Evidence-Based Medicine Conference

指導醫師　李智雄　主任

蘇富敏藥師
高醫大附設中和紀念醫院藥劑部
B.C棟大樓 B1 單一劑量藥局
07-3121101轉7192
fmsu@kmu.edu.tw

Clinical Scenario
個案病例摘要

Patient Profile

- Name：吳OO
- Age / Sex：50 / M
- BW / BH： 73 kg / 172 cm
- Chart No.：239*****

PH:

- HIV (+) CD4≧ 350
- LC / Child B
- HCV (+) Genotype 1 Infection

Problem:

使用PegIFN–RBV治療HCV後relapse，怎麼辦?

Asking Answerable Clinical Questions

Background Questions

- chronic HCV genotype 1 infection的流行病學？
- 如何診斷chronic HCV genotype 1 infection ？
- chronic HCV genotype 1 infection的分類有那幾種？
- chronic HCV genotype 1 infection的治療時機為何？
- chronic HCV genotype 1 infection的治療方法有哪些？

Foreground Question

- 有那些Rescue Therapy for patients with chronic HCV genotype 1 infection ?

➲ Peginterferon–Ribavirin Combine with

1. Boceprevir (BOC)
2. Telaprevir (TVR) ➲ not approved to treat LC.

Asking An Answerable Clinical Question (PICO)

- *Patient and /or Problem*
  - Chronic **HCV Genotype 1 Infection**
- *Intervention (treatment)*
  - **Boceprevir plus PegIFN–RBV**
- *Comparison Intervention*
  - **Placebo plus PegIFN–RBV**
- *Clinical Outcome*
  - **Sustained Virologic Response(SVR)**

Acquire ----搜尋最有用資料

- **Database:**
  - **ACP Journal Club**
  - **Cochrane Library**
  - **EBMR**
  - **PubMed**

Acquire ----搜尋最有用資料

- **Key Words:**
  - **Boceprevir AND Peginterferon AND Ribavirin**
- **Limited in :**
  - **Humans, Clinical Trial, OR**
  - **Practice Guideline, OR**
  - **Field: Title/Abstract, OR**
  - **Meta-Analysis OR**
  - **Randomized Controlled Trial OR**
  - **Clinical Trial, Phase I, OR**
  - **Clinical Trial, Phase II, OR**
  - **Clinical Trial, Phase III, OR**
  - **Clinical Trial, Phase IV, OR**
  - **Comparative Study OR**
  - **Controlled Clinical Trial OR**
  - **Multicenter Study OR**

Acquire ---- Searching Results

- ACP Journal Club (0)
- Cochrane Library (0)
- EBMR (0)
- Textbook/Access Medicine/UpToDate (2)
- **Medline/Pub-Med : RCT (5)**

➲ Bacon, B.R. et al. Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection.

N Engl J Med 2011;364:1207-17

Appraisal---資料評估準則

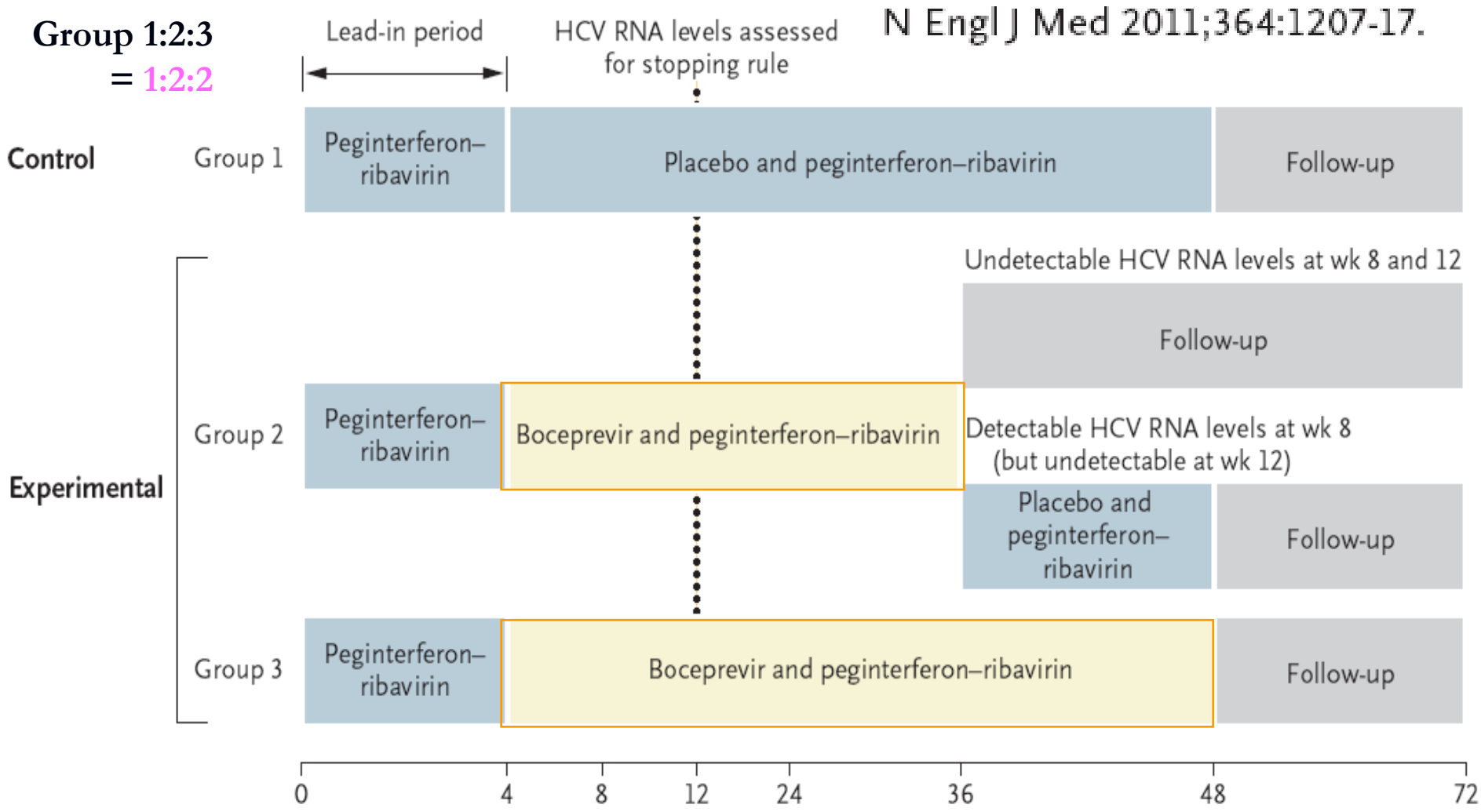
Levels of Evidence Oxford Centre for EBM

Level	Therapy/Prevention, Aetiology/Harm
1a	SR (with homogeneity) of RCTs
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT)
2c	"Outcomes" Research; Ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Appraisal

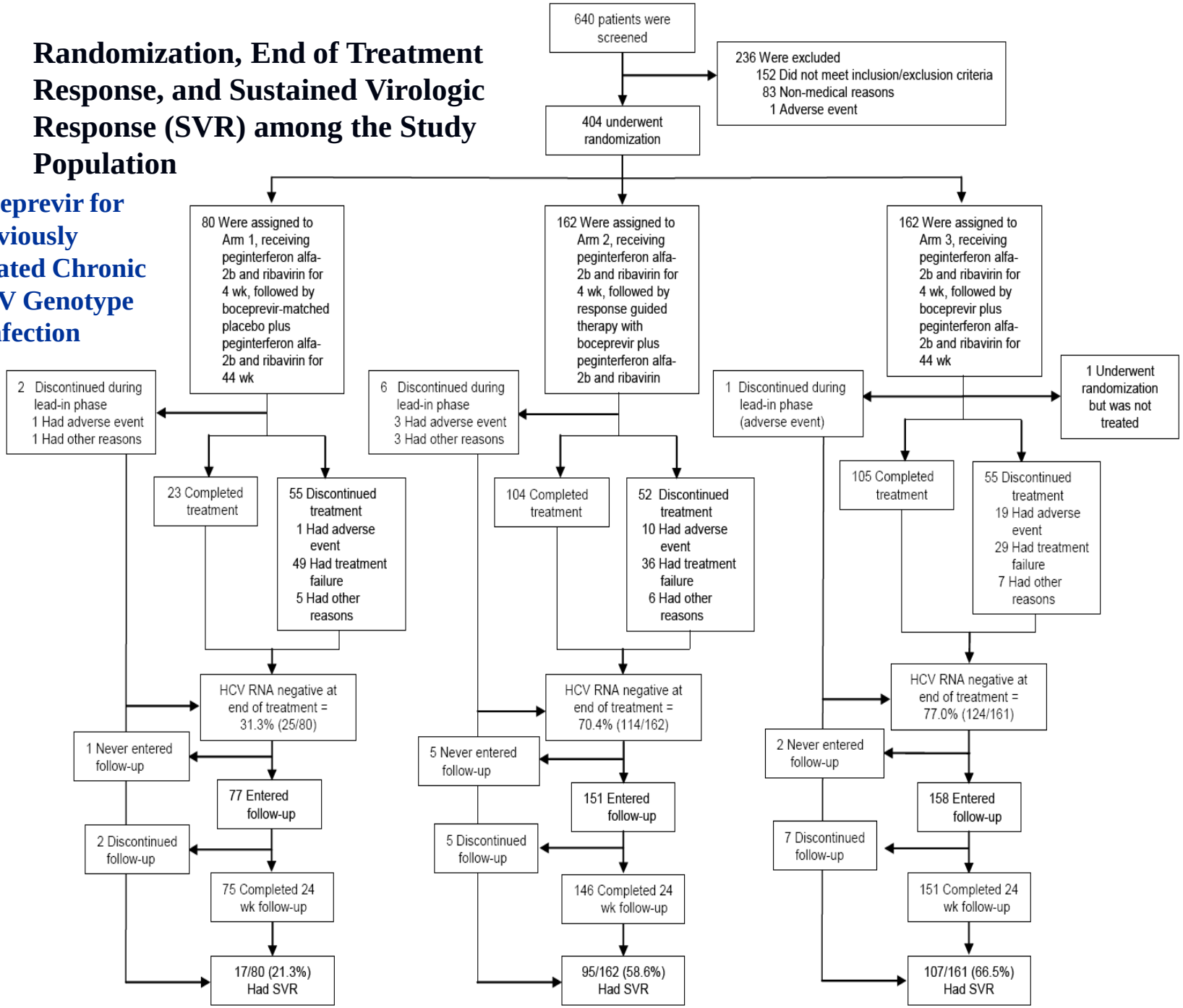
Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection

Group 1:2:3
= 1:2:2



Randomization, End of Treatment Response, and Sustained Virologic Response (SVR) among the Study Population

Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection



Appraisal by CONSORT 2010 statement

PAPER SECTION and topic	Item	Descriptor
TITLE & ABSTRACT	X	Identification as a randomized trial in the title.
	O	Structured summary of trial design, methods, results, and conclusions.
INTRODUCTION		
Background and objectives	O	Scientific background and explanation of rationale.
	O	Specific objectives or hypotheses.
Methods Trial design	O	Description of trial design (such as parallel, factorial), including allocation ratio.
	O	Important changes to methods after trial commencement (such as eligibility criteria), with reasons.

Appraisal by CONSORT 2010 statement

PAPER SECTION and topic	Item	Descriptor
		METHODS
Participants	O	Eligibility criteria for participants.
	X	Settings and locations where the data were collected.
Interventions	O	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered.
Outcomes	O	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed.
	O	Any changes to trial outcomes after the trial commenced, with reasons.

Appraisal by CONSORT 2010 statement

PAPER SECTION and topic	Item	Descriptor
Sample size	X	How sample size was determined.
	O	When applicable, explanation of any interim analyses and stopping guidelines.
Randomization - Sequence generation	O	Method used to generate the random allocation sequence.
	O	Type of randomization; details of any restriction (such as blocking and block size)
Randomization – Allocation Concealment mechanism	O	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.

Appraisal by CONSORT 2010 statement

PAPER SECTION and topic	Item	Descriptor
Randomization Implementation	O	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions.
Blinding (masking)	O	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how the success of blinding was evaluated.
	O	if relevant, description of the similarity of interventions.
Statistical methods	O	Statistical methods used to compare groups for primary and secondary outcomes.
	O	Methods for additional analyses, such as subgroup analyses and adjusted analyses.

Appraisal by CONSORT 2010 statement

PAPER SECTION and topic	Item	Descriptor
		RESULTS
Participant flow (a diagram is strongly recommended)	O	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcocme.
	O	For each group, losses and exclusions after randomization, together with reasons.
Recruitment	O	Dates defining the periods of recruitment and follow-up.
	O	Why the trial ended or was stopped.
Baseline data	O	A table showing baseline demographic and clinical characteristics of each group.

Appraisal by CONSORT 2010 statement

PAPER SECTION and topic	Item	Descriptor
Numbers analyzed	O	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups.
Outcomes and estimation	O	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval).
	O	For binary outcomes, presentation of both absolute and relative effect sizes is recommended.
Ancillary analyses	O	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.

Appraisal by CONSORT 2010 statement

PAPER SECTION and topic	Item	Descriptor
Harms	O	All important harms or unintended effects in each group.
DISCUSSION		
limitations	O	Trial limitations; addressing sources of potential bias; imprecision; and, if relevant, multiplicity of analyses.
Generalizability	O	Generalizability (external validity, applicability) of the trial findings.
Interpretation	O	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence.

Appraisal by CONSORT 2010 statement

PAPER SECTION and topic	Item	Descriptor
OTHER INFORMATION		
Registration	O	Registration number and name of trial registry.
Protocol	O	Where the full trial protocol can be accessed, if available.
Funding	O	Sources of funding and other support (such as supply of drugs), role of funders.

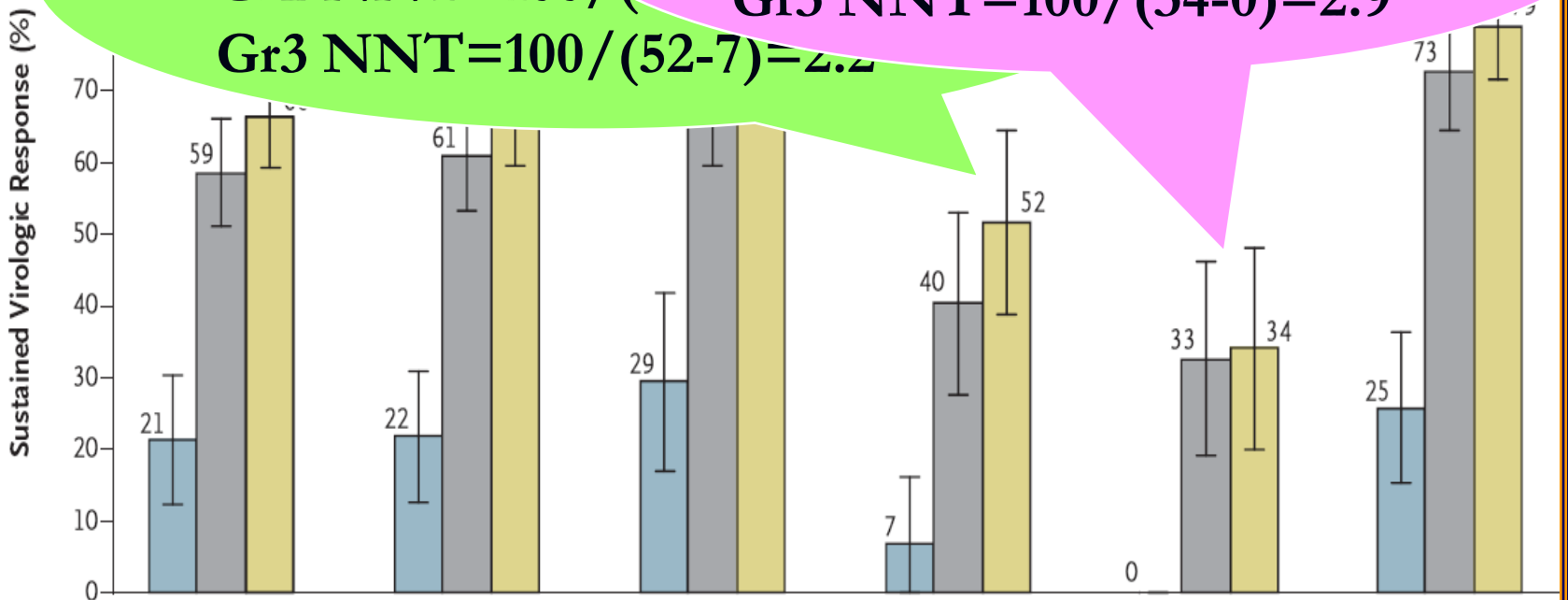
- Fulfilled items=34/37➔ good quality.
  - No identification as a randomized trial in the title.
  - No identification of the settings and locations where the data were collected.
  - No sample size calculation.

Primary analy
Gr2 NNT=10

Prior relapse
Gr2 NNT=10

Prior non-resp
Gr2 NNT=100/(
Gr3 NNT=100/(52-7)=2.2

Poor IFN responder
Gr2 NNT=100/(33-0)=3.3
Gr3 NNT=100/(34-0)=2.9



No. with SVR	17	95	107	17	95	107	15	72	77	2	23	30	0	15	15	17	80	90
No. of Patients	80	162	161	78	156	160	51	105	103	29	57	58	12	46	44	67	110	114

Application --- Boceprevir effect

- **Boceprevir does not have clinically significant activity against other HCV genotypes.**
- **HCV rapidly develop resistance when exposed to Protease-Inhibitor monotherapy. Addition of interferon reduces the rate of emergence of these resistant variants.**
- **Having a lead-in phase was in advantage to responsiveness (↑2-8 % effectiveness)→ actual effect should be lower.**

Application --- Boceprevir effect

- **Our patient has relapse after IFN Tx.**
  - **Estimated therapeutic effect of Boceprevir with standard treatment is about 70% with a NNT of 2.5 in Gr2 and 2.2 in Gr3.**
- **Our patient is a de-compensated LC (Child B) with HIV (+). Cirrhosis have a negative impact on response, and decompensated LC was excluded→ not similar to our patient.**

--- NNH

Any adverse event
Gr2 NNH
Gr3 N

Any serious adverse event
Gr2 NNH=100/(10-5)=20
Gr3 NNH=100/(14-5)=11

Event				P Value	
				Group 2 vs. Group 1	Group 3 vs. Group 1
Death — no. (%)		1 (<1)†	0	0.99	0.99
Any adverse event — no. (%)	77 (96)	160 (99)	161 (100)	0.34	0.04
Discontinuation owing to adverse event — no. (%)	2 (2)	13 (8)	20 (12)	0.15	0.02
Dose modification owing to adverse event — no. (%)	11 (14)	47 (29)	53 (33)	0.01	0.002
Any life-threatening adverse event — no. (%)	0	4 (2)	5 (3)	0.31	0.17
Any serious adverse event — no. (%)	4 (5)	16 (10)	23 (14)	0.23	0.03

- **Severe AE: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention**
- **Life-Threatening AE: immediate risk of death.**

Event	Group 1 (N=80)	Group 2 (N=162)	Group 3 (N=161)	P Value	
				Group 2 vs. Group 1	Group 3 vs. Group 1
Mean change in hemoglobin from baseline — g/dl					
At wk 12	−2.89	−4.02	−3.96	<0.001	<0.001
At wk 24	−2.69	−4.36	−4.31	<0.001	<0.001
At wk 48					0.005
Hem					
Gra					
Grade 3: 6.5 to <8.0 g/				0.67	0.07
Grade 4: <6.5 g/dl	0	0	1 (<1)	0.99	0.99
Erythropoietin use	17 (21)	66 (41)	74 (46)	0.003	<0.001
Transfusion	0	3 (2)	14 (9)	0.55	0.006
Common adverse event — no. (%)‡					
Anemia	16 (20)	70 (43)	74 (46)	<0.001	<0.001
Dry skin				0.009	0.004
Dysgeusia				01	<0.001
Rash (include DRESS)			22 (14)	0.01	0.05

Anemia that need Erythropoietin therapy
Gr2 NNH=100/(41-21)=5
Gr3 NNH=100/(46-21)=4

Gr2 NNH=100/(43-20)=4.3
Gr3 NNH=100/(46-20)=3.8

Adverse Effect is under-estimated

- The trial
  and analy
  of interes
  effect.
- Anemia i
  serious a

If anemia was included, any serious adverse event：

Gr2 NNH=100/(53-25)=3.5

Gr3 NNH=100/(60-25)=2.8

In contrast to primary analysis of NNT

Gr2 NNT=100/(59-21)=2.63

Gr3 NNT=100/(66-21)=2.2

Event	(N=80)	(N=162)	(N=161)	P Value	
				Group 2 vs. Group 1	Group 3 vs. Group 1
Any serious adverse event — no. (%)	4 (5)	16 (10)	23 (14)	0.23	0.03
Anemia (Need transfusion or EPO)	16 (20)	70 (43)	74 (46)	<0.001	<0.001

Application

- The actual effect of Boceprevir may be lower in our patient.
- Boceprevir has a NNT (2.2) similar to its NNH (2.8) in Gr 3→ benefit does not out-weight the harm.
- Potential drug-drug interaction with statin.
- Wait for more evidence to apply protease inhibitor in combination with PegIFN-RBV therapy.

謝謝您

- Thank You
- Merci
- Danke
- Gracias
- Grazie
- あなたに感謝しなさい
- 너를 감사하십시요
- Спасибо
- الشكر؛ شكر
- 谢谢

Acquire ---- Searching Results

1) Bacon, B.R., et al. Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection. N Engl J Med 2011;364:1207-17.
2) Poordad F., et al. SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.
3) Kwo P.Y., et al. SPRINT-1 investigators. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet. 2010 Aug 28;376(9742):705-16. Epub 2010 Aug 6. Erratum in: Lancet. 2010 Oct 9;376(9748):1224. SPRINT-1 investigators.
4) Susser S., et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology. 2009 Dec;50(6):1709-18.
5) Kuntzen T., et al. Naturally occurring dominant resistance mutations to hepatitis C virus protease and polymerase inhibitors in treatment-naïve patients. Hepatology. 2008 Dec;48(6):1769-78.