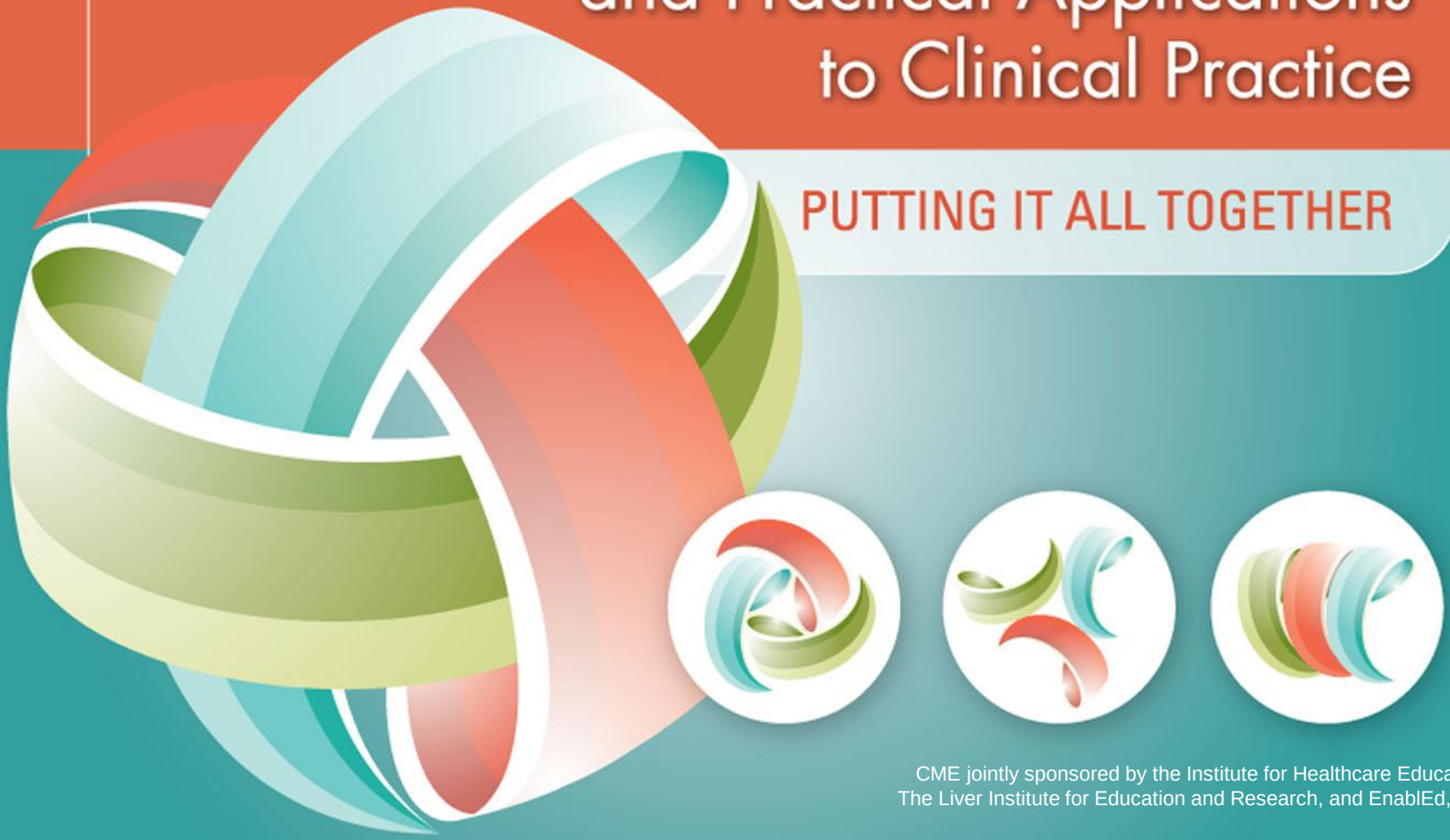
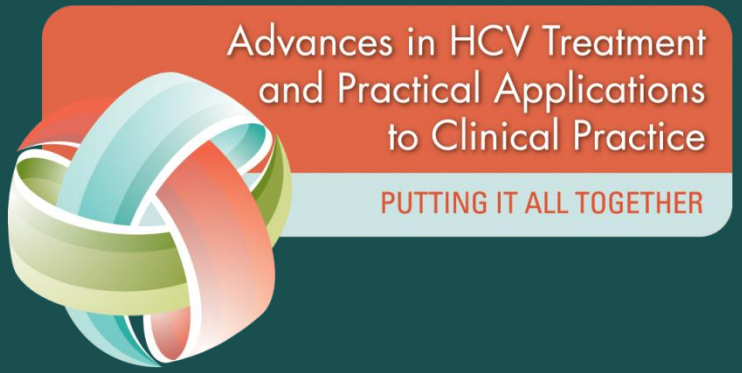
Advances in HCV Treatment and Practical Applications to Clinical Practice

PUTTING IT ALL TOGETHER



CME jointly sponsored by the Institute for Healthcare Education, The Liver Institute for Education and Research, and EnablEd, LLC



Case:
Side Effect Management

52-Year-Old White Woman with Cirrhosis

- HCV diagnosed in 1999
- Genotype 1a; HCV RNA 3.2×10^6 IU/mL
- Blood transfusion after bleeding during pregnancy 30 years ago
- Liver biopsy: Stage 4, Grade 1, sinusoidal fibrosis, steatosis > 30%
- Endoscopy: No varices
- Ultrasound: No hepatocellular carcinoma

Follow-Up Examination: 2002

- Physical examination: Splenomegaly
- Obese; weight 130 kg, BMI 42 kg/m^2
- Type 2 diabetes mellitus
- ALT 130 IU/mL, AST 165 IU/mL
- No alcohol

- What is the best treatment at this time point?

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body-mass index.

Treatment in 2002

- PEG-IFN α2b with weight-based ribavirin
- Week 4: HCV RNA 3,000 IU/mL
- Week 12: HCV RNA not detected
- End-of-treatment response
- Week 4 after treatment: relapse

PEG-IFN = pegylated interferon.

Follow-Up: 2003–2008

- ALT, AST both remain > 100 IU/mL
- CBC: Mild thrombocytopenia (platelet count 98,000/μL)
- Diabetes: Progressive, therapy switched from metformin to insulin
- Obesity worsens: BMI 44 kg/m^2

- What options do we have?

CBC = complete blood count.

Treatment in 2009

- Endoscopy: No varices
- HVPG 9 mm Hg
- Bariatric surgery (lap band) performed
- Weight decreased from 134 kg to 97 kg in 1 year, off insulin
- Repeat biopsy: Stage 4, HVPG 6 mm Hg

HVPG = hepatic vein pressure gradient.

Evaluation March 2011

- No symptoms, Child-Pugh Class A compensated cirrhosis
- *IL28b* genotype CC
- HCV genotype 1A; viral load 1.6×10^6 IU/L
- ALT 179 IU/L, AST 203 IU/L
- CBC: white cell count 3,900/μL; platelet count 86,000/μL
- Fibroscan 19.7 kPa

Wants Retreatment

Options

- Repeat therapy with PEG-IFN and ribavirin
- Triple therapy: Boceprevir? Telaprevir?

Week 4 of Treatment

- Taking full doses of PEG-IFN, ribavirin, and telaprevir
- No dose reductions
- Hemoglobin decreased from 13.9 g/dL to 8.7 g/dL
  - Started on epoetin 40,000 U weekly
  - Ribavirin reduced by 200 mg
- Severe fatigue, poor concentration
- ALT 36 IU/L, HCV RNA 312 IU/mL

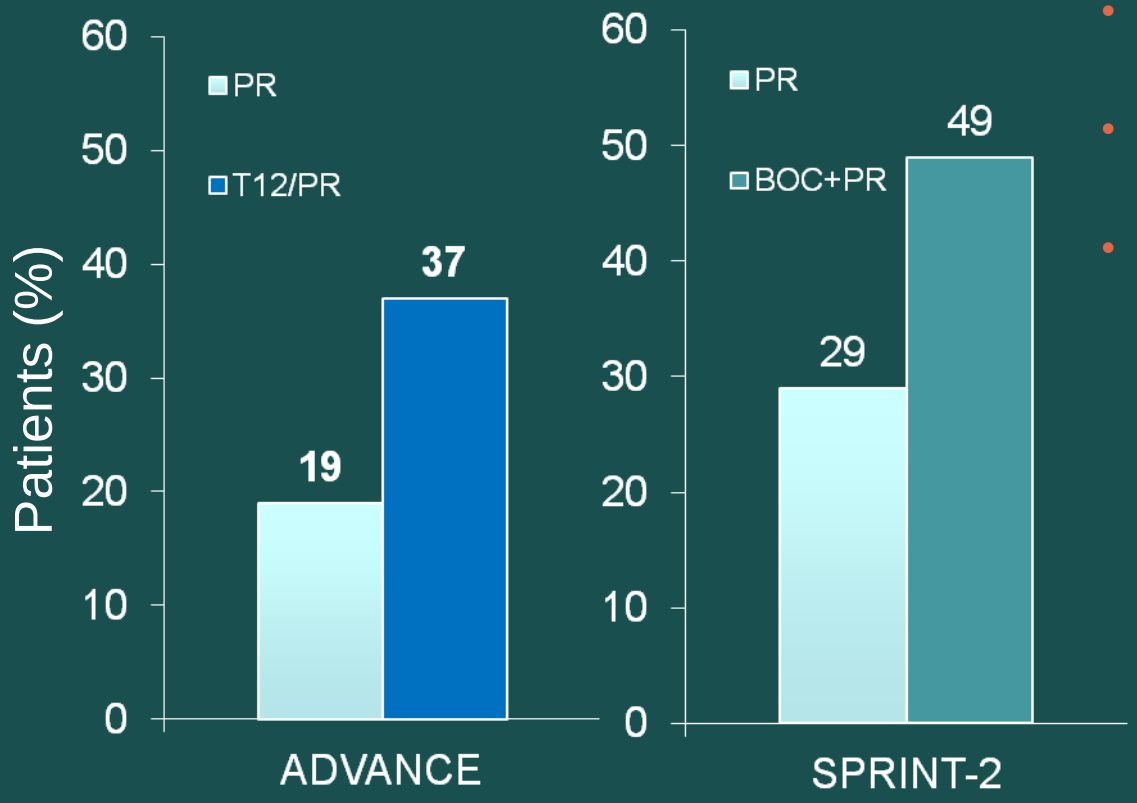
Futility Rules – When to Stop

TELAPREVIR

If >1000 IU/mL HCV RNA:	Week 12 If >1000 IU/mL HCV RNA:	Week 24 Confirmed detectable HCV RNA
Stop PEG-IFN, ribavirin, and telaprevir	**Stop** PEG-IFN, ribavirin, and telaprevir	**Stop** PEG-IFN and ribavirin

Telaprevir prescribing information. March 2012.

Prevalence of Anemia



- In 2%–4% of patients, anemia must be classified as an SAE
- Up to 4% of patients stop PI therapy due to anemia
- Overall, any SAE occurred in about 9%–12%
  - What are the results in real-life patients?
  - Higher rate of discontinuation in patients with…?
    - Advanced age
    - Cardiovascular diseases
    - Pulmonary disorders
    - Renal dysfunction
    - ???

BOC = boceprevir; PI = protease inhibitor; PR = PEG-IFN + ribavirin; SAE = serious adverse event; T12 = telaprevir.

Poordad F, et al. N Engl J Med 2011;364(13):1195-206; Jacobson IM, et al. N Engl J Med 2011; 364(25):2405-16; Sherman KE, et al. N Engl J Med 2011;365(11):1014-24.

ANRS CO20-CUPIC: 16 Week Interim Analysis of TVR or BOC Plus PR in Cirrhotic Non-Responders

Child Pugh A – PR relapsers or partial responders	TVR n=296	BOC n=159
Median PI duration (days)	84	140
Serious adverse events (SAE)	144 (48.6)	61 (38.4%)
Discontinuation	77 (26%)	38 (23.9%)
Discontinuation due to SAE	43 (14.5%)	12 (7.4%)
Death	6 (2%)	2 (1.3%)
Anemia Grade 2 (8.0–<10.0g/dL)	58 (19.6%)	36 (22.6%)
Anemia Grade 3-4 (<8.0g/dL)	30 (10.1%)	16 (10.1%)
EPO use	168 (56.8%)	105 (66%)
Blood transfusion	45 (15.2%)	17 (10.7%)
Thrombopenia Grade 3–4(<50000/mm^3)	39 (13.2%)	11 (6.9%)
Thrombopoietin use	5 (1.7%)	3 (1.9%)
Rash Grade 3	20 (6.8%)	0 (0%)
SCAR	2 (0.7%)	0 (0%)
Grade 3–4 infection	26 (8.8%)	4 (2.5%)

Hézode C, et al. EASL 2012, Barcelona, #8

Therapeutic Options to Counter Anemia

Improve hemoglobin

- Stimulate production via erythropoietin
- Blood transfusion

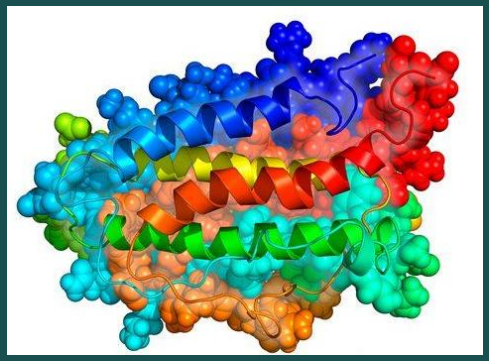
Eliminate the triggering cause

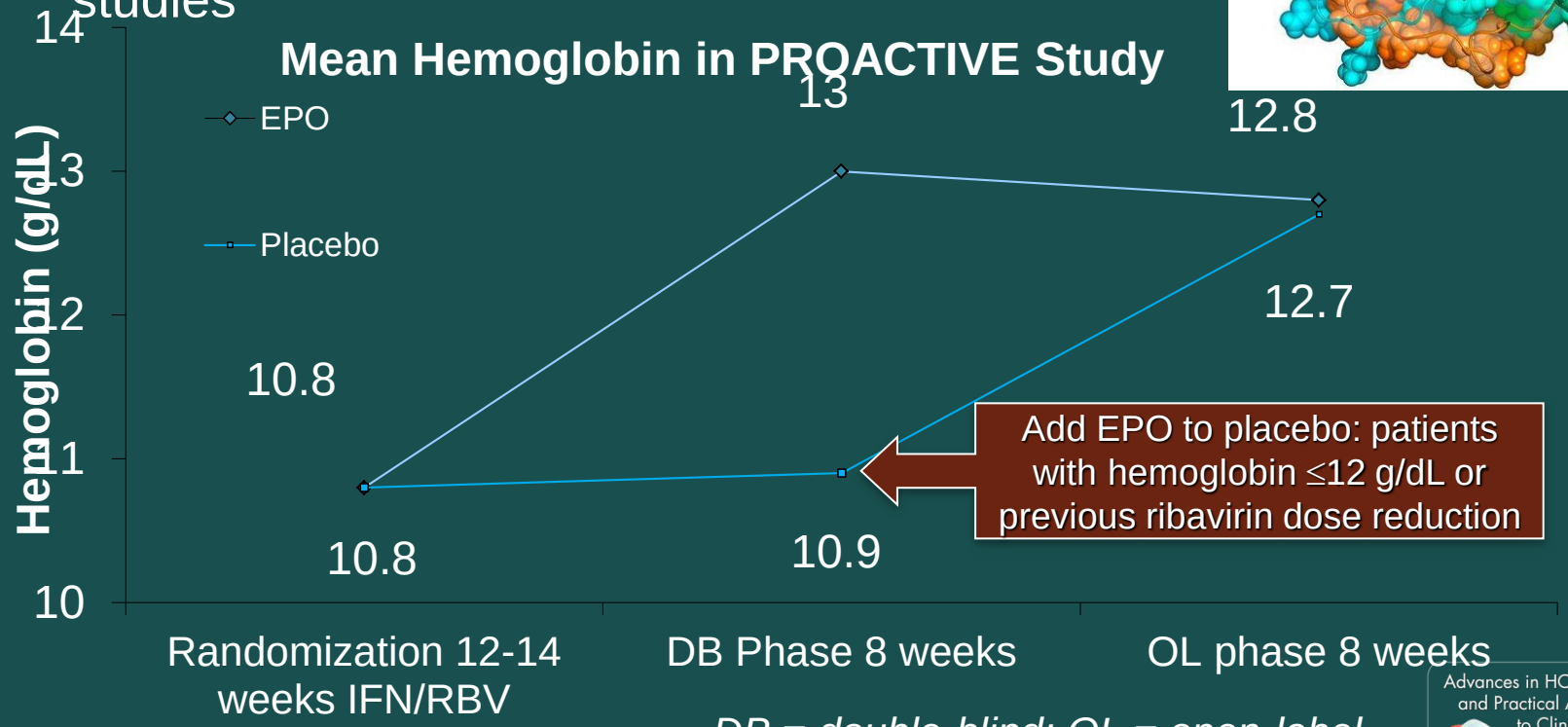
- Reduce dose of the responsible drugs

Anemia

Growth Factors: Use of Erythropoietin (EPO)

- EPO alfa, EPO beta, darbepoetin
- Dose range from 40,000–60,000 IU/week
- Efficacy: Increased hemoglobin in several studies



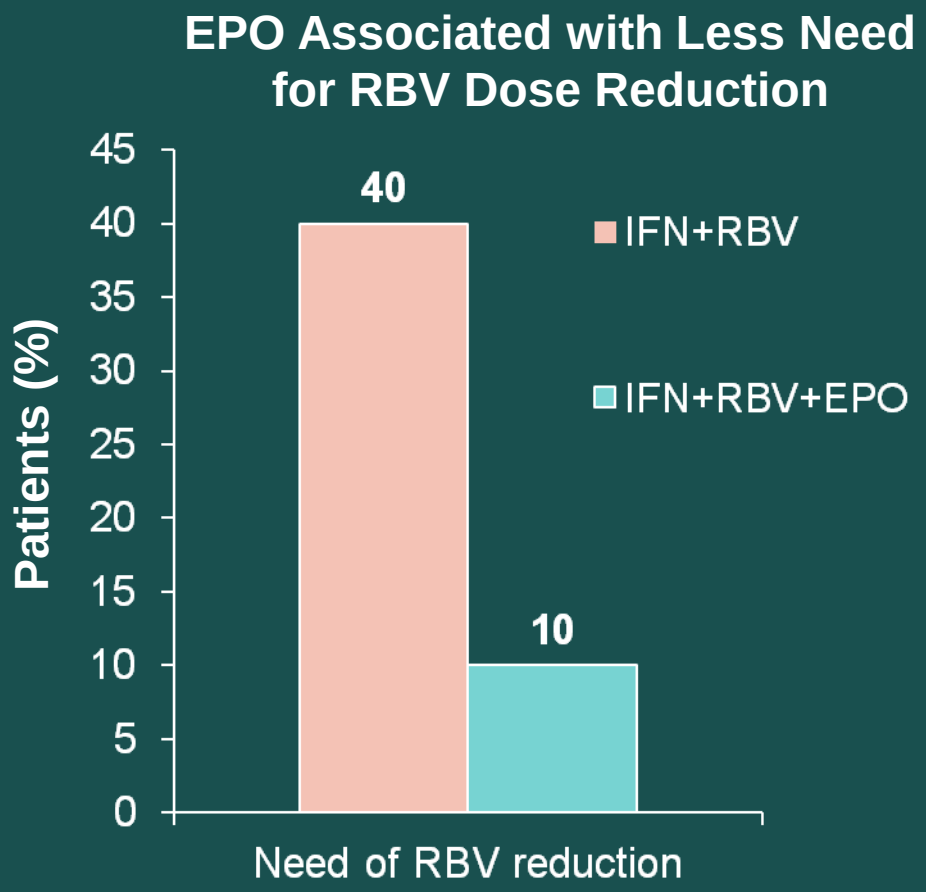


DB = double-blind; OL = open-label.

Pockros JP, et al. Hepatology 2004;40(6):1450-8.

Effect of Erythropoietin During Antiviral Therapy

- Leads to increases in hemoglobin
- Increases quality of life
- Maintenance of ribavirin dosage
  - No significant difference in SVR
  - Lower rate of relapse in third group treated with a high dose of RBV and EPO

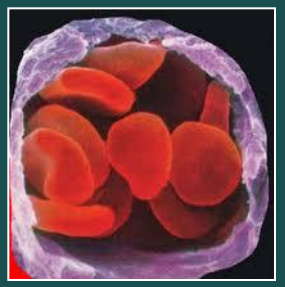


SVR = sustained virologic response.

Pockros PJ, et al. Hepatology 2004; 40(6):1450-8; Afdhal NH, et al. Gastroenterology 2004; 126(5):1302-11; Shiffman ML, et al. Hepatology 2007; 46(2):371-9.

Erythropoietin Disadvantages

- Controversial reports about safety profile
  - In general, no SAEs in HCV therapy
  - Reported AEs in other diseases
    - Hypertension
    - Thromboembolic events
    - Decreased survival rates in cancer patients
    - Antibodies against endogenous EPO
- High cost



Alavian SM, et al. J Viral Hepat 2012;19(2):88-93;
Costiniuk CT, et al. Clin Infect Dis 2008;47(2):198-202.

Blood Transfusions

- Limited resource
- Expensive
- Several risks, including transmission of disease and intolerance reactions
- Often requires hospitalization
  - Only for severe cases: anemia (Hgb <8.5 g/dL) or severe symptoms

Hgb = hemoglobin.

Madjdpour C, et al. Minerva Anestesiol 2006 May;72(5):283-98.

Antiviral Dose Reduction

Reduction of boceprevir or telaprevir

- Resistance-associated variants! No dose reduction allowed

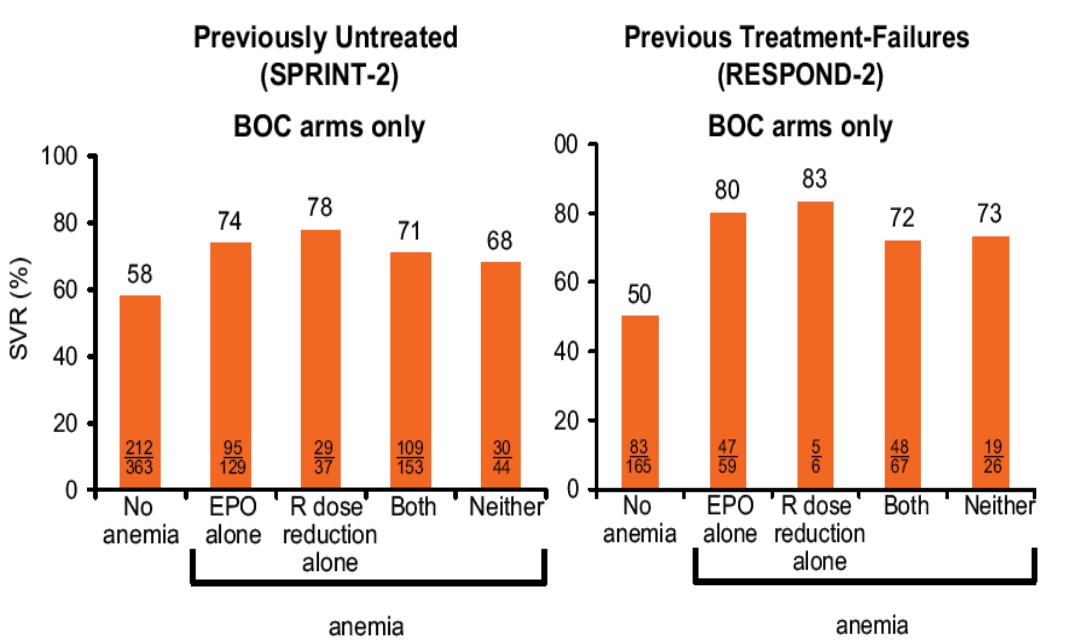
Ribavirin dose reduction

RBV Dose Reduction Versus EPO Treatment for Anemia: No Effect on SVR

Hgb <10 g/dL → RBV reduction (200 mg)

→ EPO (40,000 U sc/week)

Hgb <8.5 g/dL → RBV discontinuation



	Anemia*	Use of EPO
SPRINT-2	366/728 **(50%)**	318/734 **(43%)**
RESPOND-2	158/322 **(49%)**	140/323 **(43%)**
Total	524/1050 **(50%)**	448/1057 **(43%)**

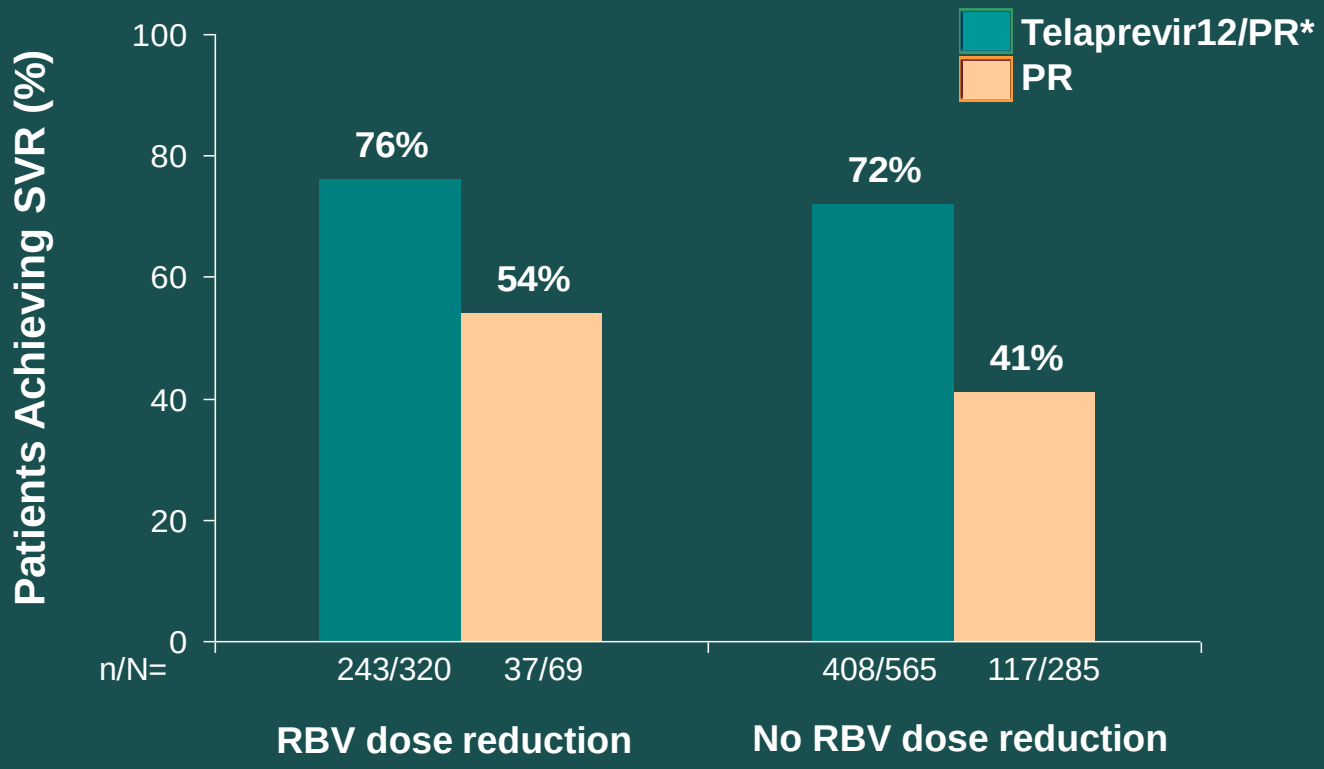
* Anemia: Hgb <10 g/dL or reported by investigator as an adverse event.

sc = subcutaneous.

Sulkowski MS, et al. 46th Annual Meeting of EASL, Berlin, Germany, March 30–April 3, 2011, Poster 476; Poordad F, et al. N Engl J Med 2011;364(13):1195-206; Bacon BR, et al. N Engl J Med 2011;364(13):1195-206.

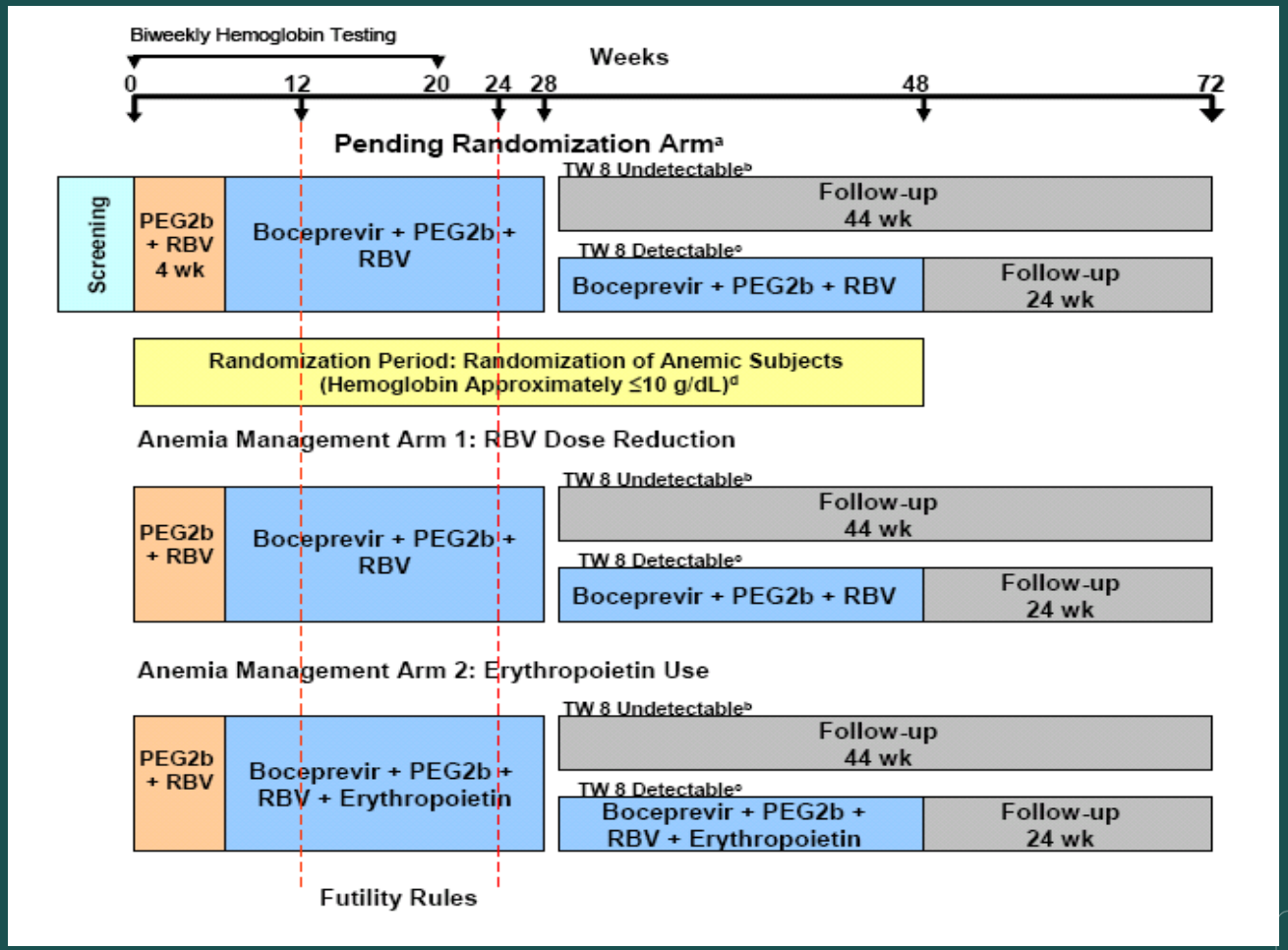
RBV Dose Reduction: No Effect on SVR in ADVANCE, ILLUMINATE

- Retrospective, pooled analysis of efficacy outcomes in HCV genotype 1 treatment-naïve patients



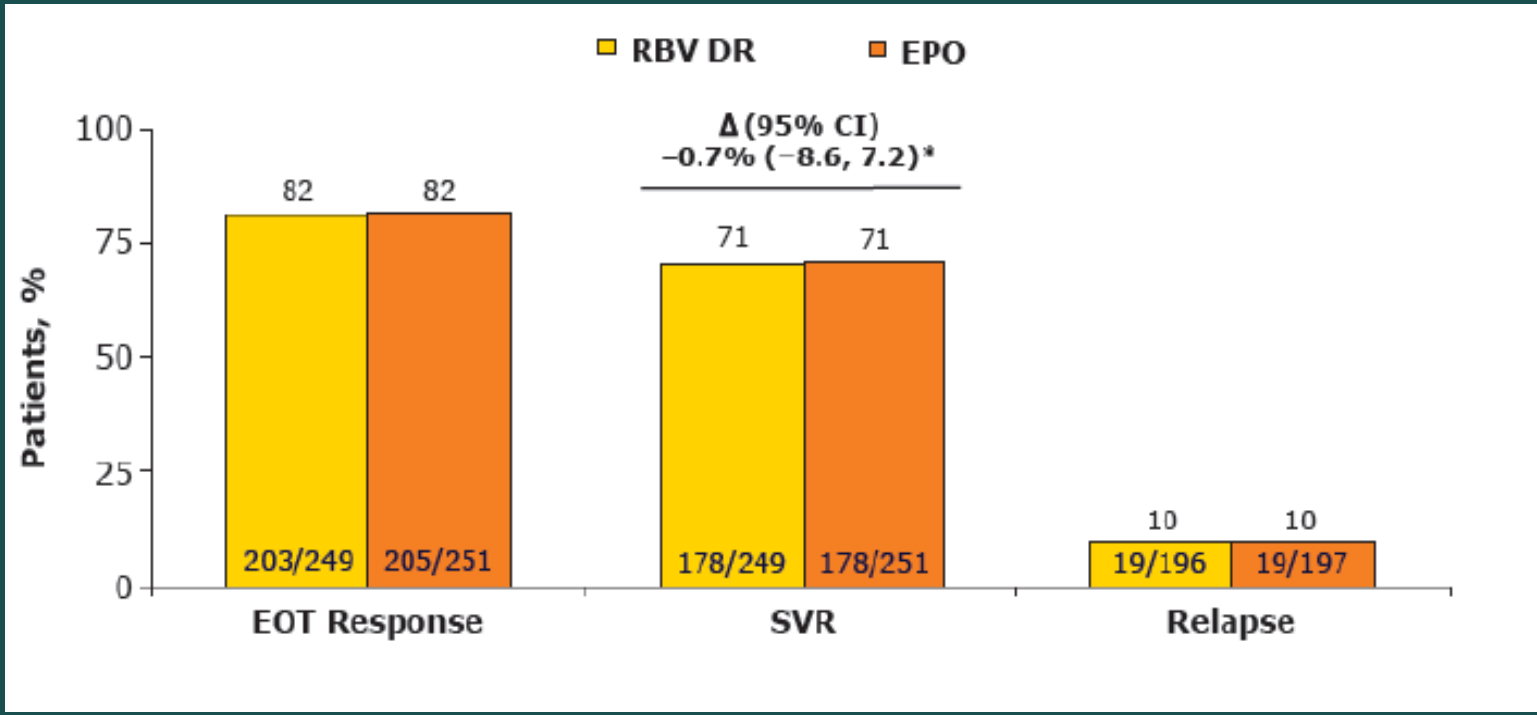
Sulkowski MS, et al. EASL 2011, Abstract 284.

RBV Dose Reduction vs. EPO Use in Patients with Anemia During Boceprevir/ PEG-IFN/RBV Therapy



Poordad F, et al. EASL 2012 Abstract 1419.

RBV Dose Reduction vs. EPO Use in Patients with Anemia During Boceprevir/ PEG-IFN/RBV Therapy



*Stratum-adjusted difference in SVR rate between groups, adjusted for stratification factors (race, time of anemia onset) and protocol cohort (response-guided therapy vs. 48 weeks of treatment). CI = confidence interval; EOT = end of treatment; DR = dose reduction.

Poordad F, et al. EASL 2012 Abstract 1419.

Conclusions

- Ribavirin dose reduction should be first choice
  - Easy to manage
  - Effective way to counter decrease in hemoglobin
  - No significant effect on SVR
- Erythropoietin is an effective but very expensive alternative
  - More difficult application
  - Possible adverse effects
- Blood transfusions are limited to severe cases

EASL Clinical Practice Guidelines. J Hepatol 2011;55:245-264;
Madjdpour C, et al. Minerva Anestesiol 2006 May;72(5):283-98.

Week 8 Treatment

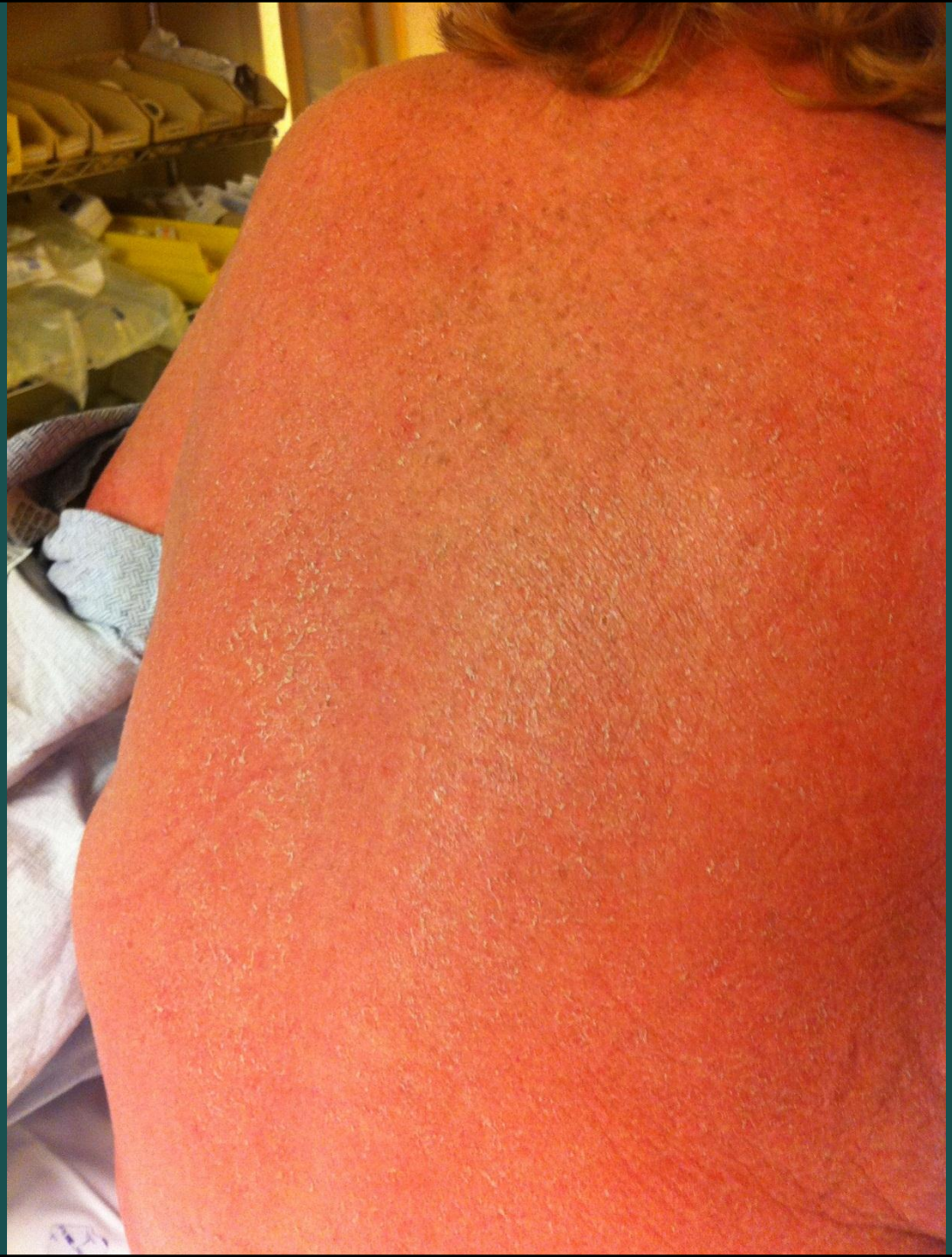
- No further dose reduction of PEG-IFN, ribavirin, or telaprevir
- Hgb between 9.8 and 10.9 g/dL on epoetin 40,000 U weekly; platelet count 45,000/μL
- HCV RNA undetectable (< 25 IU/L)
- Skin rash: maculopapular, arms, legs, trunk
  - < 50%, moderate, no mucosal lesions
- Started on clobetasol twice a day; antihistamines

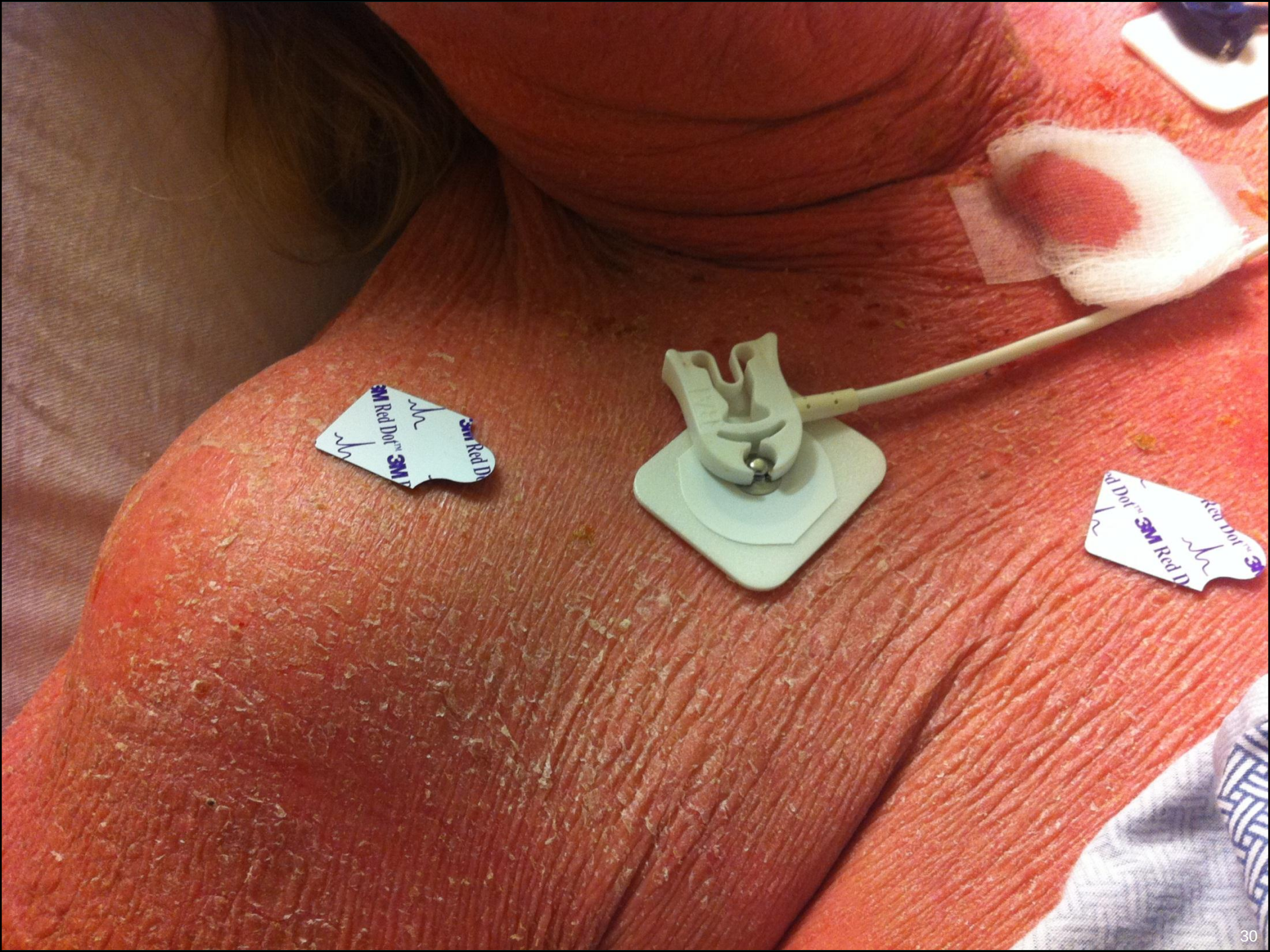
Week 12 Treatment

- No dose reduction of PEG-IFN, ribavirin, or telaprevir
- Telaprevir stopped; plan to use PEG-IFN and ribavirin for 36 weeks
- Rash still present but not worse, expected to improve with discontinuation of telaprevir
- HCV RNA undetectable at end of 12 weeks

Week 14 Treatment

- Telephone call from husband
  - Confusion, fever 101ºF, rash seems worse with pustules
  - Still taking PEG-IFN, ribavirin
- CBC: White cell count 9,700/μL (38% eosinophils), platelet count 48,000/μL, Hgb 9.4 g/dL
- Told to come to hospital

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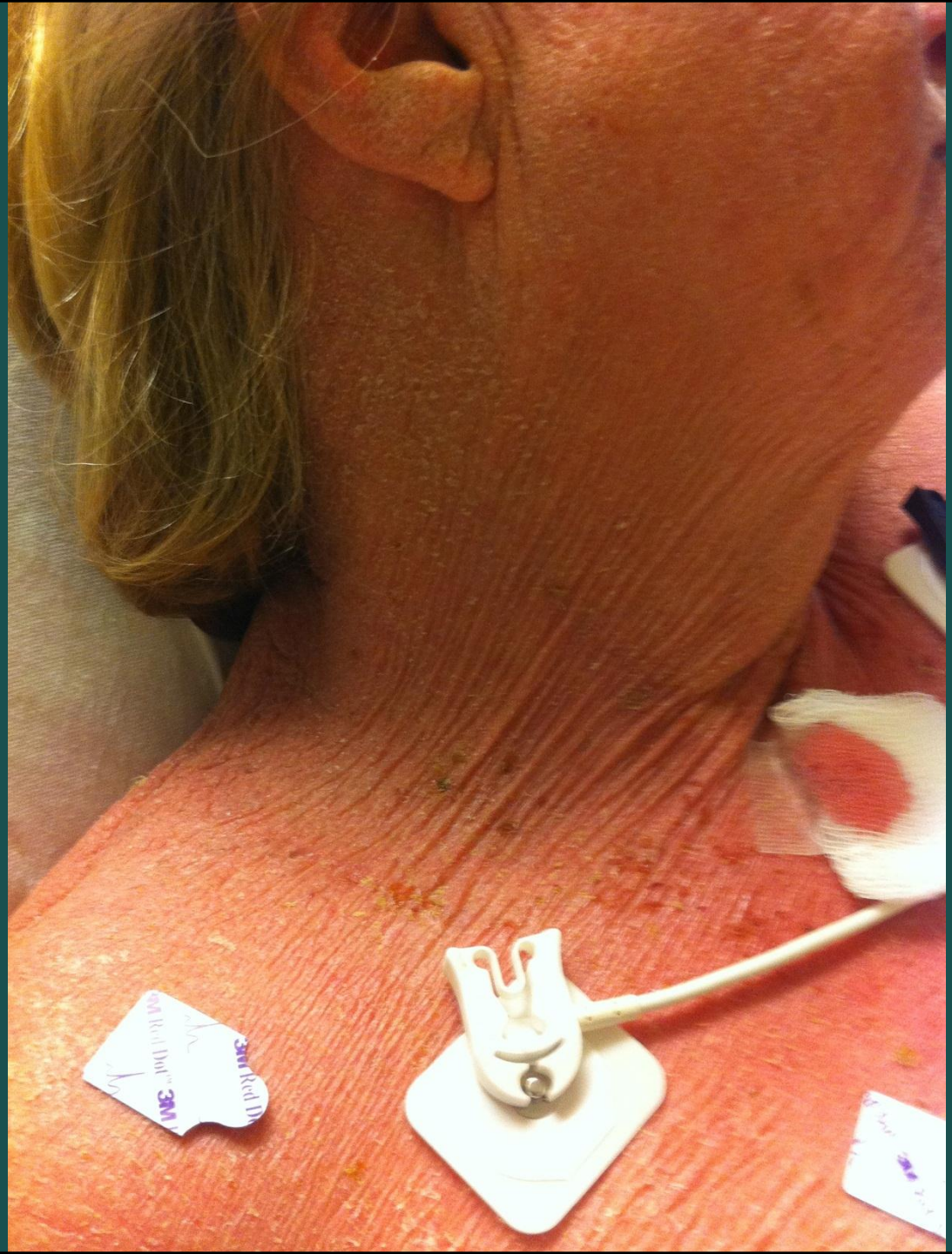

Cutaneous Side Effects
Rash

- Ribavirin dose-related
- Also associated with telaprevir
  - Can be more challenging to treat
- Can occur early or late in therapy
- Assessment
  - Mild to severe
  - Local or generalized
  - Hypersensitivity, associated pruritus, hives, erythema
  - Macular, papular, vesicular

The "Telaprevir Rash"

- Usually mild to moderate but can be severe, intensely pruritic, and/or painful
- Distributed over chest, extremities; spares face
- Counsel patients that rash is possible, assure them that it is manageable
- Results in treatment discontinuation in small numbers of patients
- DRESS syndrome, Stevens-Johnson reported

Telaprevir prescribing information, 2012.

DRESS = Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms.

Cutaneous Side Effects
Rash Management

- Begins with good hydration
- Avoid sunburn
  - Increased dermal photosensitivity with ribavirin
  - Use sunblock, long sleeves/pants, avoid peak sun
- Keep skin moisturized
  - Use Aveeno, Eucerin, Aquaphor
  - No bar soaps

Cutaneous Side Effects
Rash Management

- Rule out other etiologies (autoimmune, infectious)
- Oral antihistamines
- Low-dose hydrocortisone cream or lotion
- Cool soaks with oatmeal products
- Consider additional dermatological etiologies (lichen planus, porphyria cutanea tarda)
- Dermatology referral

Week 15 Treatment

- Rash consistent with DRESS, eosinophils 33%, lymphadenopathy, fever
- Biopsy of rash
- Blood cultures: Methicillin-sensitive *Staphylococcus aureus* sepsis; antibiotics started
- HCV RNA undetectable; ribavirin stopped
- Next steps ??

Anorectal Side Effects of Telaprevir

- Controlled trials: 29% of patients given telaprevir combination therapy had anorectal adverse events vs. 7% of those given PEG-IFN/ribavirin alone
  - Hemorrhoids
  - Anorectal discomfort
  - Anal pruritus
  - Rectal burning
- Most mild to moderate; <1% led to treatment discontinuation, all resolved during or after dosing
- Symptom management
  - Short-term use of topical corticosteroids/anesthetics can relieve itching (consider antihistamines before bedtime for nocturnal itching
  - Control bowel movements with loperamide or diphenoxylate and atropine (adding fiber to diet also can help)

Telaprevir prescribing information; telaprevir Web site.