier of Val^{36} and Arg^{155} substitutions [9,10]. When treating with direct-acting antiviral agent (DAA), HCV subtypes of genotype 1 are now an important factor that affects treatment response. The main aim of this exploratory study is to evaluate the virological response and safety of telaprevir as monotherapy for 24 weeks in Japanese patients infected with HCV subtype 1b.

PATIENTS AND METHODS

Study design and organization

This Phase 2, single-arm, open-label study was conducted from January 2008 to February 2009 at Sapporo Kosei General Hospital, Musashino Red Cross Hospital, Toranomon Hospital and Hiroshima University Hospital. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. Before starting the study, the protocol and informed consent forms were reviewed and approved by the institutional review board in each site. All patients provided written informed consent following sufficient explanation before participating in the study. All the patients received 750 mg telaprevir orally every 8 h (q8h) (2250 mg/day) after a meal for 24 weeks. Telaprevir was given as a 250-mg tablet. This study is registered in ClinicalTrials.gov NCT 00621296.

Patients

Participants enrolled in this study were treatment-naïve, male or female chronic hepatitis C patients with the characteristics shown in Table 1 who met the inclusion criteria and did not conflict the exclusion criteria described previously [11], except the age and HCV RNA levels at the time of enrolment: age from 20 to 70 years and HCV RNA levels were not defined.

Virological responses

Virological response to telaprevir was evaluated based on the HCV RNA kinetics in patients. Serum HCV RNA levels were measured using the COBAS TaqMan HCV test (Roche Diagnostics Co., Ltd., Tokyo, Japan). The linear dynamic range was 1.2–7.8 $\log_{10}$ IU/mL. A qualitative result below the lower limit of quantification (LOQ) was also determined as positive (1.0) and negative (0.5). Measurements were obtained on Week 4 before the first dose, Days 1 (prior to the first dosing) and 3, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 of the treatment period, and Weeks 2, 4, 8, 12, 16, 20, and 24 of the follow-up period. Day 1 was defined as the date of starting telaprevir treatment.

Table 1 Patient characteristics, treatment duration and viral response

	Sex	Age	BMI (kg/m^2)	Baseline HCV RNA ($\log_{10}$ IU/mL)	Treatment duration (day)	HCV RNA Nadir ($\log_{10}$ IU/mL)	Virological response
1	M	67	25.2	5.85	169 (complete)	Undetectable	Relapse
2	M	59	24.5	3.55	169 (complete)	Undetectable	SVR
3	F	45	18.7	6.80	44*	2.8	Breakthrough
4	F	68	20.9	7.05	43†	<1.2 detectable	Partial responder
5	F	48	21.5	6.45	169 (complete)	Undetectable	Breakthrough
6	F	57	20.9	4.75	43*	1.8	Breakthrough
7	F	51	19.9	5.95	170 (complete)	Undetectable	Partial responder
8	F	58	19.2	6.85	105*	1.5	Breakthrough
9	M	62	20.4	6.25	14†	1.4	Partial responder
10	M	58	24.5	7.10	39*	3.1	Breakthrough
11	M	63	16.2	7.00	74*	<1.2 detectable	Breakthrough
12	F	53	25.0	7.10	169 (complete)	Undetectable	Relapse
13	F	60	19.7	5.00	10‡	<1.2 detectable	Breakthrough
14	F	55	23.8	6.95	78*	<1.2 detectable	Breakthrough
15	M	50	27.5	6.90	26‡	1.3	Partial responder

HCV, Hepatitis C virus; SVR, sustained viral response. Subjects discontinued telaprevir because of *viral breakthrough, †AE and ‡other reasons.