I. 総　　論

C型肝炎治療における宿主因子とウイルス因子

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Host factors and viral factors in hepatitis C treatment

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Abstract

In the interferon-based therapy for hepatitis C, host factors such as age, gender, liver fibrosis and steatosis are important as a therapeutic effect predictor, and viral factors such as HCV genotype, HCV viral load, HCV gene (*IL28B, ITPA*) are also important. In addition in genotype 1b, ISDR/IRRDR and core amino acid substitution are important. Also in the DAA treatment, viral factors are also important at the view of therapeutic effect and difficulty of acquisition of drug resistance mutation. In addition, the goal of treatment of hepatitis C are suppression of liver fibrosis progression and liver cancer and improvement of quality of life due to this (quality of life: QOL) and life prognosis, it is important to understand the host factors and HCV viral factors.

Key words: IL28B, ITPA, ISDR, IRRDR, core amino acid substitution

はじめに

C型肝炎治療の目標はC型肝炎ウイルス(hepatitis C virus: HCV)の排除と，これに基づく持続炎症の鎮静化，そして肝発癌抑止である．現在これを可能とするのはインターフェロン(interferon: IFN)を中心とした治療と，HCVに直接作用するdirect antiviral agents(DAA)である．特にIFN治療は長い歴史があり，単独療法，ポリエチレングリコールを結合させ，作用期間を延長したPEG-IFN，そしてリバビリン(ribavirin: RBV)との併用療法が長く行われてきた．さらにDAAと併用し，我が国では1型のHCVに対し，HCV NS3-4 protease inhibitorのテラプレビル(telaprevir: TVR)，シメプレビル(simeprevir: SMV)，バニプレビル(vaniprevir: VPV)の3剤併用療法が，2型に対してはTVRとの併用が認可されている．一方，DAA製剤のみの治療も実用化され，2014年現在，我が国では1型のHCVに対し，NS3-4 protease inhibitorのアスナプレビル(asunaprevir: ASV)とNS5A阻害剤のダクラタスビル(daclatasvir: DCV)の2剤併用療法が行われ[1]，また海外では既に，NS5B polymerase inhibitorであるソフォスブビル(sofosbuvir: SOF)[2]も用いられている(表1)．

1. 宿主因子

これまで，C型肝炎に関する疾患関連遺伝子

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表1 わが国のC型肝炎治療(2014年現在)

IFNベースの療法
IFN単独療法(IFN各種, PEG-IFNα2a)
IFNα2bまたはIFNβ+RBV療法
PEG-IFNα2aまたはPEG-IFNα2b+RBV療法
PEG-IFNα2b+RBV+TVR療法(1型, 2型)
PEG-IFNα2aまたはPEG-IFNα2b+RBV+SMV療法(1型のみ)
PEG-IFNα2b+VPV療法(1型のみ)
DAAのみの治療
ASV+DCV

の検討が行われ，ゲノム関連分析(genome-wide association study: GWAS)から，PEG-IFN+RBV療法の治療効果規定因子として9番染色体上のIFN-λ遺伝子近傍のIL28B領域の1塩基多型(single nucleotide polymorphism: SNP)が明らかになっている．すなわちこのSNP(rs8099917)がmajor allele(TT)であれば治療効果が高く，minor allele(TG/GG)であれば治療抵抗性である[5]．このSNPはPEG-IFN+RBVの治療効果に関連するのみならず，HCVの自然排除にも関連していることが明らかになっている[5]．そのほか，C型肝炎の疾患進展・線維化に関連する因子としてRNF7，MERTK[6]，肝発癌関連因子としてMICA[6]，DEPDC5[7]などが報告されている．また，RBV併用時には貧血が問題となるが，これに関連した因子がinosine triphosphate(ITPA)遺伝子である．RBVは細胞内でリン酸化され，リバビリン3リン酸(RTP)に変化し，イノシン1リン酸(IMP)脱水素酵素を阻害し細胞内のグアノシン3リン酸(GTP)を減少させることでウイルスRNAの複製を抑制する．赤血球には核がないため脱リン酸化されないRTPが蓄積し溶血性貧血を起こすが，ITPAはイノシン3リン酸(ITP)をIMPやイノシン2リン酸(DMP)に脱リン酸化する酵素であるため，血清低下により溶血に対して保護的に作用する．すなわちITPA遺伝子多型(rs1127354)がmajor allele(CC)であれば溶血性貧血をきたしやすいが，minor allele(CA/AA)では溶血に対してprotectiveに作用する[8]．

このほか，PEG-IFN+RBVなどIFNベースの治療では，治療効果と関連する宿主因子として，年齢，性，肝線維化・脂肪化などが臨床的に明らかになっている[9](表2)が，その機序は必ずしも明らかではない．しかし，DAAのみの治療では，これら因子の治療効果に及ぼす影響は必ずしも大きくなく，年齢・性別，線維化に関係なくウイルス排除を達成できることが明らかになっているため，これら因子はIFNが宿主免疫に関与して効果を示すという機序と関連している可能性がある．

表2 インターフェロン効果と関連する宿主因子

年齢
性別
肝線維化・脂肪化
IL28B
ITPA

2. ウイルス因子

1) C型肝炎ウイルスの遺伝子構造(図1)

HCVは+1本鎖のRNAウイルスであり，ゲノムの両端に非翻訳領域が存在し，中央部には約3,010個のアミノ酸からなる1本のポリタンパク前駆体をコードするopen reading frameが存在する．この領域にはHCVの構造タンパク(コア，エンベロープタンパク)とウイルス増殖に必要な種々の酵素をコードする非構造領域(nonstructural region: NS)が存在する．このうち，NS3領域はproteaseとhelicase活性をもつ酵素をコードし，前者はポリタンパク前駆体から個々の非構造タンパクを形成し，後者は2本鎖RNAを1本鎖に解くウイルス由来のRNA生

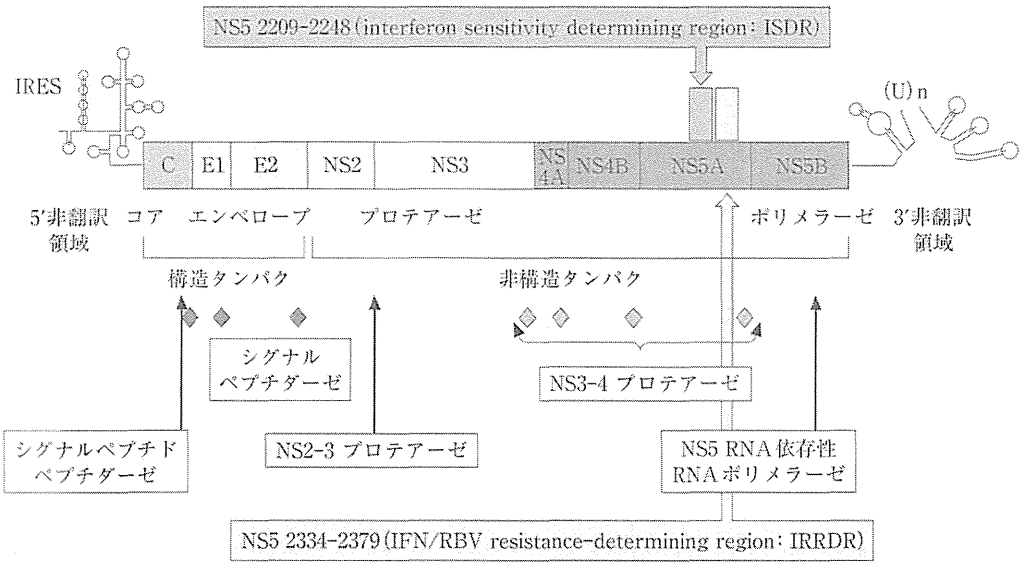

図 1　C 型肝炎ウイルスの遺伝子構造

成に関与している．NS3 protease はウイルス増殖には極めて重要で，この阻害剤が治療に用いられる．NS5A 領域は 450 アミノ酸残基からなるリン酸化タンパクで，RNA 依存性 RNA polymerase と結合し，その活性を制御するなど種々の tyrosine kinase 活性を調節しており，ウイルス RNA 複製に関与している．特に HCV の粒子生成過程でコアタンパクと相互作用し重要な役割を担っていると考えられ，NS5A 阻害剤は HCV の複製複合体を阻害することでその効果を発揮する．また，この領域内の N 末端側のアミノ酸変異は HCV の RNA の複製効率に影響し，IFN 治療効果と関連する領域が ISDR や IRRDR として報告されている．また，NS5B 領域は RNA 依存性 RNA polymerase をコードしている．この領域を標的とした核酸型の NS5B polymerase 阻害剤は polymerase に直接取り込まれ chain terminator として塩基伸長・複製を抑制する．このため，この代表的な阻害剤である SOF は，遺伝子型（genotype）によらず有効で薬剤耐性変異を生じにくい．一方 dasabuvir に代表される非核酸型の polymerase 阻害剤はタンパクの一部を標的とするため，genotype による薬効の差異や薬剤耐性変異を生じることが推測される．

2）遺伝子型

C 型肝炎治療におけるウイルス因子として，最も重要なのはウイルス遺伝子型（genotype）である．DAA 治療においては，その標的部位はウイルス構造もしくはウイルスによって生成されるタンパクであるため，DAA の効果発現や薬剤耐性変異獲得に大きく関与する．このため，DAA 製剤は，genotype により，大きく治療効果が異なるほか，耐性変異獲得の遺伝的障壁（genetic barrier）の差異が論じられている．例えば HCV-NS3 領域の 155 番アミノ酸はアルギニン（R）であるが，このアミノ酸をコードする塩基が genotype 1b では CGG であるのに対し，genotype 1a では AGG である．このため（K: AAG）に変化するために 1b では 2 個の塩基変異が必要なのに対し 1a では 1 塩基変異でアミノ酸置換が生じる[10]（**図 2**）．現在のところ多くの DAA 製剤は genotype 1 を標的として設計開発されている．

一方，IFN ベースの治療では従来から，genotype による治療効果の差異が明らかになっている．すなわち，わが国で最も多い 1b 型では IFN 感受性が劣り，2b，2a の順に効果が高まる．この相違の理由は必ずしも明らかではないが，genotype により 20％以上の塩基配列の

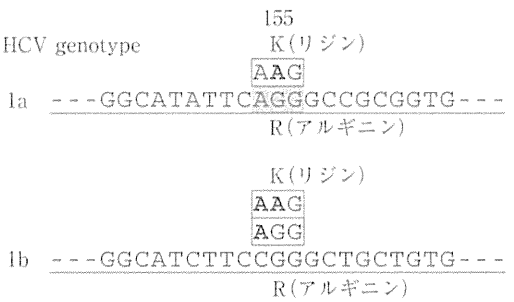

図2 HCV-NS3領域155番アミノ酸のR(アルギニン)からK(リジン)への変化へのgenotypeによる遺伝的障壁の違い

表3 インターフェロン治療効果と関連するウイルス因子

ウイルス遺伝子型(genotype)
ウイルス量
1b型の場合
ISDR
IRRDR
コアアミノ酸置換(aa70, aa91)

相違があり，ウイルス増殖様式も異なることが想定されている．

3）1b型における遺伝子変異

IFN抵抗性の1b型では，IFN単独療法において，HCVのNS5A領域内の40アミノ酸領域がインターフェロン感受性領域(interferon sensitivity determining region: ISDR)として報告され[11]，PEG-IFN+RBV療法では，IFN/RBV耐性決定領域(interferon/ribavirin resistance-determining region: IRRDR)[12,13]やコア領域のアミノ酸置換が治療効果と密接に関連することが明らかになっている[14](表3)．また，PEG-IFNとRBVにDAA製剤であるTVRやSMVを併用する3剤併用療法においても，これらが治療効果と関連することが知られている．3剤併用療法はPEG-IFN+RBV療法と比較して高いウイルス排除率(sustained viral response: SVR)が得られるため，その影響は限定されるが，治療効果予測因子として重要である．特に，3剤併用療法が以前の治療効果と関連し，PEG-IFN+RBV療法で治療中にいったんウイルスが検出感度以下に低下するも治療後にウイルスが再出現した「再燃」例では，極めて高い治療効果が期待できる反面，PEG-IFN+RBV療法で一度もウイルスが検出感度以下に低下しない「無効」例では治療効果は限定的である．したがって，3剤併用療法でもPEG-IFN+RBV治療効果を規定するウイルス因子が重要であることは自明である．

3. C型肝炎治療における，宿主因子・ウイルス因子の意義と臨床応用

C型肝炎治療において，IFNベースの治療では治療効果規定因子として，宿主因子・ウイルス因子は重要であったが，DAAのみの治療では，その高い治療効果ゆえに治療効果規定因子としての重要性は低い．しかし一方，DAAはウイルス遺伝子もしくはタンパクに直接作用するため，genotypeなどのウイルス因子は治療法選択には不可欠である．genotypeによっては治療効果がない薬剤があるばかりか，遺伝的障壁の相違から薬剤耐性変異獲得の可能性の難易に関与する．

さらに，C型肝炎の治療目標は肝炎の沈静化と肝線維化進展抑制，肝癌抑止であり，これによる生活の質(quality of life: QOL)改善と生命予後の延長である[15]．HCV排除はこのための手段であるにすぎず，宿主因子・ウイルス因子は治療効果規定因子として重要であるが，肝線維化進展そして肝発癌予測に宿主因子が極めて重要であることも忘れてはならない．

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Daclatasvir combined with peginterferon alfa-2a and ribavirin in Japanese patients infected with hepatitis C genotype 1

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Original article

Daclatasvir combined with peginterferon alfa-2a and ribavirin in Japanese patients infected with hepatitis C genotype 1

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ABSTRACT

Background: New direct-acting antiviral agents are currently being developed to treat chronic hepatitis C virus (HCV). The efficacy and safety of daclatasvir combined with peginterferon alfa-2a (alfa-2a) and ribavirin were assessed in a randomized, double-blind phase 2a study of Japanese patients with chronic HCV genotype-1 infection.

Methods: Japanese patients who were treatment-naïve (n=25) or prior null (n=12) or partial (n=5) responders received once-daily daclatasvir 10mg or 60mg or placebo in combination with alfa-2a and ribavirin. Daclatasvir recipients with a protocol-defined response (HCV RNA<15 IU/mL at Week 4 and undetectable at Week 12) were treated for 24 weeks; placebo recipients and patients without a protocol-defined response were treated for 48 weeks.

Results: Sustained virologic response at 24 weeks post-treatment (SVR_{24}) was achieved by 89% and 100% of treatment-naïve patients receiving daclatasvir 10mg and 60mg, respectively, versus 75% in placebo recipients. Virologic failure was more frequent in prior nonresponder patients, with 50% and 78% achieving SVR_{24} in daclatasvir 10mg and 60mg groups, respectively. Adverse events occurred with similar frequency among treatment groups and were consistent

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with the adverse event profile of alfa-2a/ribavirin alone. The most commonly reported adverse events included pyrexia, alopecia, anemia, lymphopenia, neutropenia, pruritus, and diarrhea. Three patients discontinued treatment due to anemia.

Conclusions: Daclatasvir combined with alfa-2a/ribavirin in treatment-naive patients showed greater efficacy than alfa-2a/ribavirin alone and was generally well tolerated. The 60-mg dose of daclatasvir achieved the highest rates of SVR_{24} in both treatment-naive and nonresponder populations and will be evaluated in a phase 3 clinical trial.

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Running title: Daclatasvir combined with peginterferon alfa-2a and ribavirin

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is estimated to affect approximately 160 million people worldwide, and 3 to 4 million people become infected with HCV every year [1,2]. In Japan, approximately 1.5 to 2 million people are infected with chronic HCV, primarily HCV genotype 1b [3]. While HCV genotype 1 is the most common, it is also the most challenging to treat.

Treatment for chronic HCV infection has consisted primarily of a combination of interferon and ribavirin. Among treatment-naive patients with HCV genotype 1 infection treated with peginterferon-alfa (alfa) plus ribavirin, the rates of sustained virologic response (SVR) ranged from 34 to 46% [4–6]. Recent clinical trials that combined the direct-acting anti-HCV agents boceprevir or telaprevir with alfa plus ribavirin achieved higher rates of SVR (68 to 75%) in treatment-naïve patients with HCV genotype 1 infection compared with alfa/ribavirin alone [7–12]. However, the high pill burden and associated side effects of these new treatment regimens underscore the need for direct-acting agents with different mechanisms of action, simplified dosing regimens, and more desirable tolerability profiles.

Daclatasvir (BMS-790052) is a highly selective, first-in-class HCV nonstructural protein 5A (NS5A) replication complex inhibitor with broad genotypic coverage (HCV genotypes 1 to 6) *in vitro* [13,14]. Daclatasvir inhibits HCV RNA replication through interactions with the NS5A protein, a critical component for HCV viral replication [13,15]. Early clinical studies of daclatasvir demonstrated potent antiviral activity and a pharmacokinetic profile that supports once-daily dosing [16]. A previous phase 2a study demonstrated that a combination of daclatasvir 10 mg or 60 mg once daily plus alfa-2a and ribavirin for 48 weeks resulted in high rates of SVR (83%) in treatment-naïve patients with primarily HCV genotype 1a [17]. The tolerability and side effect profile of this triple therapy regimen was similar to that reported with alfa/ribavirin alone.

The efficacy and safety of daclatasvir combined with alfa-2a (Pegasys®) and ribavirin were assessed in Japanese patients with chronic HCV who were naïve to treatment or nonresponsive to prior

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treatment with alfa/ribavirin. Response-guided therapy was utilized to determine whether a shorter treatment duration (24 weeks) with daclatasvir would achieve sustained virologic responses.

METHODS

Study Design

This double-blind, randomized, phase 2a study (Clinicaltrials.gov identifier NCT01017575) assessed the antiviral activity and safety of daclatasvir in combination with alfa-2a/ribavirin in Japanese patients with HCV genotype 1 infection, who were either treatment-naïve or prior nonresponders (null or partial) to treatment with alfa-2a/ribavirin or alfa-2b/ribavirin. Written informed consent was obtained from all patients. The study was approved by institutional review boards/independent ethics committees at each site and was conducted in compliance with Good Clinical Practice Guidelines and local regulatory requirements, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Patients were enrolled at 6 sites in Japan from 03-Dec-2009 through 30-Apr-2010. Randomization was conducted by the sponsor at a central randomization center, which provided the patient identification number upon receipt of the investigator's patient registration form. Investigators received treatment kit number assignments by fax from the randomization center for eligible screened patients.

The main objective of the study was to identify a safe and efficacious dose of daclatasvir in combination with alfa-2a/ribavirin that will allow further evaluation in larger studies.

Patient Eligibility Criteria

Study participants included Japanese men and women 20 to 70 years of age chronically infected with HCV genotype 1 (HCV RNA $\geq 10^5$ IU/mL) who were treatment-naive, (defined as those who had never been exposed to any HCV therapy with interferon-containing regimens, including alfa-2a/ribavirin, or those containing direct-acting agents against HCV), or who were nonresponders to previous therapy (defined as patients who failed to achieve ≥ 2 $\log_{10}$ reduction of HCV RNA at Week 12 [null responder] or had achieved a ≥ 2 $\log_{10}$ reduction but never attained undetectable HCV RNA levels after at least 12 weeks [partial responder] of the current standard of care, alfa-2a/ribavirin or alfa-2b/ribavirin). Women of childbearing potential were required to use effective methods of contraception, due particularly to the use of ribavirin.

Patients with a history of hepatocellular carcinoma, coinfection with hepatitis B virus or HIV, other chronic liver disease, or evidence of hepatic decompensation were not eligible to participate. Other reasons for exclusion included liver cirrhosis confirmed by laparoscopy, imaging studies, or liver biopsy within 24 months prior to screening; ALT $\geq 5 \times$ upper limit of normal; total bilirubin ≥ 2 mg/dL; international

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normalized ratio ≥1.7; albumin ≤3.5 g/dL; hemoglobin <12 g/dL; white blood cells <3 $\times 10^9$/L; absolute neutrophil count <1.5 $\times 10^9$/L; platelets <90 $\times 10^9$/L; creatinine clearance <50 mL/m; inability to tolerate oral medication or gastrointestinal disease; or surgical procedure that may impact absorption of study drug. Patients exposed to any investigational drug (including direct-acting agents) or placebo within 4 weeks prior to dosing of study therapy, or previous exposure to new or investigational HCV therapeutic agents could not participate. Prohibited medications included proton pump inhibitors, moderate/strong inducers or inhibitors of CYP3A4, erythropoiesis-stimulating agents to achieve inclusion criteria, and long-term treatment with immunosuppressive agents or agents associated with a high risk of hepatotoxicity or nephrotoxicity.

Treatments

Patients were randomly assigned to receive once-daily oral daclatasvir 10 mg or 60 mg or placebo (treatment-naïve only) in combination with weight-based, twice-daily ribavirin (600, 800, or 1000 mg/day for patients weighing ≤ 60 kg, > 60 kg to ≤ 80 kg, or > 80 kg, respectively) and once weekly subcutaneous alfa-2a (180 μg) (Figure 1). Patients receiving daclatasvir plus alfa-2a/ribavirin who achieved a protocol-defined response (PDR) were treated for 24 weeks. PDR was defined as HCV RNA less than the lower limit of quantitation (LLOQ; 15 IU/mL) at Week 4 and undetectable at Week 12. Patients not achieving PDR received daclatasvir plus alfa-2a/ribavirin for 48 weeks. Patients treated with placebo (treatment-naive only) received alfa-2a/ribavirin for 48 weeks.

Randomized treatment assignment was double-blind and placebo-controlled for daclatasvir during the first 24 weeks of treatment. The study was unblinded at week 24 and conducted subsequently as open label for patients who did not achieve PDR or were receiving placebo.

Efficacy and Safety Assessments

The primary efficacy assessment was the proportion of patients with extended rapid virologic response (eRVR), defined as undetectable HCV RNA at both Week 4 and Week 12. Secondary efficacy assessments included the proportion of patients with RVR, defined as undetectable HCV RNA at Week 4; the proportion of patients with complete early virologic response (cEVR), defined as undetectable HCV RNA at Week 12; the proportion of patients with sustained virologic response (defined as undetectable HCV RNA) at week 12 (SVR_{12}) and week 24 (SVR_{24}) post-treatment.

The possible presence of daclatasvir-resistant variants was analyzed using stored plasma specimens. Total RNA was isolated, the NS5A region amplified by RT-PCR, and the resultant amplicon assessed by population sequencing [15]. Resistance testing was performed centrally on all samples at baseline, and on samples indicative of virologic failure when HCV RNA was ≥ 1000 IU/mL. Virologic failure was defined as virologic breakthrough (confirmed > 1 $\log_{10}$ increase in HCV RNA over nadir or confirmed HCV RNA > LLOQ after confirmed undetectable HCV RNA while on treatment), < 1 $\log_{10}$ decrease in HCV RNA from baseline at Week 4 of treatment, failure to achieve EVR (defined as < 2 $\log_{10}$

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decrease in HCV RNA from baseline at Week 12 of treatment), detectable HCV RNA at Week 12 and HCV RNA > LOQ at Week 24 of treatment, detectable HCV RNA at end of treatment (EOT, including early discontinuation), and relapse (defined as detectable HCV RNA during follow-up after undetectable HCV RNA at EOT).

Assessments including HCV RNA, physical examination, adverse events, laboratory tests, pregnancy test, and concomitant medications, were conducted at screening, study day 1 (baseline), Weeks 1, 2, 4, 6, 8, 12, then every 4 weeks until the end of therapy, and post-treatment Weeks 4, 12, and 24. Twelve-lead electrocardiograms were recorded at screening and on-treatment at Weeks 4, 12, 24, and 48. Serum HCV RNA levels were determined at a central laboratory (SRL Inc, Tokyo, Japan) using Roche COBAS® TaqMan® HCV Auto assay, (Roche Diagnostics KK, Tokyo, Japan), with LLOQ of 15 IU/mL. HCV genotype and subtype were determined at the central laboratory by PCR amplification and sequencing. *IL28B* genotype was determined by PCR amplification and sequencing of the rs12979860 single nucleotide polymorphism.

Statistical Analysis

Using a target sample size of 8 patients per treatment group, a safety event with an incident rate of 19% could be detected with 80% probability. Categorical variables were summarized with counts and percents, and continuous variables were summarized with univariate statistics. Confidence intervals (CIs) were 2-sided with 80% confidence levels; CIs for binary endpoints were exact binomial, and CIs for continuous endpoints were based on the normal distribution. All statistical analyses were conducted using SAS/STAT® Version 8.2.

RESULTS

Patient Disposition and Demographic Characteristics

Fifty-five patients were enrolled in the study; 2 patients withdrew consent, and 10 patients were excluded due to HCV RNA viral load $<10^5$ IU/mL at screening (2 patients), chronic infection with HCV other than genotype 1 (2 patients), albumin levels ≤3.5 g/dL (3 patients), gastrointestinal disease/surgical procedure potentially impacting study drug absorption (2 patients), abnormal thyroid function (1), or hemoglobin levels <12 g/dL (1 patient had both low albumin and low hemoglobin levels). Forty-two patients met study criteria and were randomized and treated; 1 patient was randomized but did not receive treatment due to an enlarged lymph node.

Twenty-five patients were naive to treatment. The nonresponder group included 12 null responders (<2 $\log_{10}$ decrease in HCV RNA after ≥12 weeks of alfa-2a/ribavirin or alfa-2b/ribavirin) and 5 partial responders (≥2 $\log_{10}$ decrease but never attained undetectable HCV RNA after ≥12 weeks of alfa-2a or 2b/ribavirin).

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The majority of Japanese patients were infected with HCV genotype 1b (Table 1), reflecting the high proportion of this subtype in Japan; 2 treatment-naive patients in the 10-mg daclatasvir dose group were HCV genotype 1a. Other than an imbalance in gender distribution, baseline characteristics were similar across treatment groups (Table 1). Mean HCV RNA levels ranged from 6.5 to 6.9 $\log_{10}$ IU/mL, and most patients had a high baseline viral load (> 800,000 IU/mL). Treatment-naive patients (19/25) were primarily *IL28B* genotype CC (rs12979860), consistent with the overall distribution of *IL28B* genotypes in Japan (Table 1). Prior nonresponders (16/17) were primarily *IL28B* genotypes CT or TT (Table 1).

Thirty-nine of 42 patients completed the 24-week double-blind phase of the study. Three patients discontinued due to anemia; 1 treatment-naive patient receiving 10 mg daclatasvir discontinued at Week 12, and 2 prior nonresponder patients receiving 60 mg daclatasvir discontinued at Week 14 and Week 17 of treatment. Twelve patients continued treatment in the open-label phase of the study, 3 of whom discontinued treatment due to virologic breakthrough (1 treatment-naive patient receiving 10 mg DCV, 1 nonresponder patient receiving 10 mg daclatasvir, and 1 nonresponder patient receiving 60 mg daclatasvir). One patient in the placebo group requested to discontinue treatment.

A similar number of patients in each treatment group required dose reductions of alfa-2a and ribavirin. Seventeen patients required alfa-2a reductions (4 in the placebo group, and 2 to 4 in each of the daclatasvir treatment groups), and 35 patients required ribavirin reductions (7 in the placebo group and 6 to 8 in each of the daclatasvir treatment groups).

Virologic Response and Outcomes

HCV RNA suppression was more rapid in patients treated with daclatasvir compared with patients receiving placebo (Figure 2). By Week 2, the mean reduction from baseline in HCV RNA was 5.1 to 5.3 $\log_{10}$ IU/mL in the daclatasvir treatment groups compared with 3.1 $\log_{10}$ IU/mL in the placebo group. The mean improvement in HCV RNA was maintained through Week 48 for all daclatasvir dose groups.

Table 2 shows the virologic outcomes (RVR, eRVR, cEVR, EOTR, and SVR_{24}) in all patients and in daclatasvir recipients who achieved PDR. The primary efficacy endpoint, eRVR, was achieved by 63% to 78% of patients in the daclatasvir treatment groups compared with 13% in the placebo group (Table 2). The rate of eRVR was highest in the nonresponder daclatasvir 60 mg dose group. Twenty-nine patients (15/25 treatment-naive and 14/17 nonresponders) in the daclatasvir treatment groups achieved PDR and completed treatment at Week 24 with 24 weeks of follow-up.

Treatment-naive patients

Overall, SVR_{24} was achieved by 89% and 100% of treatment-naive patients receiving daclatasvir 10 mg and 60 mg, respectively, versus 75% of those receiving placebo. PDR was achieved by 78% (7/9) and 100% (8/8) of treatment-naive patients receiving daclatasvir 10 mg and 60 mg, respectively, compared with 13% (1/8) of patients receiving placebo (Table 2). All treatment-naïve patients who achieved PDR subsequently achieved EOTR and SVR_{24} after 24 weeks of therapy. One treatment-naive patient in the

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daclatasvir 10-mg dose group, who was infected with HCV genotype 1b, did not achieve PDR and also failed to achieve SVR_{24}. In treatment-naïve patients with *IL28B* genotype CC (rs12979860), HCV RNA was undetectable at week 12 (cEVR) in 92% of daclatasvir recipients (7/8 daclatasvir 10 mg and 5/5 daclatasvir 60 mg recipients, respectively) and in 67% (4/6) of patients receiving placebo; by post-treatment week 24 (SVR_{24}), HCV RNA was undetectable in all daclatasvir recipients with *IL28B* genotype CC. Among the small number of treatment-naïve patients with *IL28B* genotype CT, 0/1 receiving daclatasvir 10 mg, 3/3 receiving daclatasvir 60 mg, and 1/1 receiving placebo achieved SVR_{24}.

Nonresponder patients

In the nonresponder population, all of whom were non-CC *IL28B* genotype, SVR_{24} was achieved by 50% (4/8) receiving daclatasvir 10 mg and 78% (7/9) receiving daclatasvir 60 mg. PDR was achieved by 88% (7/8) and 78% (7/9) of nonresponder patients receiving daclatasvir 10 mg and daclatasvir 60 mg, respectively (Table 2). All nonresponder patients who achieved PDR maintained response through the end of therapy. Among patients with PDR, SVR_{24} was achieved by 57% (4/7) of nonresponders receiving daclatasvir 10 mg, and 86% (6/7) of nonresponders receiving daclatasvir 60 mg. In the nonresponder group of patients who did not achieve SVR_{24}, 5 were *IL28B* genotype CT (3 daclatasvir 10 mg, 2 daclatasvir 60 mg) and 1 patient (daclatasvir 10 mg) was *IL28B* genotype TT.

Virologic Failure

As expected, virologic failure was less frequent in treatment-naïve patients than in nonresponder patients (Table 2). Treatment-naïve recipients of daclatasvir 60 mg had no virologic failures, no virologic breakthrough, and no post-treatment relapse. One treatment-naïve patient receiving daclatasvir 10 mg had viral breakthrough, with emergence of the NS5A variants L31V–Y93H. Emergence of the NS5A variants L28M-Y93H, L31M/V-Y93H, or R30H-L31V was detected in 6 prior nonresponder patients who failed treatment (4 receiving daclatasvir 10 mg, 2 receiving daclatasvir 60 mg). The predominant resistance pathway to virologic failure in patients infected with HCV genotype 1b in this study was via the emergence of substitutions at L31–Y93. Most patients with virologic failure had *IL28B* non-CC genotypes (rs12979860), including all 6 nonresponder patients, and 1 treatment-naive patient receiving daclatasvir 10 mg. Y93H was detected at baseline in one treatment-naïve patient and in one prior nonresponder; both of these patients subsequently achieved SVR. No patient had detectable L31 polymorphisms at baseline.

Safety

There were no consistent differences in adverse events between groups receiving either dose of daclatasvir or placebo, nor were there apparent differences in the adverse events profile between treatment-naive versus nonresponder patients in the daclatasvir dose groups. No unique adverse events were identified that were attributable to daclatasvir. The most commonly reported adverse events in all dose groups were pyrexia, alopecia, anemia, lymphopenia, neutropenia, pruritus, and diarrhea (Table 3).

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The frequency of grade 3/4 adverse events was comparable across treatment groups (Table 3). Severe anemia was the cause of 3 patients discontinuing treatment. The events resolved after treatment in 1 treatment-naïve patient in the daclatasvir 10-mg dose group, and without treatment in 2 nonresponder patients receiving daclatasvir 60 mg. There were two serious adverse events (acute pancreatitis and back pain), both occurring in treatment-naïve patients receiving daclatasvir 10 mg. No deaths occurred during the study. Overall, the adverse events observed in both the placebo and daclatasvir-containing treatment groups were consistent with the adverse event profile of alfa-2a/ribavirin alone.

Table 3 shows the hematologic and laboratory abnormalities by treatment group and between treatment-naive and nonresponder patients. The most common abnormalities were hematologic related, similar to those frequently observed with alfa-2a/ribavirin. There were no consistent differences in hematologic or laboratory abnormalities among groups receiving placebo or daclatasvir (Table 3).

DISCUSSION

The combination of direct-acting antiviral agents, boceprevir or telaprevir, plus alfa/ribavirin has been shown to improve the rates of SVR over that achieved with alfa/ribavirin alone. These newer agents, however, have a high pill burden, are complicated by inconvenient dosing schedules, and are associated with frequent adverse events that can be severe, such as rash and anemia, which may impact tolerability and adherence. Thus, there is a need for more tolerable direct-acting antivirals that provide better efficacy than the standard of care [7,8,11,12].

The results from this phase 2a study demonstrated rapid antiviral activity when daclatasvir was combined with alfa-2a/ribavirin. The primary antiviral activity endpoint for this study was the proportion of patients with eRVR, (defined as undetectable HCV RNA at both Weeks 4 and 12). Both doses of daclatasvir (10 mg and 60 mg) in combination with alfa-2a/ribavirin exhibited greater efficacy than placebo (alfa-2a/ribavirin alone) in inducing eRVR, (63% to 78% versus 13%, respectively). The rate of eRVR was highest for nonresponder patients receiving daclatasvir 60 mg compared with the nonresponder daclatasvir 10 mg dose group and the treatment-naive daclatasvir dose groups.

A high proportion of treatment-naïve patients receiving daclatasvir plus alfa-2a/ribavirin achieved PDR and was treated for only 24 weeks, and all of these patients achieved SVR_{24}. Compared with treatment-naïve patients, a similar proportion of patients with prior nonresponse to alfa/ribavirin achieved PDR, although post-treatment relapse was more frequent in these patients. Rates of post-treatment relapse were comparable in treatment-naïve patients and prior nonresponder patients who received daclatasvir 60 mg, and more frequent in nonresponder patients in the daclatasvir 10-mg dose group. No virologic failures were reported in treatment-naive patients receiving daclatasvir 60 mg. One patient receiving daclatasvir 10 mg and 1 placebo recipient had virologic failure (virologic breakthrough and post-treatment relapse, respectively). As anticipated, virologic failure was more frequent in the nonresponder

patients (4/8 receiving daclatasvir 10 mg, 2/9 receiving daclatasvir 60 mg). Collectively, these data suggest the higher dose of daclatasvir (60 mg) in combination with alfa-2a/ribavirin can achieve better virologic outcomes than the 10 mg daclatasvir dose in both treatment-naive and non-responder patient populations.

In a phase 3 study of treatment-naive patients with HCV genotype 1 who were treated with the direct-acting agent telaprevir combined with alfa-2a/ribavirin, the rate of SVR_{24} was 79% among patients with HCV genotype 1b [8]. Kumada and colleagues reported similar results among treatment-naive Japanese patients chronically infected with HCV genotype 1b [18]. The SVR_{24} rates were 73% in patients who received telaprevir combined with alfa-2b and ribavirin compared with 49% in those receiving alfa-2b/ribavirin, although skin disorders, rash, and anemia were more frequent in patients receiving telaprevir [18]. In the present study, the overall rates of SVR_{24} in the treatment-naive population receiving both doses of daclatasvir compared favorably (100% daclatasvir 60 mg, 89% daclatasvir 10 mg) with the studies of telaprevir-treated patients. The SVR rates in this study were also comparable to those reported in a previous dose-finding phase 2 study (83%) in which treatment-naive patients infected with HCV genotype 1 (primarily genotype 1a) received 48 weeks of daclatasvir (10 mg or 60 mg) combined with alfa-2a/ribavirin [17].

The efficacy results of this phase 2a trial clearly demonstrate that the addition of daclatasvir to alfa-2a/ribavirin increases the antiviral activity of the regimen. As might be anticipated, however, response to the addition of a single direct-acting agent such as daclatasvir to alfa-2a/ribavirin appears to remain somewhat dependent on patients' response to alfa-2a/ribavirin, as suggested by the different antiviral activity observed in the treatment-naive and nonresponder populations. Of note, the addition of a second direct-acting antiviral may improve the interferon non-responsiveness in this population. A recent study demonstrated SVR rates exceeding 90% in nonresponder patients receiving daclatasvir (60 mg) combined with the NS3 protease inhibitor asunaprevir and alfa/ribavirin [21]. This last study suggests that the dependence of a regimen with a single direct-acting antiviral to the patient's response to alfa-2a/ribavirin can be overcome by the addition of a second direct-acting antiviral.

IL28B genotype has been shown to be a strong predictor of alfa-2a/ribavirin-responsiveness, with CC genotype showing the strongest response [19,20]. Data in the present study are limited but generally consistent with a similar effect with this regimen. All treatment-naive patients with *IL28B* CC genotype achieved SVR_{24}, as did 3 of the 4 treatment-naive patients with *IL28B* CT genotype. All patients in the nonresponder group had *IL28B* non-CC genotypes, which may have contributed to their previous lack of response to alfa/ribavirin as well as the higher rate of virologic failure in the present study. Only two patients had signature daclatasvir resistance polymorphisms (Y93H) at baseline, and both achieved SVR. Future studies in larger populations are needed to determine the influence of *IL28B* genotype and baseline NS5A polymorphisms on virologic responses with this regimen.

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This study showed that both doses of daclatasvir in combination with alfa-2a/ribavirin were generally well tolerated. Adverse events in patients receiving daclatasvir plus alfa-2a/ribavirin were similar to those observed with alfa-2a/ribavirin alone. The observed safety profile of daclatasvir appears consistent with previous reports of daclatasvir administered alone [16] or in combination with alfa/ribavirin [17,22,23] or other direct-acting antivirals [21,24,25]. In contrast to the recently approved direct-acting antivirals, telaprevir and boceprevir, the addition of daclatasvir to alfa-2a/ribavirin did not appear to impact hematologic safety. Patients receiving telaprevir combined with alfa/ribavirin had a higher incidence of adverse events, including anemia, rash, and gastrointestinal disorders, compared with patients receiving alfa/ribavirin alone [8,12,18]. Serious to potentially life-threatening skin reactions have been reported when telaprevir was used in combination with alfa/ribavirin [10]. Anemia was also reported more frequently in patients receiving boceprevir plus alfa/ribavirin compared with alfa/ribavirin alone [7,11].

The limitations of this phase 2a study include the relatively small sample size, which precludes definitive conclusions regarding efficacy outcomes as well as safety and tolerability of daclatasvir in combination with alfa-2a/ribavirin. The study population consisted of a Japanese cohort, and thus the data may not be extrapolated to other ethnic populations. Additionally, while most of the patients in this study were HCV genotype 1b, 2 patients were HCV genotype 1a.

This study demonstrates that addition of daclatasvir to alfa/ribavirin confers a markedly more rapid early virologic response in patients with primarily genotype 1b infection. These data, coupled with similarly positive results from a companion study with alfa-2b [26], suggest that further evaluation of daclatasvir in combination with both types of alfa is warranted. Phase 3 clinical trials of daclatasvir (60 mg once daily) in combination with alfa/ribavirin and/or asunaprevir are currently ongoing.

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Figure Legends

Figure 1 Study design.

Protocol-defined response (PDR): HCV RNA < LLOQ (15 IU/mL) at Week 4 and undetectable at Week 12. DCV: daclatasvir; alfa-2a: peginterferon alfa-2a; RBV: ribavirin

Figure 2 HCV RNA reductions through Week 24.

Virologic outcomes in treatment-naïve and nonresponder patients.

DCV: daclatasvir

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Table 1. Baseline demographic and disease characteristics

	Treatment-naïve Patients			Nonresponder Patients	
Baseline Parameter	**Placebo n =8**	**DCV 10 mg n = 9**	**DCV 60 mg n = 8**	**DCV 10 mg n = 8**	**DCV 60 mg n = 9**
Age, median years (range)	54 (41, 65)	56 (28, 66)	57 (31, 67)	53 (26, 68)	55 (36, 67)
Male gender, n (%)	3 (38)	4 (44)	2 (25)	6 (75)	5 (56)
HCV genotype 1b, n (%)	8 (100)	7 (78)	8 (100)	8 (100)	9 (100)
HCV RNA, mean log_{10} IU/mL (SD)	6.5 (0.65)	6.9 (0.28)	6.5 (0.77)	6.7 (0.43)	6.7 (0.36)
Response to prior alfa/RBV					
Null response, n (%)	N/A	N/A	N/A	5 (63)	7 (78)
Partial response, n (%)				3 (38)	2 (22)
IL28B genotype (rs12979860), n (%)					
CC	6 (75)	8 (89)	5 (63)	0	0
CT	1 (13)	1 (11)	3 (38)	6 (75)	8 (89)
TT	0	0	0	2 (25)	0
Not reported	1 (13)	0	0	0	1 (11)

DCV: daclatasvir; alfa: peginterferon alfa

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Table 2. Virologic Outcomes in Treatment-naive and Nonresponder Patients

		Treatment-naïve			Prior Nonresponders	
Endpoint, n/N (%) [80% CI]		Placebo n = 8	DCV 10 mg n = 9	DCV 60 mg n = 8	DCV 10 mg n = 8	DCV 60 mg n = 9
All patients	HCV RNA undetectable Week 4 (RVR)	1/8 (12.5) [1.3, 40.6]	7/9 (77.8) [51.0, 93.9]	5/8 (62.5) [34.5, 85.3]	5/8 (62.5) [34.5, 85.3]	8/9 (88.9) [63.2, 98.8]
	HCV RNA undetectable Week 12 (cEVR)	5/8 (62.5) [34.5, 85.3]	8/9 (88.9) [63.2, 98.8]	8/8 (100) [75.0, 100.0]	7/8 (87.5) [59.4, 98.7]	8/9 (88.9) [63.2, 98.8]
	HCV RNA undetectable Weeks 4 and 12 (eRVR)	1/8 (12.5) [1.3, 40.6]	6/9 (66.7) [40.1, 87.1]	5/8 (62.5) [34.5, 85.3]	5/8 (62.5) [34.5, 85.3]	7/9 (77.8) [51.0, 93.9]
	HCV RNA undetectable End of treatment response (EOTR)	8/8 (100) [75.0, 100.0]	8/9 (88.9) [63.2, 98.8]	8/8 (100) [75.0, 100.0]	7/8 (87.5) [59.4, 98.7]	8/9 (88.9) [63.2, 98.8]
	SVR_{24}	6/8 (75.0) [46.2, 93.1]	8/9 (88.9) [63.2, 98.8]	8/8 (100) [75.0, 100.0]	4/8 (50.0) [24.0, 76.0]	7/9 (77.8) [51.0, 93.9]
	Virologic breakthrough	0/8 (0)	1/9 (11.1)*	0/8 (0)	1/8 (12.5)*	1/9 (11.1)*
	Posttreatment relapse	1/8 (12.5)†	0/9 (0)	0/8 (0)	3/8 (37.5)‡	1/9 (11.1)*
Patients with PDR	HCV RNA <15 IU/mL at week 4, undetectable at week 12 (PDR)	1/8 (12.5) [1.3, 40.6]	7/9 (77.8) [51.0, 93.9]	8/8 (100) [75.0, 100.0]	7/8 (87.5) [59.4, 98.7]	7/9 (77.8) [51.0, 93.9]
	HCV RNA undetectable EOTR	1/1 (100) [10.0, 100.0]	7/7 (100) [72.0, 100.0]	8/8 (100) [75.0, 100.0]	7/7 (100) [72.0, 100.0]	7/7 (100) [72.0, 100.0]
	SVR_{24}	1/1 (100) [10.0, 100.0]	7/7 (100) [72.0, 100.0]	8/8 (100) [75.0, 100.0]	4/7 (57.1) [27.9, 83.0]	6/7 (85.7) [54.7, 98.5]

DCV: daclatasvir; PDR (protocol-defined response): HCV RNA < LLOQ Week 4 and undetectable Week 12
*Genotype *IL28B* CT
†Genotype *IL28B* CC
‡Two patients had *IL28B* CT, one patient had *IL28B* TT