Triple therapy with BOC or TVR

management of side effects

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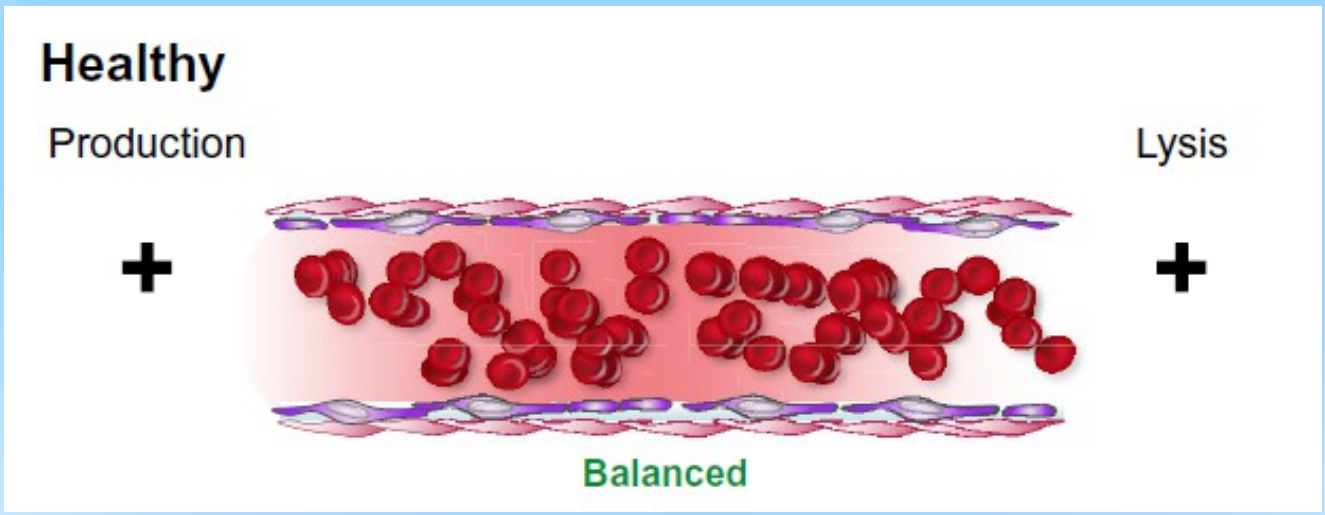
Safety and tolerability with DAAs

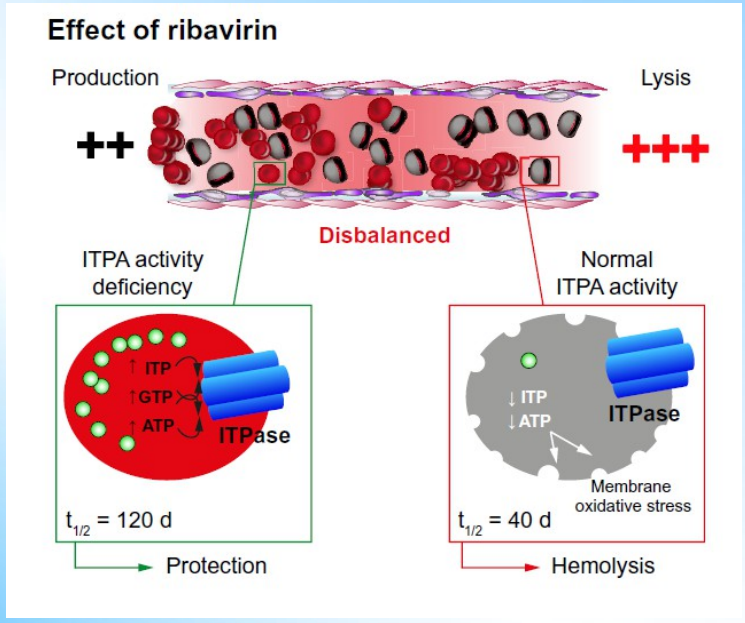
- **Common AEs with PR include:**[1-3]
  - Fatigue, headache, nausea, pyrexia and myalgia
  - Anemia and neutropenia
  - Depression, irritability and insomnia
  - Rash
- **Additional management considerations with DAAs**
  - Telaprevir:[4-7] rash, pruritus, anemia, anorectal symptoms, nausea and diarrhea
  - Boceprevir:[8-10] anemia, dry skin, dysgeusia, rash and neutropenia

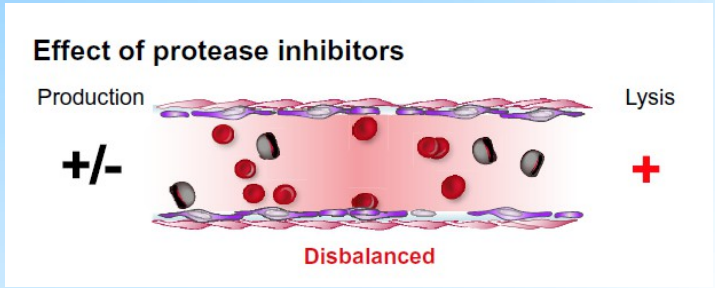
1. Pegintron EU SmPC; 2. Pegasys EU SmPC; 3. Rebetol EU SmPC; 4. Jacobson IM, et al. N Engl J Med 2011;364:2405–16
5. Sherman KE, et al. N Engl J Med 2011;365:1014–24; 6. Zeuzem S, et al. N Engl J Med 2011;364:2417–28
7. INCIVO (telaprevir) EU SmPC; 8. Poordad F, et al. N Engl J Med 2011;364:1195–206
9. Bacon BR, et al. N Engl J Med 2011;364:1207–17; 10. VICTRELIS (boceprevir) EU SmPC

Specific AEs with DAAs: anemia

Mechanisms of RBV and PI – induced anemia

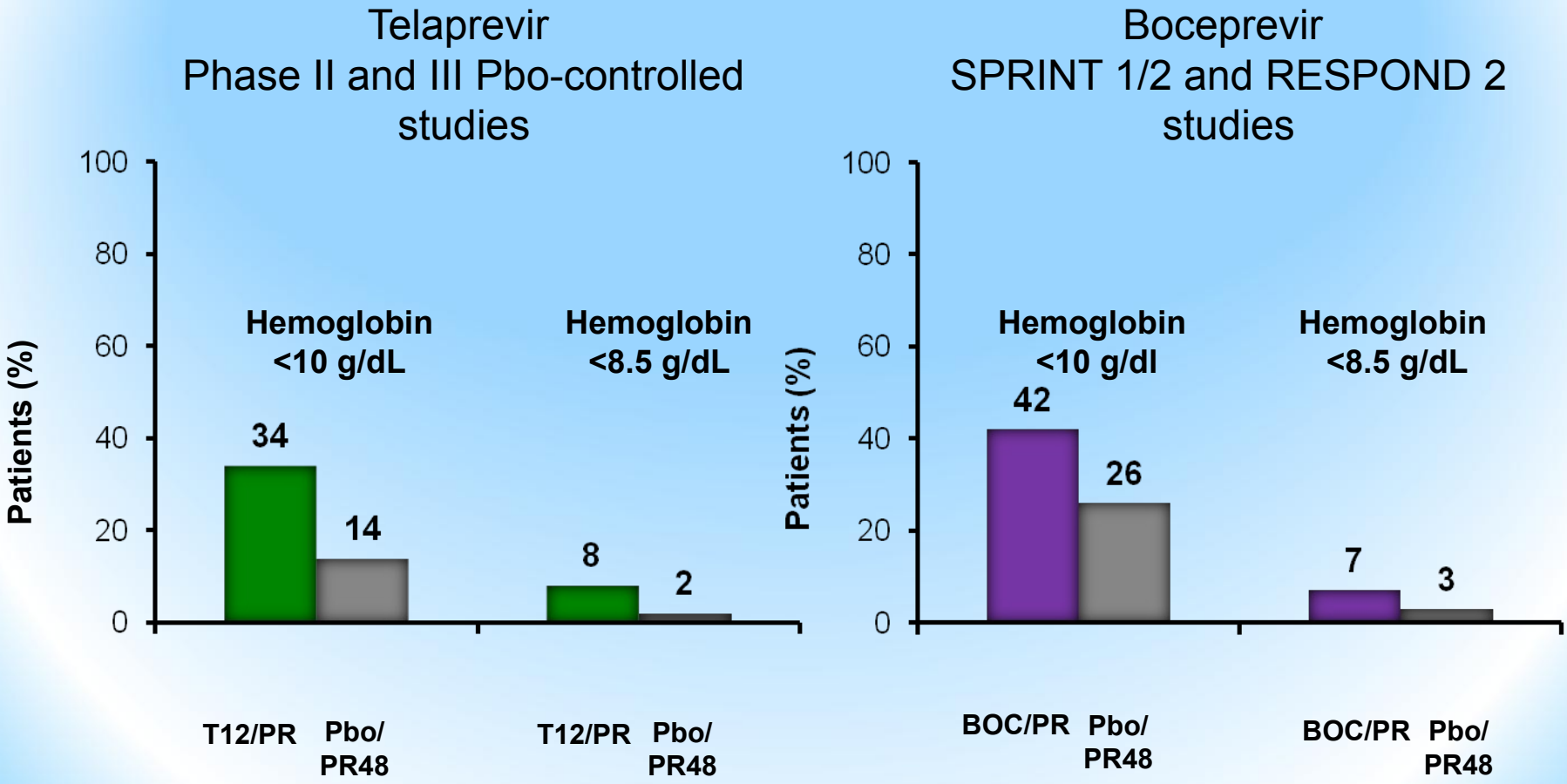






Romero-Goméz M et al. J Hepatol 2013; 59:1323
Thompson AJ, J Hepatol 2012; 56:313-9

Frequency of anemia with telaprevir and boceprevir



INCIVO (telaprevir) EU SmPC
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252343.pdf

Anemia in clinical practice

	CUPIC cohort		EAP Telaprevir cohort	Veterans cohort	
	TPV (n=205)	BOC (n=292)	TPV (n=609)	TPV (n=198)	BOC (n=661)
HGB 8-9,9 g/dl	19%	23%	-	37%	43%
HGB < 8 g/dl	12%	4%	29%	13%	7%

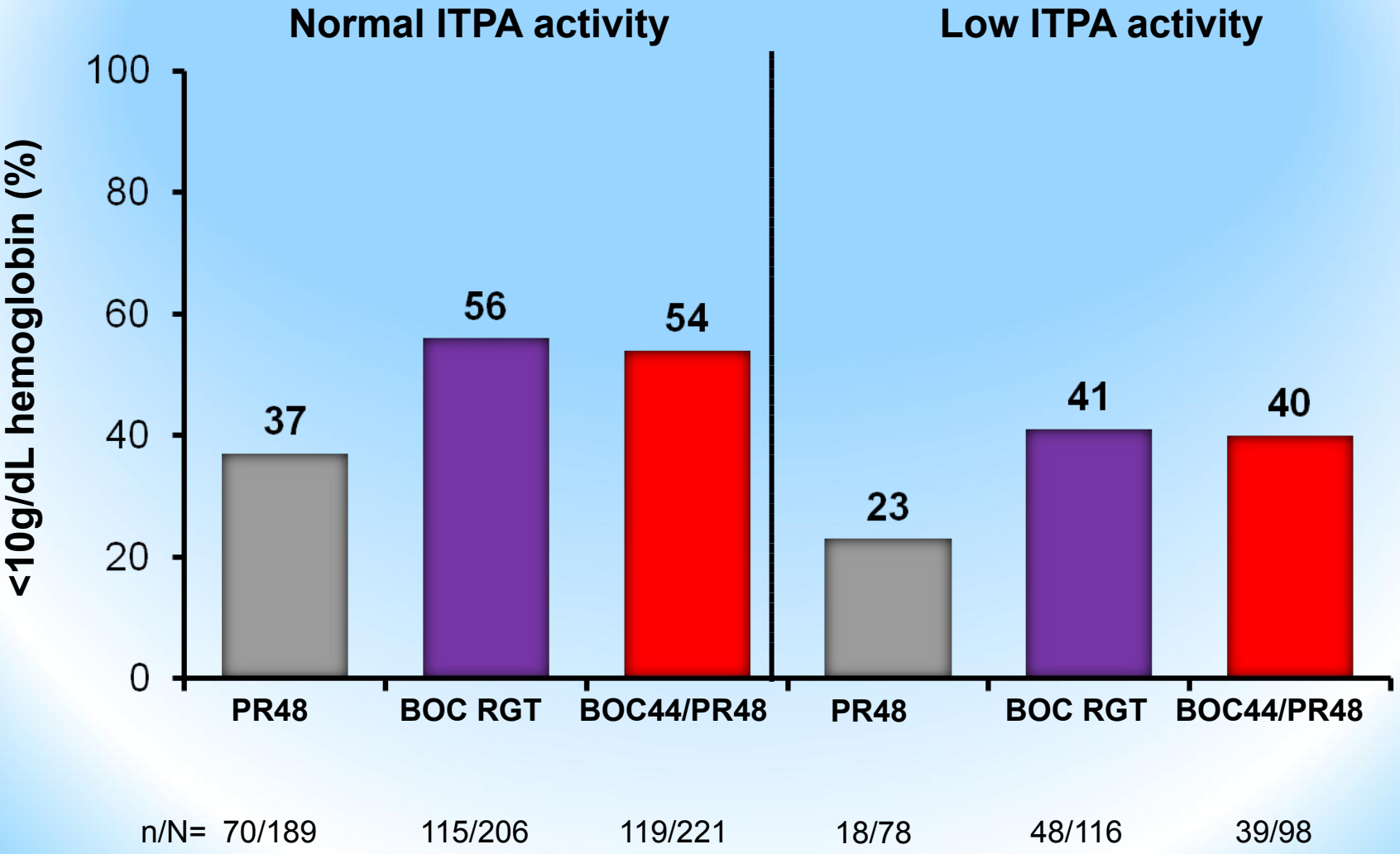
Romero-Goméz M et al. J Hepatol 2013; 59:1323, Hezóde C et al. Hepatology, 2012; 56: 217A-218A Colombo M, et al. J Hepatol, 2013; 58:S329, Belperio BS et al. Clin Gastroenterol Hepatol , 2013: 11:1021

Factors associated with anemia

Type of treatment/Factor	Dual therapy	Triple therapy with telaprevir	Triple therapy with boceprevir
Age	>50 yr	>50 yr	>40 yr
Sex	Female	Female in univariate analysis	Female
Body mass index		<23 kg/m^2	
Statin use			Statin use
Baseline hemoglobin levels	Lower baseline hemoglobin levels	Lower baseline hemoglobin levels	Lower baseline hemoglobin levels
Stage of disease	Cirrhosis	Advanced fibrosis	Advanced fibrosis
Renal function	Creatinine >1.5 mg/dl; creatinine clearance <80 ml/min		Creatinine clearance <80 ml/min
Ribavirin dose	>12 mg/kg		
ITPA polymorphism	*ITPA* polymorphism	*ITPA* polymorphism	*ITPA* polymorphism
On-treatment factors	Fast hemoglobin drop during the first weeks of treatment (>1.5-2 g/dl at week 2)	Low hemoglobin levels (<13 g/dl) at week 2	Degree of hemoglobin decrease during the lead-in phase

Romero-Goméz M et al. J Hepatol 2013; 59:1323

Patients with low ITPA activity have lower rate of anemia while on treatment



Normal ITPA activity = 0; low ITPA activity = 1 and 2

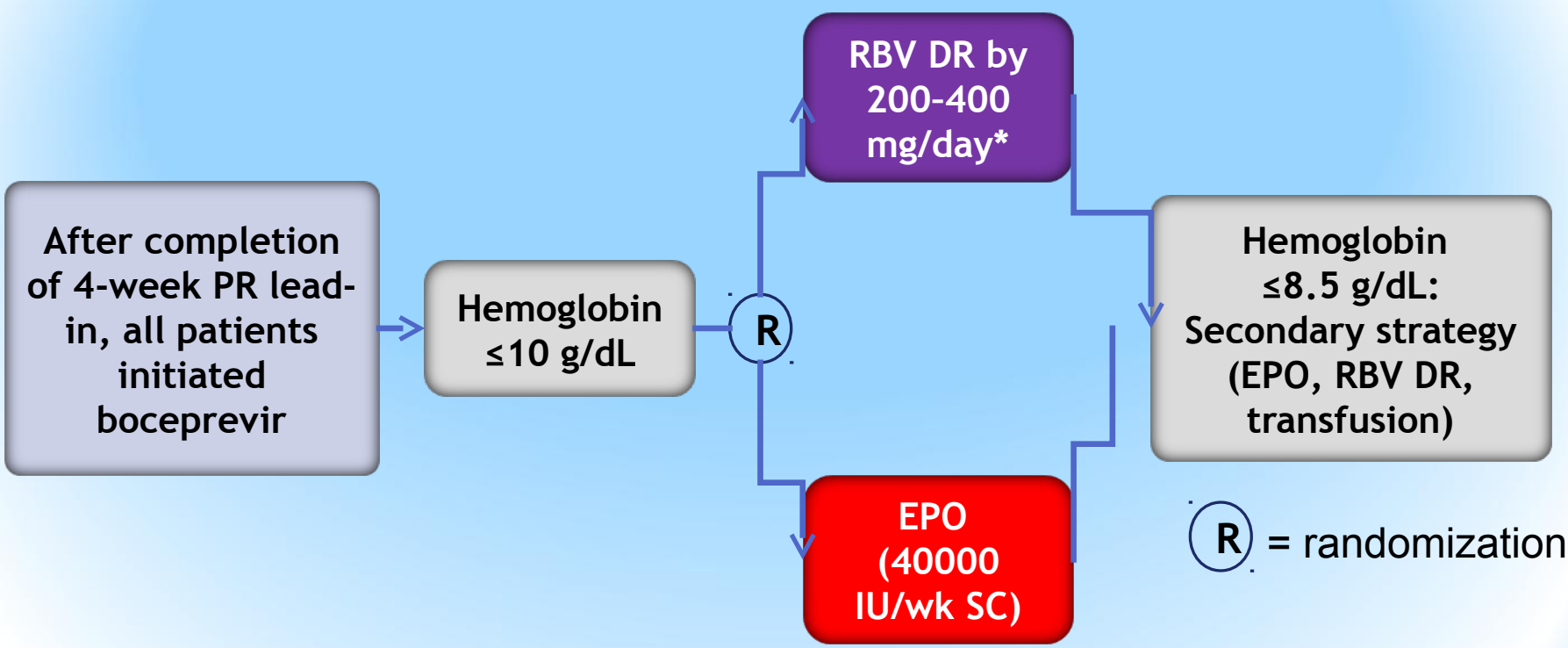
Sulkowski MS, et al. Hepatology 2011;54(Suppl. S1):798A

Anemia in clinical practice

	CUPIC cohort		EAP Telaprevir cohort	Veterans cohort	
RBV dose reduction	13%	11%	34%	38%	44%
ESA use	54%	46%	24%	26%	25%
Blood Transfusion	16%	6%	11%	8%	5%

Romero-Goméz M et al. J Hepatol 2013; 59:1323, Hezóde C et al. Hepatology, 2012; 56: 217A-218A Colombo M, et al. J Hepatol, 2013; 58:S329, Belperio BS et al. Clin Gastroenterol Hepatol , 2013: 11:1021

Trial design: EPO versus RBV dose reduction for managing anemia with boceprevir



* Secondary anemia management was permitted when hemoglobin ≤8.5 g/dL; discontinuation when hemoglobin ≤7.5 g/dL
* Patients with hemoglobin >10 g/dL throughout the study remained in the pending randomization arm

*Follow-up assessment at 2 weeks. If further DR was required, a second or third level of DR (by 200 mg/day) could be used

Poordad FF, et al. J Hepatol 2012;56 (Suppl 2):S559

Safety and tolerability of EPO vs RBV dose reduction for managing anemia with boceprevir

Event, n (%)	RBV dose reductions (n=249)	EPO (n=251)
Treatment-emergent AE	248 (100)	248 (99)
Serious AE Anemia	39 (16) 4 (2)	33 (13) 2 (1)
Death	1* (<1)	0
Life-threatening treatment-emergent AE	6 (2)	5 (2)
Study drug discontinuation due to AE	27 (11)	32 (13)
Discontinuation due to anemia	5 (2)	6 (2)
PRBC transfusion	10 (4)	5 (2)

Poordad FF, et al. J Hepatol 2012;56 (Suppl 2):S559
Poordad FF et al. Gastroenterology 2013, 145:1035

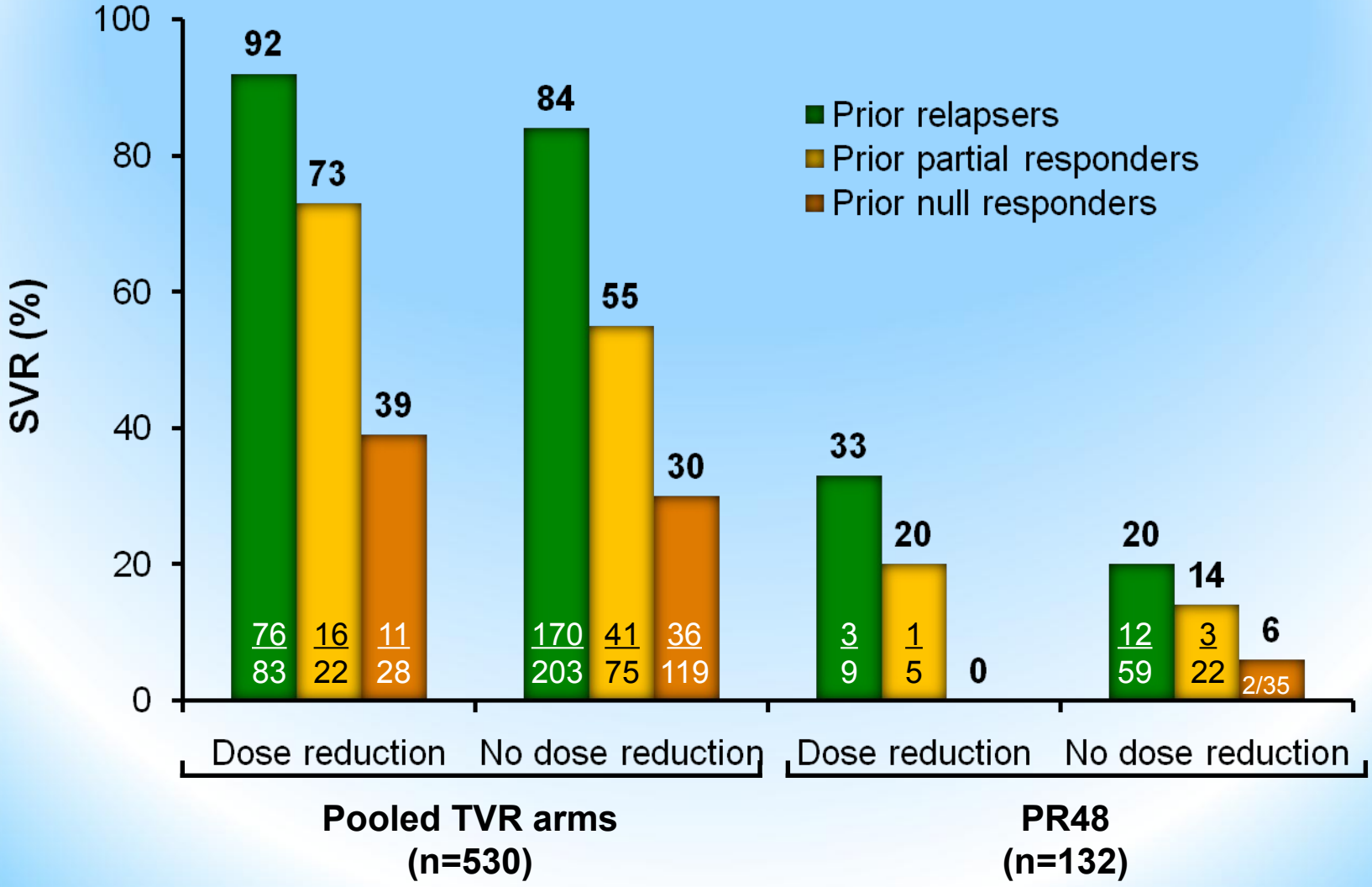
*Sudden cardiac death 3 weeks after completion of treatment

RBV dose reduction or EPO?

Patients, %

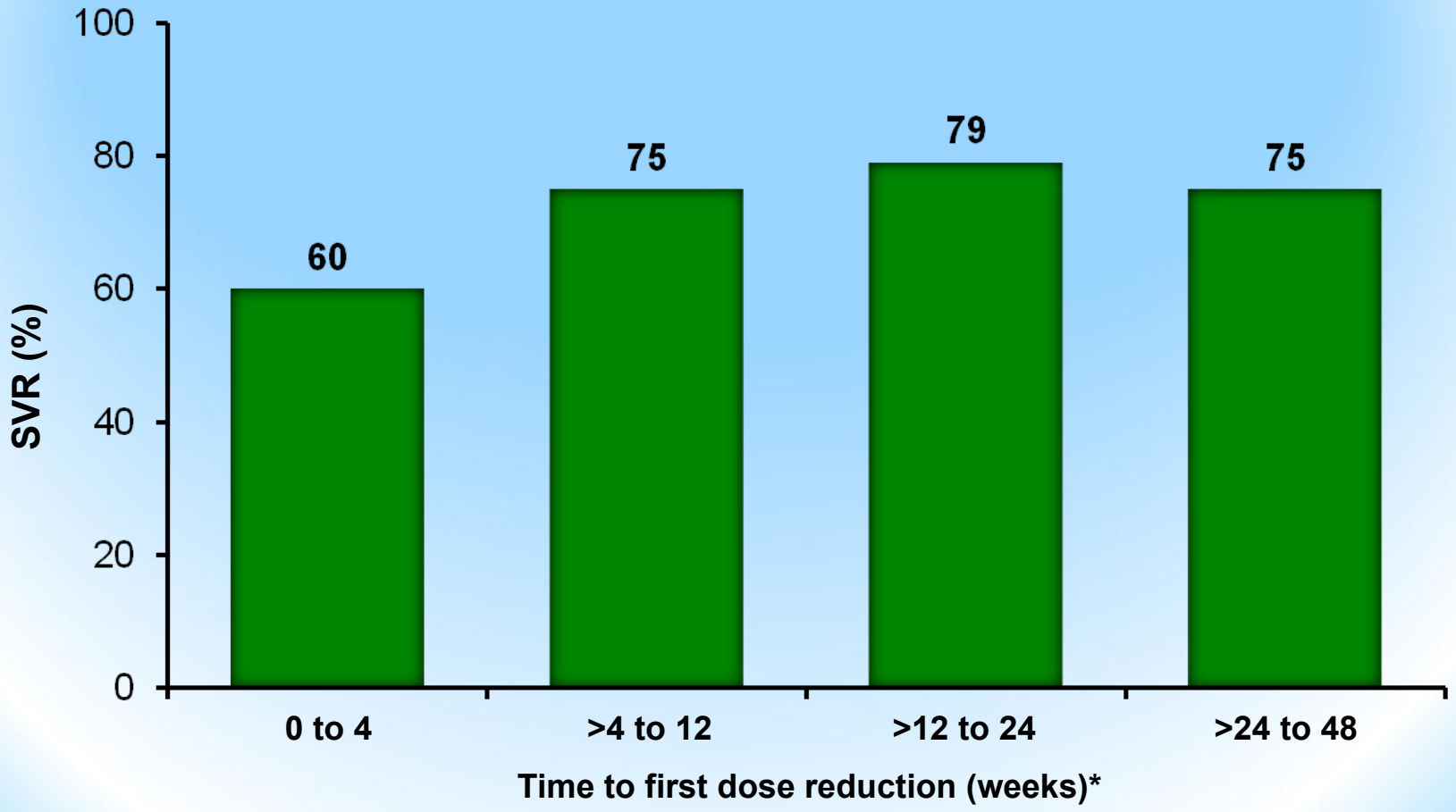
Poordad FF, et al. J Hepatol 2012;56 (Suppl 2):S559
Poordad FF et al. Gastroenterology 2013, 145:1035

REALIZE (telaprevir): no negative effect of RBV dose reduction on SVR



Roberts SK, et al. Hepatology 2011;54(Suppl. S1):1007A

REALIZE (telaprevir: SVR according to timing of first RBV dose reduction (T12PR or T12PR48 arms)

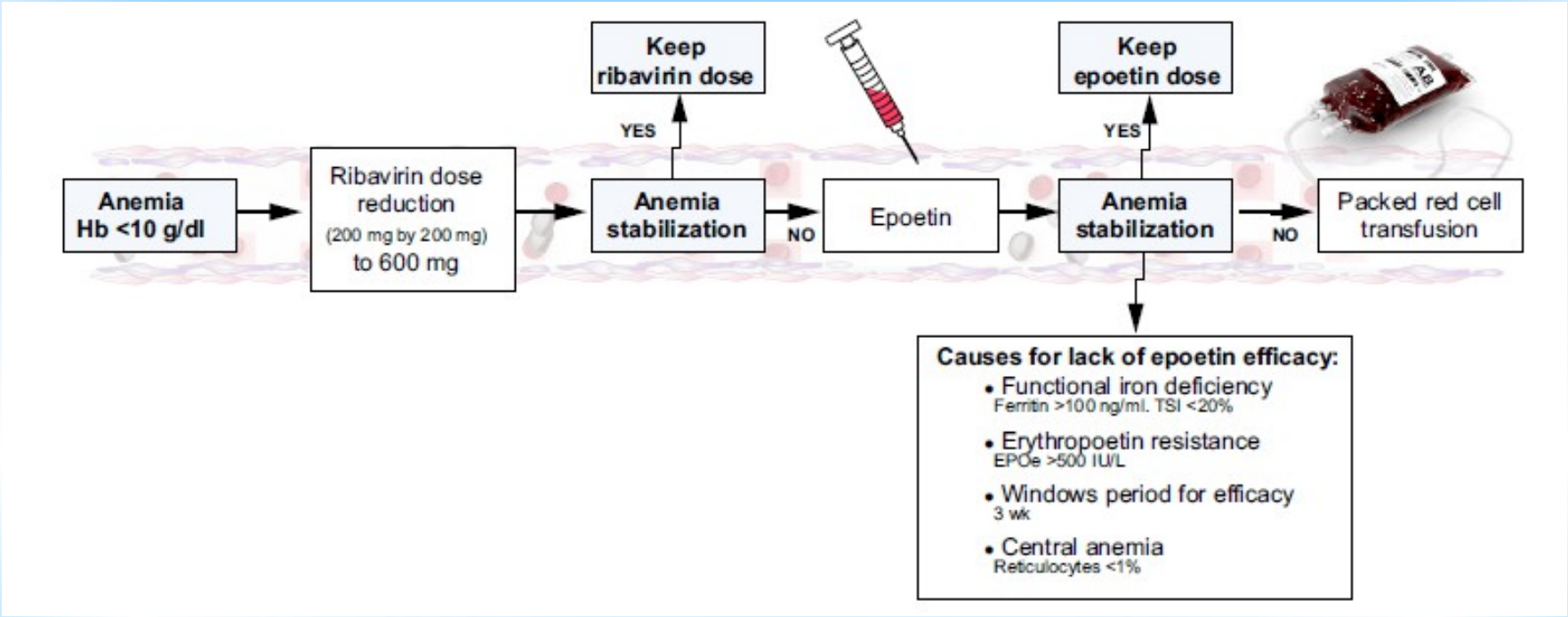


n/N=	6/10	40/53	19/24	6/8

*Time from first dose to first dose reduction

Sulkowski MS, et al. J Hepatol 2012;56 (Suppl 2):S459–60

Management of anemia in pts on triple therapy



Romero-Goméz M et al. J Hepatol 2013; 59:1323

Specific adverse events with DAAs: rash

Rash* during telaprevir treatment period in placebo-controlled Phase II and III studies

Proportion (%) of patients with	Pooled placebo-controlled Phase II and III studies T12/PR (N=1346)
Incidence of rash during telaprevir/placebo treatment period: Telaprevir/PR vs Placebo/PR48	55 vs 33
Severity	
Mild	37
Moderate	14
At least Severe	5
Permanent stop of telaprevir only	5.8

The median time to onset of the first rash event during the telaprevir treatment phase in the T12/PR group of the pooled placebo-controlled Phase II/III studies was 25 days

*Reported within a special search category

http://www.fda.gov/downloads/AdvisoryCommittees/Committees/MeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf

Discontinuation of study drugs as a surrogate marker for effectiveness of clinician education and experience

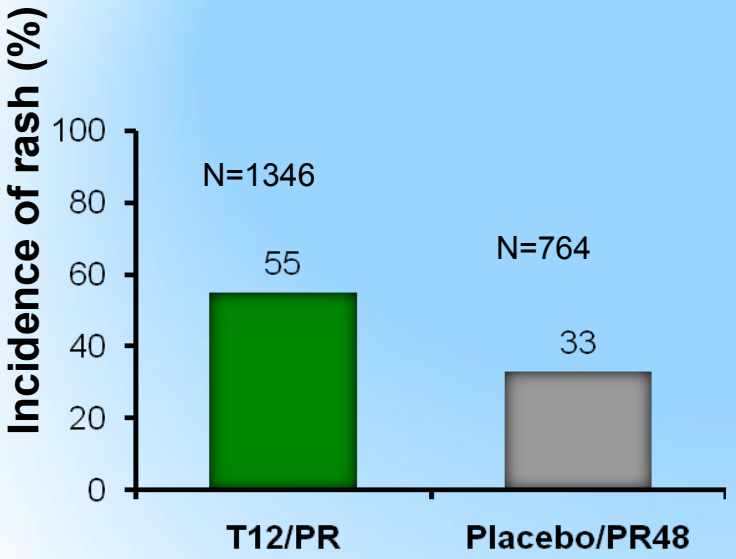
- **Following implementation of a rash management plan in Phase III studies, permanent discontinuation of all study drugs due to rash events was lower in than in Phase II studies***

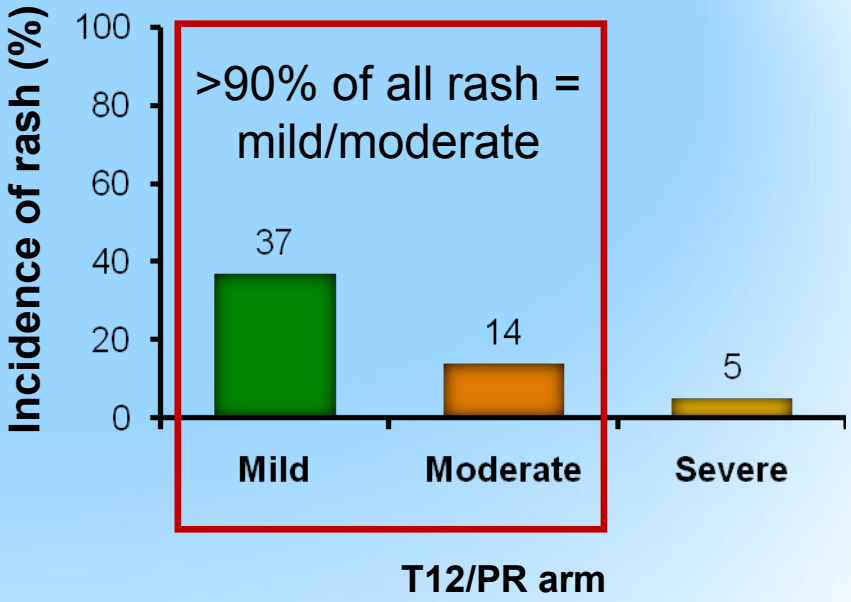
Permanent discontinuation of all study drugs due to rash‡	T12/PR (750 mg q8h)		Placebo/PR48	
	%	n/N	%	n/N
Phase II studies	**6**	28/450	**0.4**	1/271
Phase III studies	**1**	10/893	**0**	0/493

*Results based on peginterferon discontinuation since patients had to discontinue all other drugs if peginterferon was discontinued
‡During overall treatment phase

http://www.fda.gov/downloads/AdvisoryCommittees/Committees/MeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf

Summary of rash data from placebo-controlled Phase II and III trials: telaprevir treatment phase





Features:

- Typically pruritic and eczematous, and involving <30% BSA
- Progression was infrequent (<10% of cases)

Time to onset:

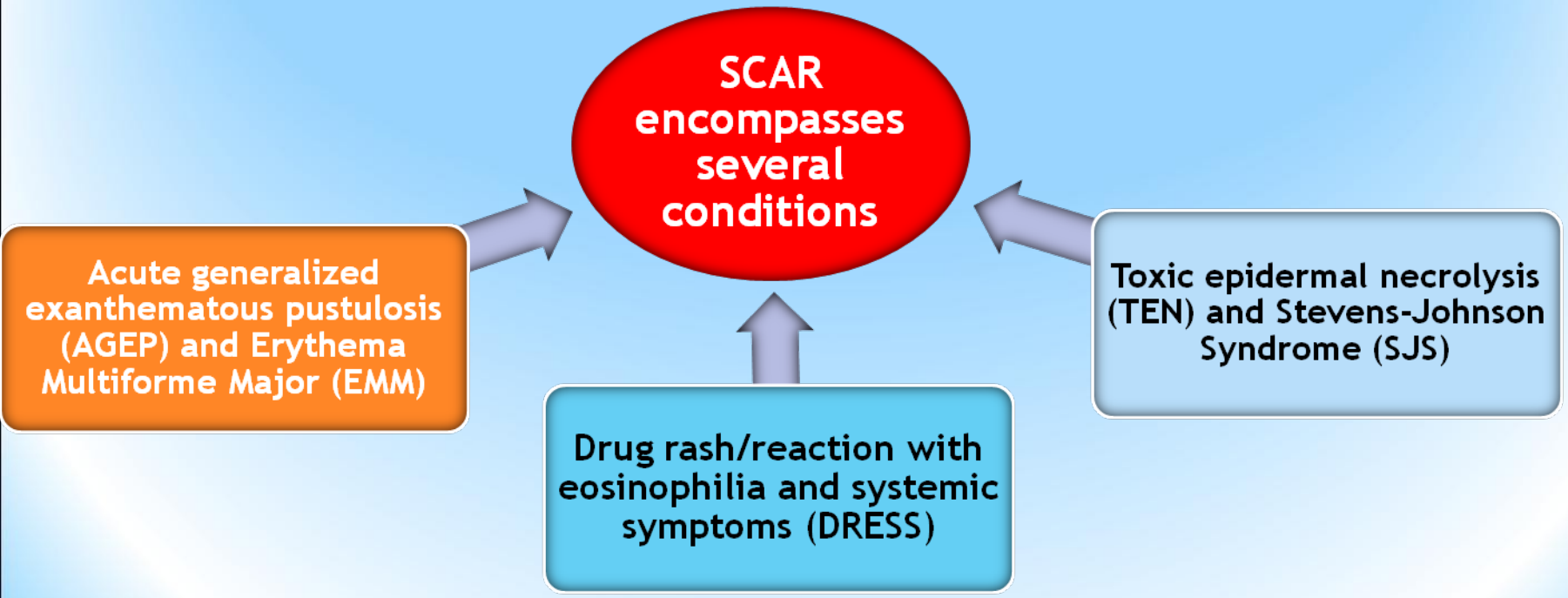
- Approximately 50% of rashes started during the first 4 weeks
- But rash can occur at any time during telaprevir treatment

INCIVO (telaprevir) EU SmPC
http://www.fda.gov/downloads/AdvisoryCommittees/Committees/MeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf

Reported within a special search category

Definition of SCAR: Severe Cutaneous Adverse Reaction

- Collective term for severe drug-related skin conditions that can be associated with significant morbidity[1–3]

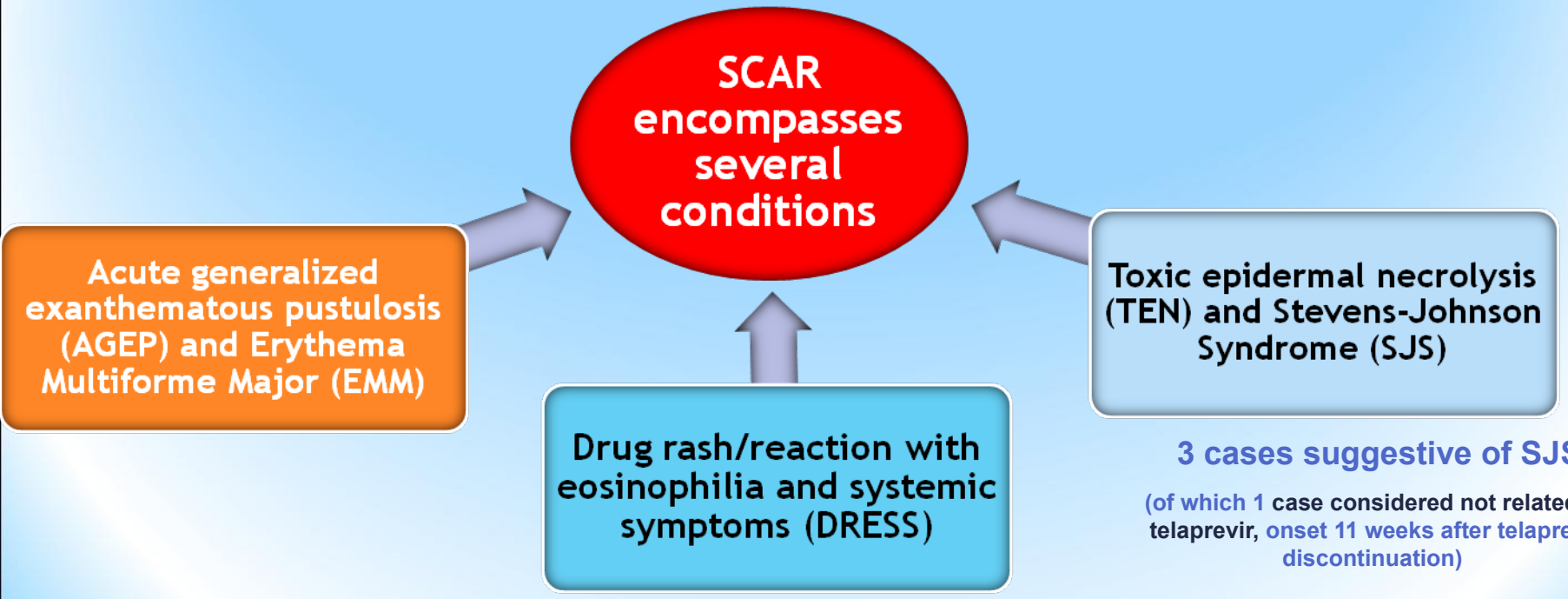


DRESS also called drug-induced hypersensitivity syndrome (DIHS)
SJS and TEN may be considered as variants of single disorder
SJS has been reported as an adverse drug reaction with Peg-IFN and RBV[4–6]

1. Roujeau JC, Stern RS. N Eng J Med 1994;331:1272–85
2. Roujeau JC, et al. Dermatol Sinica 2009;27:203–9
3. Mockenhaupt M. J Dtsch Dermatol Ges 2009;7:142–160
4. Pegintron EU SmPC; 5. Pegasys EU SmPC
6. Rebetol EU SmPC

SCAR reported with telaprevir

- Collective term for severe drug-related skin conditions that can be associated with significant morbidity



*In placebo-controlled Phase II/III trials, 0.4% of patients had suspected DRESS; in telaprevir clinical experience, less than 0.1% of patients had SJS; all of these reactions resolved with treatment discontinuation

INCIVO (telaprevir) EU SmPC
http://www.fda.gov/downloads/AdvisoryCommittees/Committees/MeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf

Rash management plan

When to suspect DRESS

* Alert criteria:
  * Onset from 6–10 weeks after first dose
  * Rapidly progressing exanthema
  * Prolonged fever (>38.5°C)
  * Facial oedema

What to do?

- **If any DRESS alert criteria are found, the patient should be assessed for the following confirmation criteria**
  - Enlarged lymph nodes (at least 2 sites)
  - Eosinophilia (≥700/μL or ≥10%)
  - Atypical lymphocytes
  - Internal organ involvement
    - Liver: ALT, alkaline phosphatase ≥2 x upper limit of normal
    - Kidney: rise in creatinine ≥150% basal level
- **If any DRESS confirmation criteria are also found:**
  - Stop all drugs
  - Hospitalize the patient
  - Consult a dermatologist

Cacoub P, et al. J Hepatol 2012;56:455–63

When to suspect SJS/TEN

* Rapidly progressing exanthema
* Skin pain
* Mucosal involvement at ≥2 sites
* Blisters or epidermal detachment
* Atypical/typical target lesions

What to do?

- Stop all drugs
- Hospitalize the patient
- Consult a dermatologist

Cacoub P, et al. J Hepatol 2012;56:455–63

Specific AEs with DAAs: anorectal signs

Anorectal signs and symptoms

- First reported with telaprevir in PROVE1 as ‘hemorrhoids’
- Subsequently reported under various terms such as anal pruritus, anorectal discomfort as well as hemorrhoids
  - Onset is most commonly in the first 2 weeks of treatment
- Mechanism is unknown
  - Telaprevir is extensively metabolized and metabolites primarily excreted in the feces
  - No rectal findings in any of the toxicology studies
  - No evident association with either generalized pruritus or skin rash

Anorectal disorders* during the telaprevir treatment period in Phase II and III studies

Proportion (%) of patients with:[1]	T12/PR (750 mg q8h) N=1346	Placebo/PR48 N=764
AE	26.2	5
AE of at least Grade 3	0.7	0
AE leading to permanent discontinuation of telaprevir/placebo	0.5	0

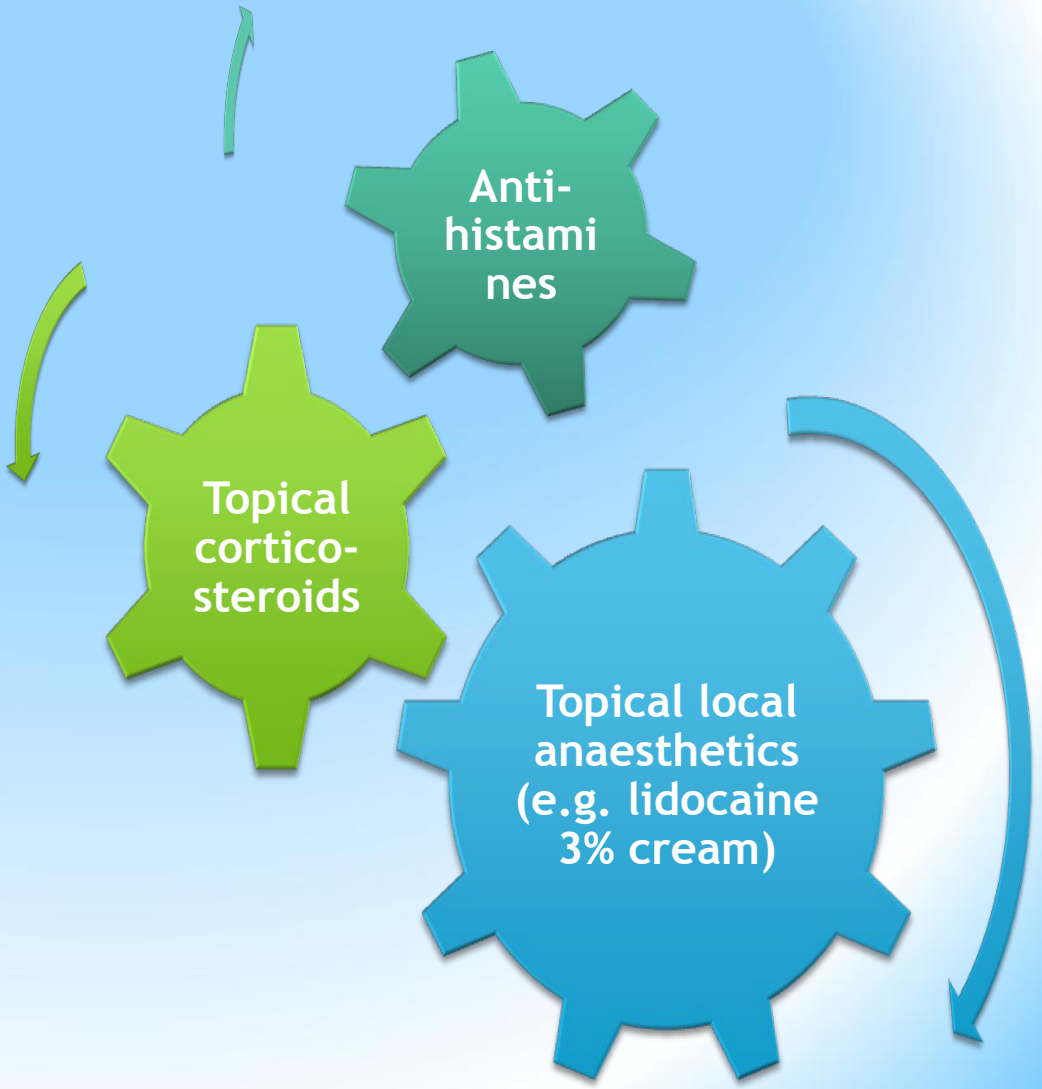
- In clinical trials, the majority of these events (e.g., haemorrhoids, anorectal discomfort, anal pruritus and rectal burning) were mild to moderate, very few led to treatment discontinuation and resolved after completion of telaprevir dosing[2]

1. http://www.fda.gov/downloads/AdvisoryCommittees/Committees/MeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf
2. INCIVO (telaprevir) EU SmPC

*Reported within a special search category

Anorectal signs and symptoms: management

* Standard, short-term symptomatic care may be warranted
* Consider proprietary combination hemorrhoid preparations according to the nature of the event



Hézode C. Liver International 2012;32 Suppl 1:32-8; Basu P, et al. Gastroenterology 2012;142(Suppl. 1):S-962

Conclusions

* RBV dose reduction is the first line approach for managing anemia

* Anemia management is critical for avoiding discontinuation of the PI
  * Once a PI has been stopped, it should not be restarted
  * PIs cannot be dose reduced

* Patients should be educated prior to treatment initiation regarding the signs and symptoms so rash can be quickly identified and managed
  * Topical steroids and antihistamines are primary management;

* Suggestions for anorectal symptom management include administration of any of the following: fiber, loperamide, hydrocortisone, or pramoxine topical cream