別添（1年目用）

平成21年度 肝炎等克服緊急対策研究事業 成果概要

研究課題：B型肝炎の核酸アナログ薬治療における治療中止基準の作成と治療中止を目指したインターフェロン治療の有用性に関する研究
課題番号：H21-肝炎-一般-001
研究代表者：田中榮司

Ⅰ．研究の意義

(1)B型慢性肝炎の核酸アナログ薬治療において、現在、有効な中止基準がない。
(2)B型慢性肝炎の核酸アナログ薬治療において、現在、効果的な中止方法がない。

Ⅱ．研究の目的、期待される成果

(1)核酸アナログ薬治療の中止基準を作成することを目的。
(2)核酸アナログ薬治療の効果的な中止方法を開発することを目的。

Ⅲ．1年間の研究成果

・研究代表者
(1) 後ろ向きの共同研究で核酸アナログ薬中止例を検討し、予備的検討の段階ではあるが、HBe抗原・抗体とHBV DNA量に加え、HBコア関連抗原量、HBs抗原量などが中止基準作成の有用なマーカーになる可能性が示唆された。
(2) 核酸アナログ薬治療例の前向き検討を開始した。
(3) シークエンシャル治療の後ろ向き研究で、症例および保存血清の登録を行った。
(4) シークエンシャル治療の前向き研究のプロトコールを検討した。
(5) HBV RNA測定法を、一般検査として使用できるように改良を行った。
(6) HBs抗原量の自然経過での推移を検討し、HBVの活動性の他に年齢の影響を大きく受けることを明らかにした。

・研究分担者 (鈴木 義之)
(1) HBs抗原消失例では核酸アナログ薬を中止しても予後が良いことを明らかにした。
(2) HBコア関連抗原量が肝細胞中のHBV cccDNA量と相関することを明らかにした。
(3) 核酸アナログ薬治療例の前向き検討を開始した。

・研究分担者 (新海 登)
(1) HBコア関連抗原量とHBs抗原量が核酸アナログ薬中止基準のマーカーとして有用である可能性を示唆した。また、遺伝子型との関連も検討した。
(2) 核酸アナログ薬治療例の前向き検討を開始した。

・研究分担者 (平松 直樹)
(1) インターフェロン治療と各種HBVマーカの推移との関連を検討した
(2) 核酸アナログ薬治療例の前向き検討を開始した。

・研究分担者(豊田 成司)
(1) 多数の核酸アナログ薬治療例について、HBe抗原・抗体、RTD-PCR法によるHBV DNA量、HBコア関連抗原量、その他の推移を検討した。
(2) 核酸アナログ薬治療例の前向き検討を開始した。

・研究分担者(柘植 雅貴)
(1) HBV RNA量と核酸アナログ薬中止後の経過との関連を検討した。
(2) 核酸アナログ薬治療例の前向き検討を開始した。

・研究分担者(今関 文夫)

(1) HBs 抗原量の自然経過での推移を検討し、中止基準マーカーとして用いる場合の基礎データーを検討した。
(2) 核酸アナログ薬治療例の前向き検討を開始した。
・研究分担者(髭　　修平)
(1) 肝細胞中 HBV cccDNA 量と血中 HBV DNA 量、HB コア関連抗原量、HBs 抗原量との関連を検討した。
(2) 核酸アナログ薬治療例の前向き検討を開始した。
・研究分担者(八橋　　弘)
(1) HBs 抗原量の自然経過での推移を検討し、中止基準マーカーとして用いる場合の基礎データーを検討した。
(2) 核酸アナログ薬治療例の前向き検討を開始した。
・研究分担者(齋藤　正紀)
(1) HBs 抗原量の自然経過での推移を検討し、中止基準マーカーとして用いる場合の基礎データーを検討した。
(2) 核酸アナログ薬治療例の前向き検討を開始した。

Ⅳ. 22～23 年度の課題

(1) 後ろ向き共同研究での核酸アナログ薬中止例の検討について、さらに症例数を増やして解析を行う。治療中止基準に使用するウイルスマーカーとしては、HBe 抗原・抗体、HBV DNA 量、HB コア関連抗原量、HBs 抗原量などに加え、RTD-PCR 法による HBV DNA 量、HBV RNA 量、遺伝子型、ウイルス変異（CP、PreC 変異など）などを加える。
(2)前向き共同研究として、核酸アナログ薬投与例を前向きに経過観察し、その経過と各種マーカーとの関連を検討する。さらに、治療中止例について中止の条件を前向きに検討する。
(3)核酸アナログ薬治療の中止を促進する方法を検討する。特に、本研究班では、核酸アナログ薬を長期に使用した後にインターフェロンを併用し、同治療の中止を目指したシークエンシャル治療を検討する。

Ⅴ. 行政施策への貢献の可能性

(1)核酸アナログ薬治療の中止基準作成の可能性
(2)核酸アナログ薬治療の効果的な中止方法開発の可能性

Ⅵ. 本研究の成果(発表論文・ガイドライン・マニュアル等)

(1)研究代表者

1. Akihiro Matsumoto, Noboru Maki, Noriko Misawa-Kobayashi, Kaname Yoshizawa, Tetsuya Ichijo, Takeji Umemura, Naoki Tanaka, Kaoru Arai, Michiharu Komatsu, Satoru Joshita, Kendo Kiyosawa, Eiji Tanaka. Comparison of hepatitis B virus DNA, RNA, and core related antigen as predictors of lamivudine resistance in patients with chronic hepatitis B. Hepatol Res (in submission)
2. Kumada H, Okanoue T, Onji M, Moriwaki H, Izumi N, Tanaka E, Cyayama K, Sakisaka S, Takehara T, Oketani M, Suzuki F, Toyota J, Nomura H, Yoshioka K, Seike M, Yotsuyanagi H, Ueno Y. Guidelines for the treatment of cronic hepatitis and cirrhosis induced by hepatitis B virus infection for the fiscal year 2008 in Japan. Hepatol Res (in press)

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Ⅶ. Ⅲ(1年間の研究成果)の概要図等

《目的》
1. B型肝炎の核酸アナログ薬治療において、より効率的な治療中止基準の作成する。
2. 核酸アナログ薬中止を目指したIFN治療の有用性を検討する。

《対象》
1. 通常のB型慢性肝炎例
2. HBV再活性化予防のため核酸アナログ薬を使用したB型肝炎例

《検討項目》
通常のHBV関連マーカー、HBコア関連抗原量、HBV RNA量、HBV cccDNA量、HBs抗原量、遺伝子型、ウイルス変異、等

核酸アナログ薬中止基準の検討

後向き検討

4施設の症例で予備的検討を行った

他施設の中止例の登録を行った。提供された保存血清を用いて、さらに検討を行う

前向き検討

プロトコールを決め、共同で症例の登録を開始した

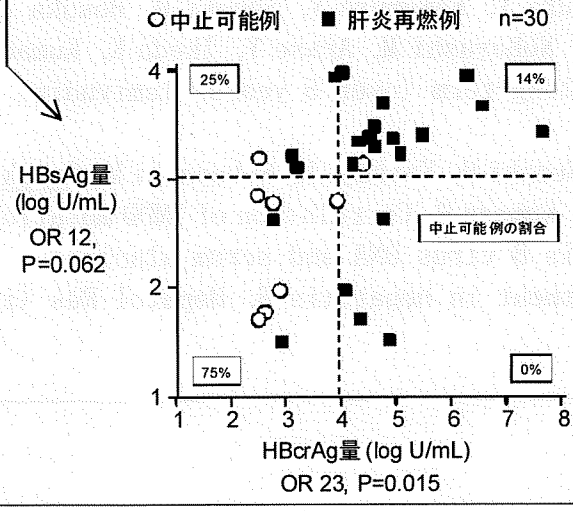
核酸アナログ薬中止を目指したIFN治療の有用性の検討

後向き検討

IFN治療例の登録を行った。提供された保存血清も利用して、有用性を検討する

前向き検討

前向き研究のプロトコールを今年度中に決定する



図：核酸アナログ薬中止時のHBcrAg量とHBsAg量別にみた中止可能例の分布。
全例、中止時はHBe抗原陰性で血中HBV DNA陰性であった。□内の%は各領域の中止可能例の割合を示す。

この成績より以下のことが明らかになった。核酸アナログ薬中止時、HBcrAg量やHBsAg量が高い症例では中止後の肝炎再燃率が高く、中止は推奨されない。また、両者が低値の症例では中止可能例が多数になるが、十分条件ではなく、今後さらに条件を検討する必要がある。

○研究代表者の研究歴等

・過去に所属した研究機関の履歴

1. 1987年10月1日～現在　信州大学医学部内科学第二
2. 1999年2月22日～1999年3月15日　Roche診断薬ペンツベルグ研究所
3. 1995年10月1日～1996年3月31日　米国国立衛生研究所（NIH）
4. 1982年7月1日～1984年12月31日　自治医科大学予防生態
5. 1978年4月1日～1982年6月30日　信州大学大学院医学研究科

・主な共同研究者（又は指導を受けた研究者）

1. 清澤研道教授（信州大学医学部内科学第二）
2. Dr. Georg Hess（Roche診断薬ペンツベルグ研究所、ドイツ）
3. Dr. Harvey J Alter（米国国立衛生研究所、米国）
4. 真弓　忠教授（自治医科大学予防生態）
5. 古田精市教授（信州大学大学院医学研究科）

・主な研究課題

1. ウイルス肝炎の診断、疫学、治療
2. HBs145変異抗原測定系の開発と臨床応用
3. G型肝炎ウイルスの検出と臨床的意義
4. HBV DNA量の測定、IFNの基礎研究、新しい肝炎ウイルスのクローニン
5. 肝腎相関、ウイルス肝炎の診断と治療

・これまでの研究実績

《知的財産権の取得》

1. 特願 2003-83283：HBV-RNA を含む HBV 粒子（2003/3/25）
2. 特願 2004-558464：B 型肝炎ウイルスの薬物抵抗性を識別する方法（2003/12/10）
3. 特願平 8-167497：C 型慢性肝炎の治療効果を事前に予測するためのキット（1996/6/27）
4. 特願平 6-71701：競合 PCR 法による核酸の簡易定量法（1994/3/15）

《研究課題の実施を通じた政策提言》

1. B型肝炎治療ガイドライン2009
2. C型肝炎治療ガイドライン2009
3. 免疫抑制・化学療法により発症するB型肝炎の診療ガイドライン（案）
4. 肝疾患における肝炎ウイルスマーカーの選択基準（4版）
5. 肝機能検査法の選択基準（7版）

《主な発表論文》

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2. ***Kumada H, Okanoue T, Onji M, Moriwaki H, Izumi N, Tanaka E, Cyayama K, Sakisaka S, Takehara T, Oketani M, Suzuki F, Toyota J, Nomura H, Yoshioka K, Seike M, Yotsuyanagi H, Ueno Y. Guidelines for the treatment of cronic hepatitis***

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平成21年度　肝炎等克服緊急対策研究事業　成果概要

研究課題：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
課題番号：H21-肝炎-一般-002
研究代表者：持田　智

Ⅰ．研究の意義

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の既往感染例に投与すると再活性化が生じて重症肝炎を発症する場合がある。その実態と核酸アナログ製剤による予防法に関しては，厚労科研費補助金「楠本班」がprospectiveな検討を開始した。リツキシマブ以外の免疫抑制薬，抗悪性腫瘍薬でも同様の現象を生じる可能性があるが，その実態は明らかでない。免疫抑制･化学療法によって生じるHBVの再活性化に関しては，平成20年に厚労科研費補助金「坪内班」，「熊田班」が合同で予防法に関するガイドラインを発表した。同ガイドライン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が，その意義は不明である。

Ⅱ．研究の目的，期待される成果

本研究ではリツキシマブ以外の免疫抑制・化学療法をうけるHBV既往感染・キャリア例を対象に再活性化の実態をprospective調査で解明することを目指す。

血液，腎臓，リウマチ・膠原病，腫瘍内科などの診療分野で免疫抑制薬，抗悪性腫瘍薬を頻用する研究協力者を組織し，既往感染・キャリア例を登録してHBV-DNAを定期的に測定し，再活性化の頻度と治療法との関連を明らかにする。本研究によってHBV再活性化の実態が明らかになれば，HBV-DNAを測定する症例を絞り込むことによって医療費を削減することが可能になる。

Ⅲ．1年間の研究成果

・研究代表者（持田　智）

(1)　患者の登録システム，患者血清の輸送及び保存方法の確立
(2)　登録患者の説明文書，同意文書，調査用紙の作成
(3)　研究協力者を含む全国研究組織の確立
(4)　第1回班会議の開催：研究分担者による研究方法の最終決定
　　平成21年6月22日：東京国際フォーラム
(5)　第2回班会議の開催：研究分担者，協力者による研究方法の確認および修正
　　平成22年2~3月（予定）
(6)　埼玉医科大学における倫理委員会への申請，承認獲得

・研究分担者：事務局（楠本　茂，池田健次，井戸章雄）

(1)　患者の登録システムの確立，研究方法の最終決定に関する助言，補助作業
(2)　登録患者の説明文書，同意文書，調査用紙の作成の関する助言，補助作業

(3) 所属施設における倫理委員会の申請
(4) HBV の遺伝子解析に関する実験系の確立に際しての基礎的検討

・研究分担者：各領域責任者（別所正美，檀　和夫，三村俊英，山本一彦，鈴木洋通，浦　信行，佐々木康綱，藤井博文）

(1) 所属施設における倫理委員会の申請
(2) 各専門領域において対象とする疾患，治療法の決定
(3) 研究組織（研究協力者）の選任
(4) 研究協力者の施設における倫理委員会申請の補助
(5) 埼玉医科大学および倫理委員会の承認を得た施設では HBV スクリーニングと該当症例の登録を開始している。

・研究協力者

(1) 所属施設における倫理委員会の申請

血液領域：北海道大学，旭川医科大学，国立北海道がんセンター，岩手医科大学，秋田大学，群馬大学，自治医科大学，筑波大学，防衛医科大学校，埼玉医科大学総合医療センター，埼玉県立がんセンター，小川赤十字病院，独協医科大学越谷病院，武蔵野赤十字病院，多摩北部医療センター，昭和大学，東京医科大学，都立駒込病院，東京女子医科大学，NTT 東日本関東病院，東京慈恵医科大学付属第三病院，国立がんセンター東病院，千葉県がんセンター，神奈川県立がんセンター，北里大学，福井大学，浜松医科大学，名古屋大学，愛知医科大学，名古屋市立東部医療センター，愛知県厚生農業協同連合会江南厚生病院，三重大学，滋賀県立成人病センター，愛媛大学，国立九州がんセンター，佐賀大学，国立長崎医療センター，佐世保市立総合病院，国立熊本医療センター，熊本大学，鹿児島大学

リウマチ・膠原病領域：北海道大学，自治医科大学，筑波大学，群馬大学，東京医科歯科大学，慶応義塾大学，杏林大学，藤田保健衛生大学，京都大学，神戸大学，産業医科大学，長崎大学

腎臓領域および腫瘍内科領域：血液領域，リウマチ・膠原病領域の研究施設が倫理委員会の承認を得た後に，同施設の当該診療科に協力者を依頼する。

Ⅳ. 22~23 年度の課題

(1) 倫理委員会の承認を得た施設から順次に対象症例の HBV スクリーニングを開始する。
(2) 平成 22 年度中に 4 領域全体で HBV キャリア 30 例，既往感染 500 例を登録し，研究計画に従って血清 HBV-DNA を測定する。
(3) 事務局は登録症例が研究対象として適切であるかどうかを，当該領域の研究分担者とともに検討する。
(4) 事務局では血清 HBV-DNA の成績および付帯情報を管理し，再活性化例では当該領域の研究分担者とともに核酸アナログ製剤が適切に投与されたかどうかを確認する。
(5) 事務局は核酸アナログ製剤を開始した症例の経過を，付帯情報を基に当該領域の研究分担者とともに定期的に検討し，必要に応じて保存血清によるウイルス遺伝子解析の適応を決定す