6th Paris Hepatitis Congress, 14/1/2013

OPTIMIZING HCV THERAPY: MANAGEMENT OF SIDE EFFECTS

Dr. Sam Lee
University of Calgary Liver Unit

Speaker disclosure

- Research support: Abbott, Achilion, Bristol Myers Squibb, Boehringer Ingelheim, Gilead, Janssen, Merck, GlaxoSmithKline, Novartis, Roche, Vertex
- Consultant: Abbott, BI, BMS, Gilead, Janssen, Merck, Roche, Vertex
- Speakers Bureau: BMS, Gilead, Merck, Roche

Disclaimer/Warning

This presentation contains the following material

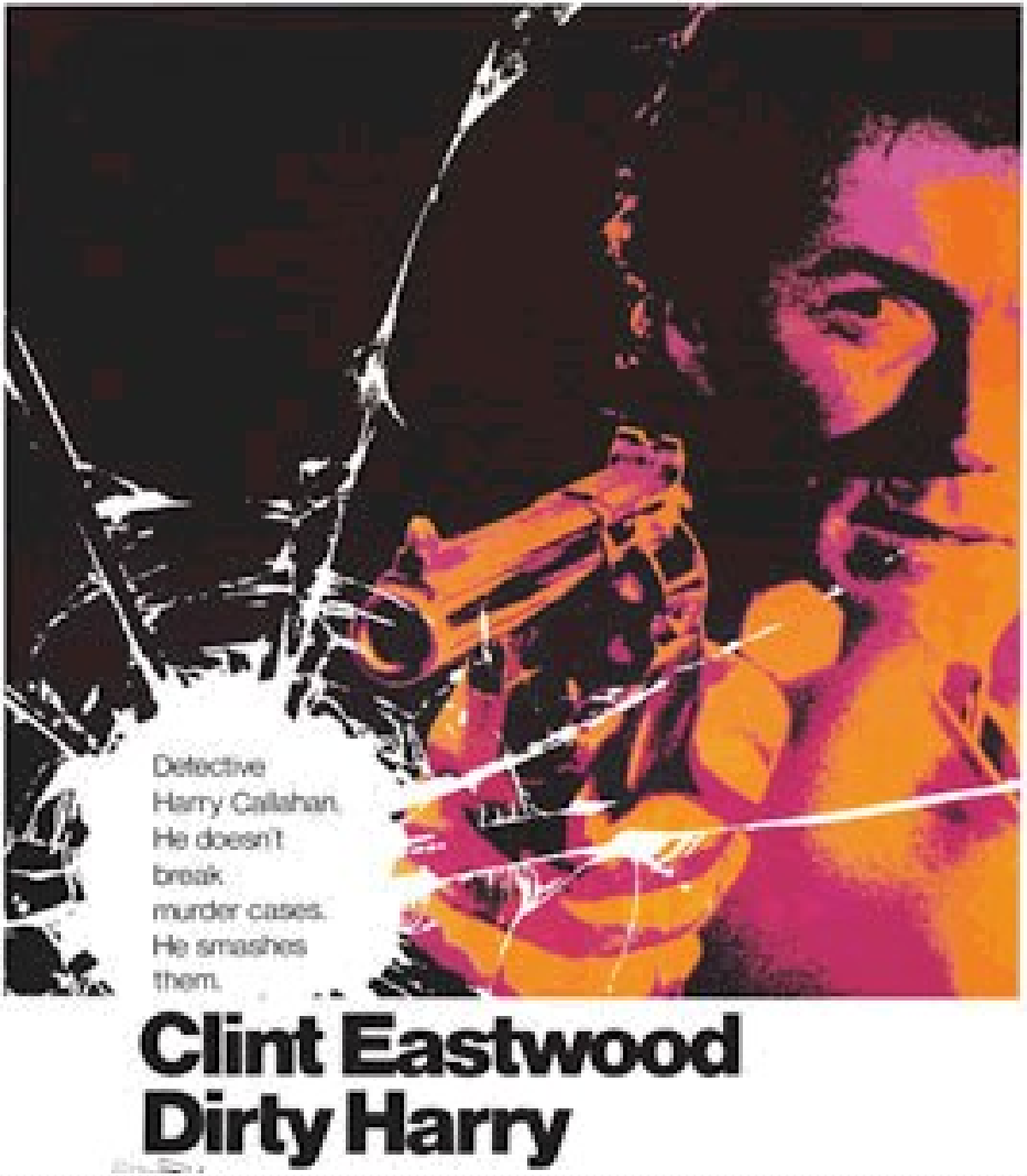
- Partial nudity
- Frightening scenes
- Violence
- Sexual content

Therefore, recommended for mature audiences only

OBJECTIVES

- Review management of HCV antiviral therapy side effects
- telaprevir and boceprevir
- Practical suggestions for management
- Special considerations in cirrhosis


MANAGING SIDE EFFECTS
OF TREATMENT…



BIG WEAPONS HAVE BIG SIDE EFFECTS

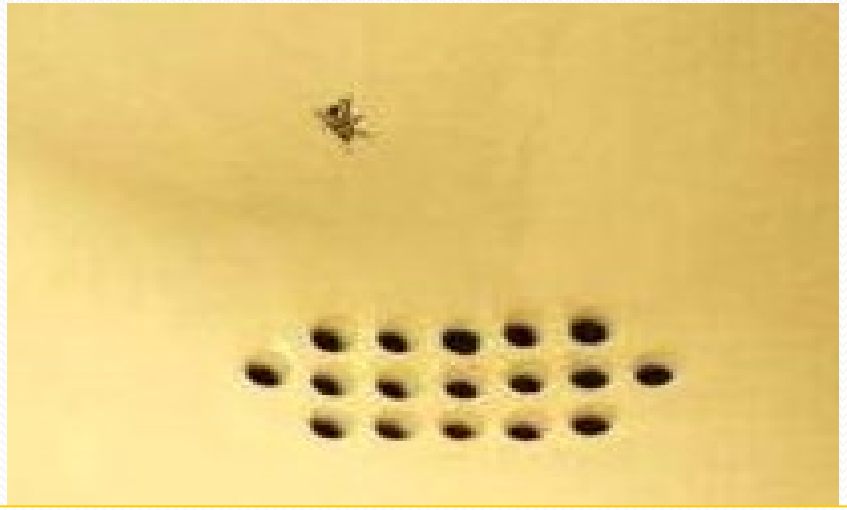
MANAGING SIDE EFFECTS: summary

Table 1. Common adverse effects and management

Adverse effect	Suggested management
Fatigue	Maintain active lifestyle, balanced diet, social support, rest as needed, caffeinated beverages (moderate), acetaminophen, nonsteroidal anti-inflammatory drugs
Fever/myalgia	Acetaminophen, change peginterferon dose timing
Insomnia	Regular evening schedule, avoid prebedtime stress or heavy exertion, hypnotics/sedatives
Anorexia/weight loss	No intervention usually needed; if severe, small frequent meals, nutritional supplements
Anaemia	Aggressive ribavirin dose reduction, blood transfusions, oral iron, erythropoieitin
Neutropaenia	Peginterferon dose reduction, granulocyte-stimulating factors if severe
Thrombocytopaenia	No intervention needed unless symptomatic or severe; peginterferon dose reduction, thrombopoietin if severe
Skin rash	Moisturizers, corticosteroid cream, anti-histamines, dermatology referral if severe
Diarrhoea/anal Discomfort	Corticosteroid ointment, barrier cream/paste, anti-diarrhoeals, increased dietary fibre, anti-histamines
Dysgeusia	Oral care, frequent water drinking, mouth washes, small frequent meals, plastic utensils, fruits and vegetables, lozenges, hard candies
Depression	Social support, psychology/psychiatry referral, SSRI antidepressants
Emotional lability/irritability	Social support especially spouse/partner/family, psychology/counselling Referral, SSRI anti-depressant if severe

Chopra et al. Liver Int 2013 (Suppl 1)

SIMPLE CHANGES CAN BE EFFECTIVE



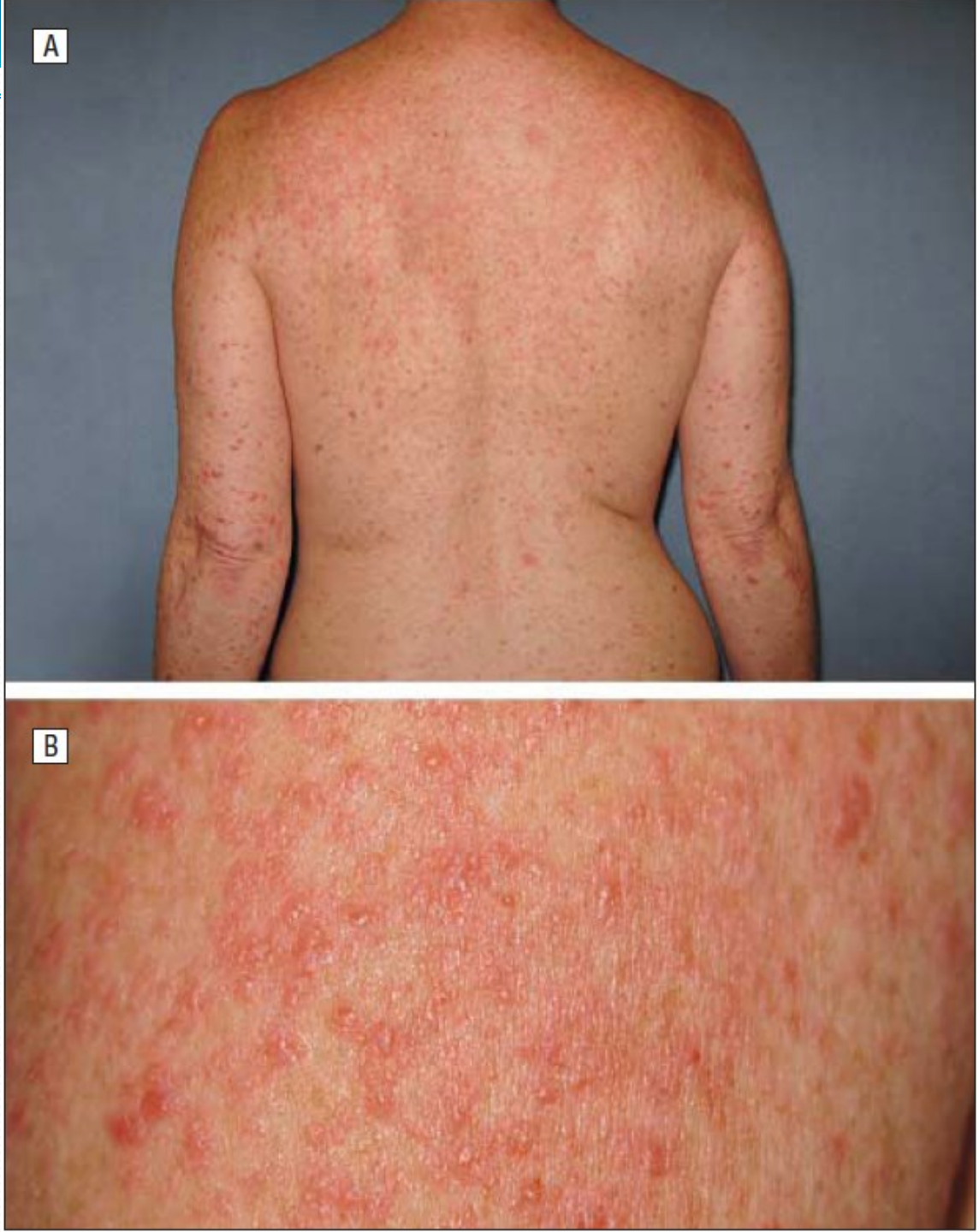
SIMPLE MANAGEMENT STRATEGIES

- Patient must be totally committed/motivated (timing of therapy; no financial worries)
- Multidisciplinary treatment team: doctors (incl psych and dermatology consultants), nurses, counselors, pharmacists, clerical help (filling forms)
- Effective communication between patient and team: on-demand nurse access, fast MD access, after-hours telephone link/consultation

Moderate telaprevir rash with eczematoid features

Mild-localized.
Moderate-diffuse, <50% of body surface.
Severe->50% , or any bullae, vesicles, purpura, epidermal detachment, mucus membrane erosions.

Roujeau et al. Arch Dermatol 2013



SKIN RASHES IN TELAPREVIR PHASE 3 TRIALS

Variable	Patients, No. (%)	
	Telaprevir Plus Peginterferon and Ribavirin (n = 1797)	Placebo Plus Peginterferon and Ribavirin (n = 493)
Adverse skin reaction	1009 (56)	168 (34)
Mild	725 (40)	143 (29)
Moderate	218 (12)	23 (5)
Severe	66 (4)	2 (<1)
Discontinuation of telaprevir or placebo due to skin eruption	115 (6)	2 (<1)
Discontinuation of all drugs due to skin eruption	15 (1)	2 (<1)

SJS 3; DRESS 11

Roujeau et al. Arch Dermatol 2013

SKIN RASH MANAGEMENT

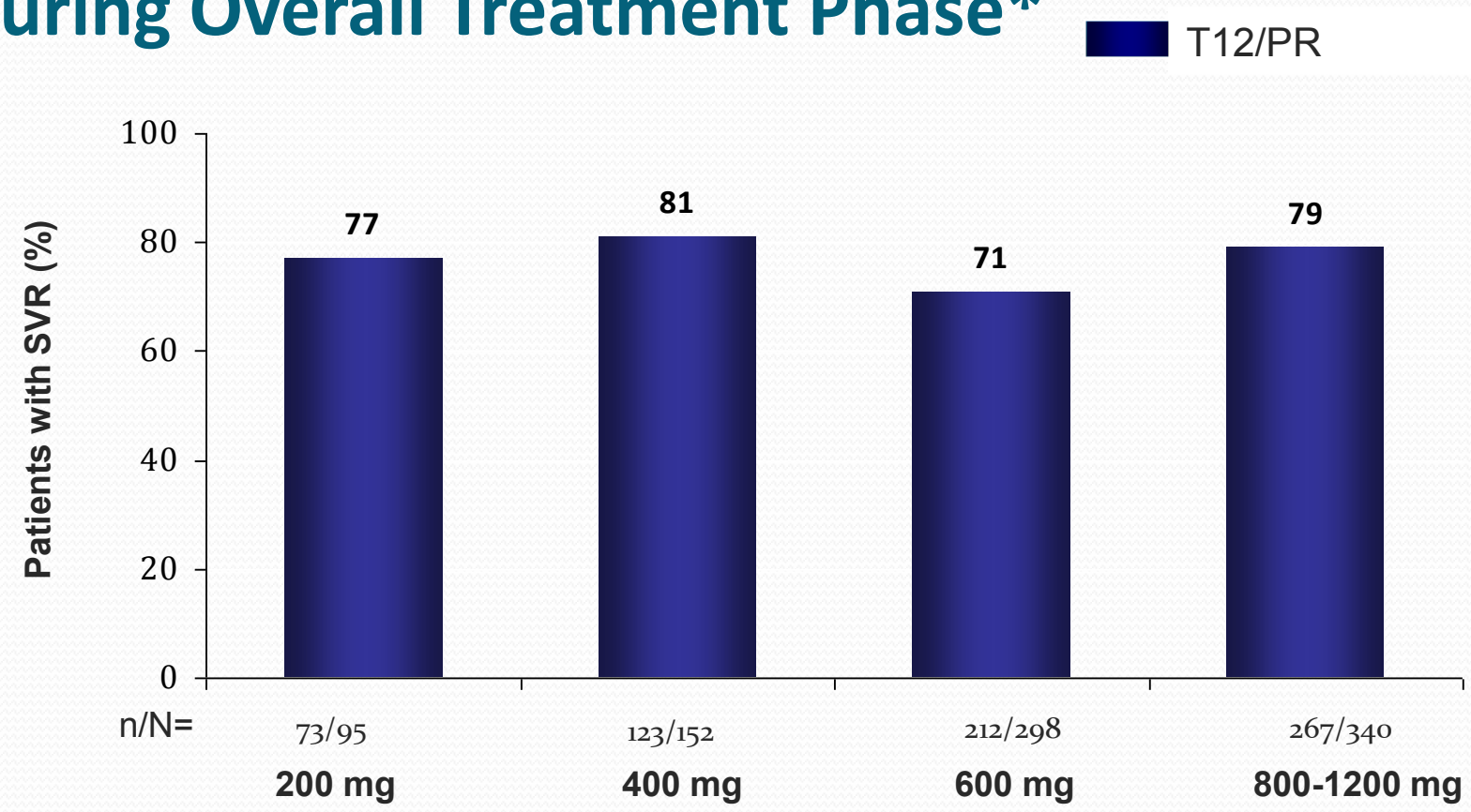
- Moisturizing cream
- Steroid ointment
- Anti-histamines
- If telaprevir characteristis (eczematoid and pruritic), monitor carefully and stop telaprevir if not responding to local therapies, or severe
- Urgent consultation with dermatologist for moderate and severe

ANEMIA IN THE DAA AGE

- Probably similar rates with both triple-therapies
- Paradigm that anemia during therapy is favorable prognostic marker likely not correct
- Paradigm that RBV dosing must be maximized likely not correct with telaprevir
- Manage with RBV dose reduction, transfusions and EPO
- Boceprevir study: RBV dose reduction = EPO

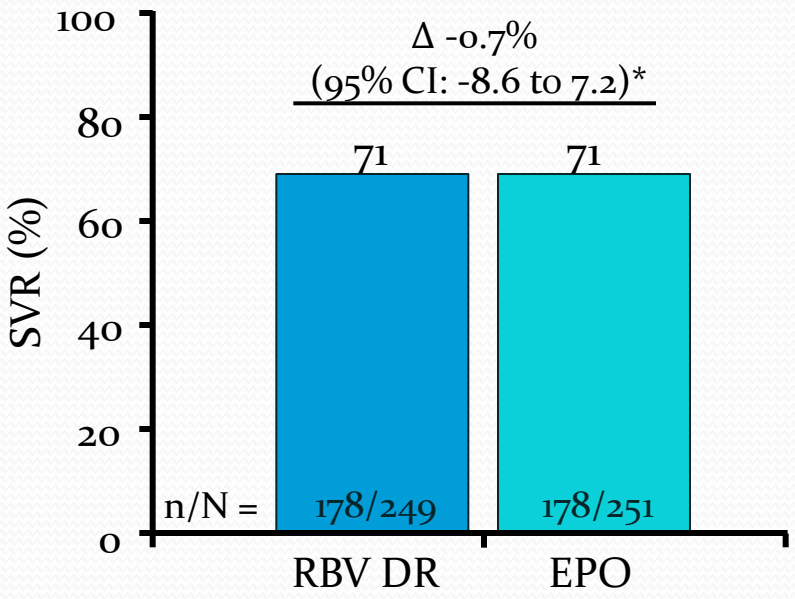
Treatment Naïve Patients: ADVANCE and ILLUMINATE (T12 PR arms, N=885)

SVR Rates and Minimum Ribavirin Dose/Day During Overall Treatment Phase*



ADVANCE and ILLUMINATE (INCIVEK 12/PR arms; N=885)
*Length of RBV exposure=0 - >36 weeks.
Vertex data on file.

BOCEPREVIR SVR: RBV reduction was equivalent to EPO for First-line Anemia Management



*Stratum-adjusted difference in SVR rates, adjusted for stratification factors and protocol cohort.

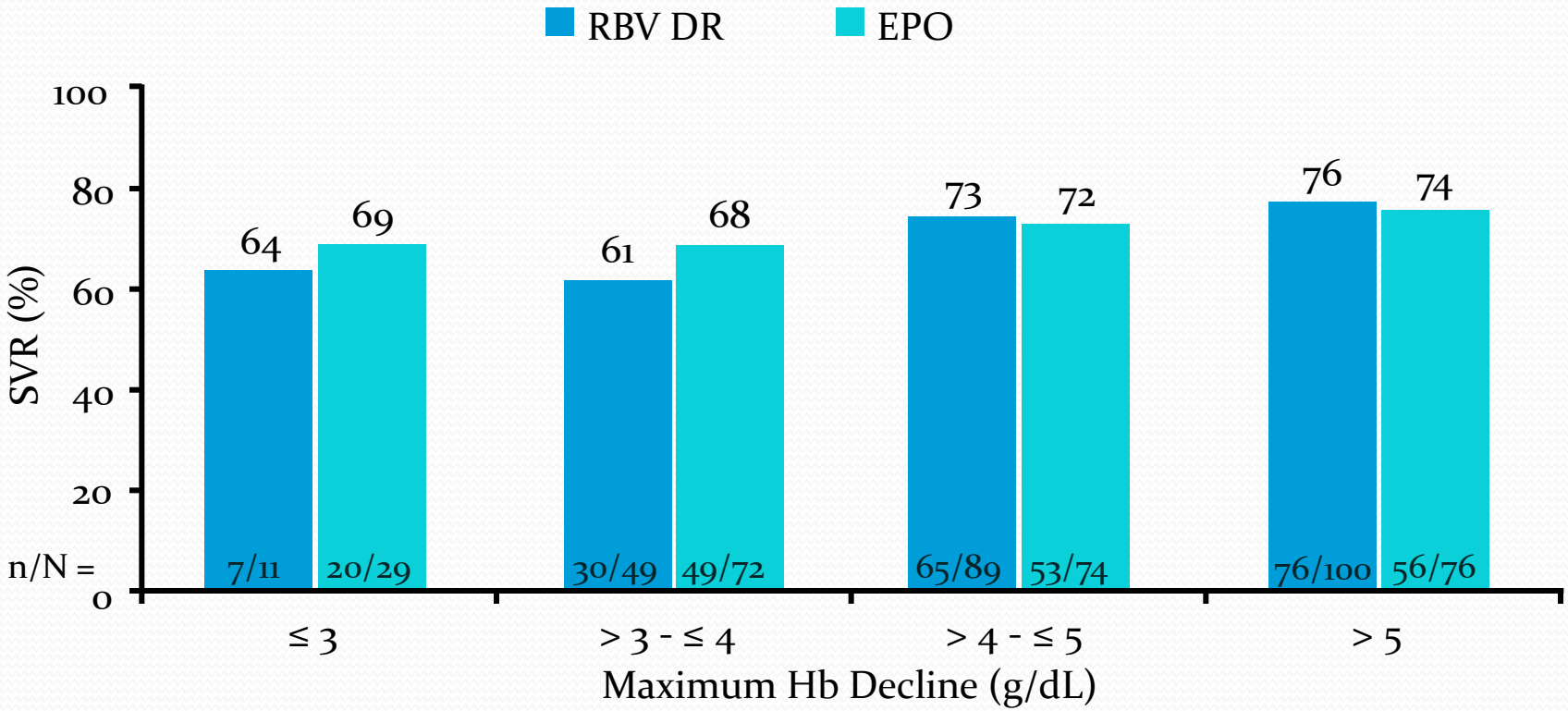
- 82% of RBV dose reduction group vs 62% in EPO group did not require secondary anemia intervention

- Similar SVR rates with 2 strategies, regardless of baseline characteristics

Subgroup, %	RBV Dose Reduction (n = 249)	EPO (n = 251)
Sex		
▪ Female	69	72
▪ Male	77	69
Race		
▪ Black	53	49
▪ Nonblack	75	76
Weight		
▪ < 75 kg	72	70
▪ ≥ 75 kg	71	72
IL28B		
▪ TT	65	65
▪ CT	70	67
▪ CC	78	82
Fibrosis score		
▪ F0/1/2	74	72
▪ F3/4	58	67

Poordad F, et al. EASL 2012. Abstract 1419.

No Association Between Degree of Hb Decline and SVR in Pts Developing Anemia



Poordad F, et al. EASL 2012. Abstract 1419.

TELAPREVIR: anorectal burning

13% in ADVANCE study; approx 1/3 in our experience

MANAGING ANORECTAL DISCOMFORT

- Reduce diarrhea
- Rule out infection/anal fissures
- Barrier cream
- Sitz baths
- Steroid ointment
- Lidocaine ointment
- Local relief (cold pack or frozen sanitary napkin)

BOCEPREVIR: managing dysgeusia

- 30-40% prevalence
- Many patients don't mind losing weight/appetite
- Adequate hydration; peppermints/ candy lozenges
- Small frequent meals
- Eat more tart foods
- Lidocaine mouthwashes
- Change from metal to plastic utensils

REAL-WORLD CIRRHOSIS: CUPIC

- Ongoing real-world French multicentric nonrandomized study of telaprevir and boceprevir triple-therapies in patients with cirrhosis
- Preliminary results of 296 telaprevir and 159 boceprevir patients presented at EASL 2012*

Hezode C et al. EASL 2012

CUPIC: Safety of Telaprevir

Safety Outcome, %	Telaprevir-Based Therapy (n = 296)
Serious adverse events	48.6
Premature treatment discontinuation	26.0
▪ Resulting from serious adverse events	14.5
Death	2.0 (sepsis [n = 2], pneumopathy [n = 1], bleeding of esophageal varices [n = 1], encephalopathy [n = 1], and lung carcinoma [n = 1])
Grade 3/4 nonhematologic adverse events	
▪ Infection	8.8
▪ Rash	7.5
▪ Hepatic decompensation	4.4
Hematologic adverse events and support	
▪ Anemia	
• Grade 2	19.6
• Grade 3/4	10.1
• Use of erythropoietin	56.8
• Blood transfusion	15.2
▪ Thrombocytopenia	
• Grade 3/4	13.1
• Use of thrombopoietin	1.7
▪ Neutropenia	
• Grade 3/4	4.7
• Use of G-CSF	2.4

Herrode C, et al. EASL 2012. Abstract 8.

CUPIC: SAFETY OF BOCEPREVIR

Safety Outcome, %	Boceprevir-Based Therapy (n = 159)
Serious adverse events	38.4
Premature treatment discontinuation	23.9
▪ Resulting from serious adverse events	7.4
Death	1.3 (bronchopulmonary infection [n = 1] and sepsis [n = 1])
Grade 3/4 nonhematologic adverse events	
▪ Infection	2.5
▪ Rash	0
▪ Hepatic decompensation	4.4
Hematologic adverse events and support	
▪ Anemia	
• Grade 2	22.6
• Grade 3/4	10.1
• Use of erythropoietin	66.0
• Blood transfusion	10.7
• Thrombocytopenia	
• Grade 3/4	6.9
• Use of thrombopoietin	1.9
▪ Neutropenia	
• Grade 3/4	5.0
• Use of G-CSF	3.8

Herrode C, et al. EASL 2012. Abstract 8.

MANAGING CIRRHOTIC PATIENTS

- LESSONS FROM CUPIC STUDY
- Serious adverse events (SAEs) are common (T/B: 49/38%)
- Discontinuation rates 26/24%; due to drug AE, 14/7%
- Anemia is dominant AE with both drugs
- Approx 4% decompensated, with several deaths
- Sepsis/bacterial infections not rare
- **Cirrhotic patients must be carefully monitored**

CONCLUSIONS

- Triad is key: patient, team, connection/communication
- Several simple measures can help
- AEs: telaprevir > boceprevir
- Severe side effects uncommon
- Moderate side effects can be reduced/managed
- All side effects increased in cirrhotics—monitor very carefully

Goals of therapy: a healthy patient