Triple therapy with telaprevir or boceprevir: management of side effects

skin reactions and infections

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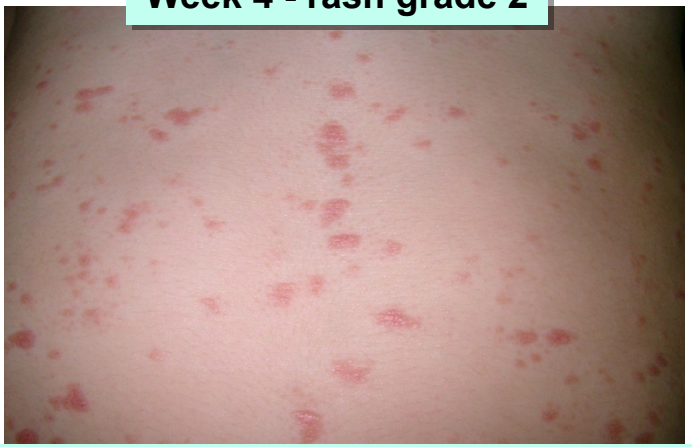
Case report

- 54-years old, male
- Null-responder to PegIFNa+RBV
- Fibrosis: F-3

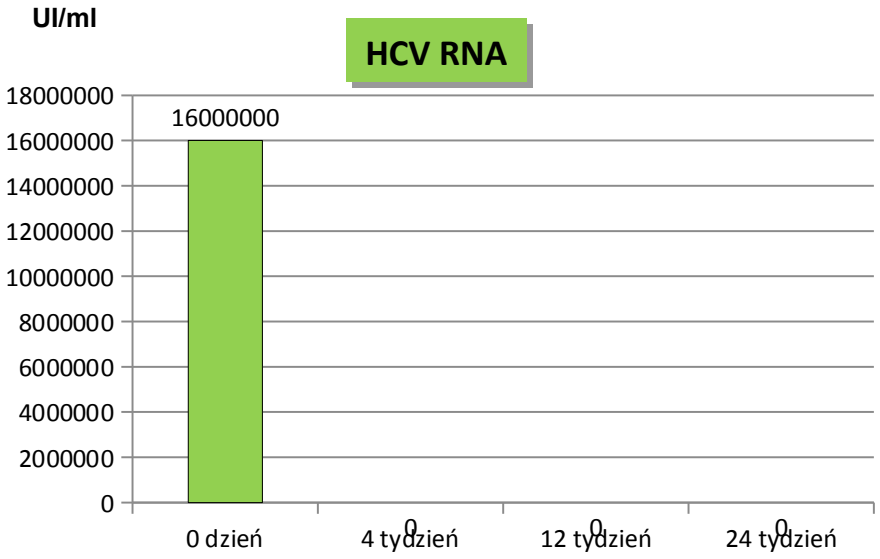
Current treatment:

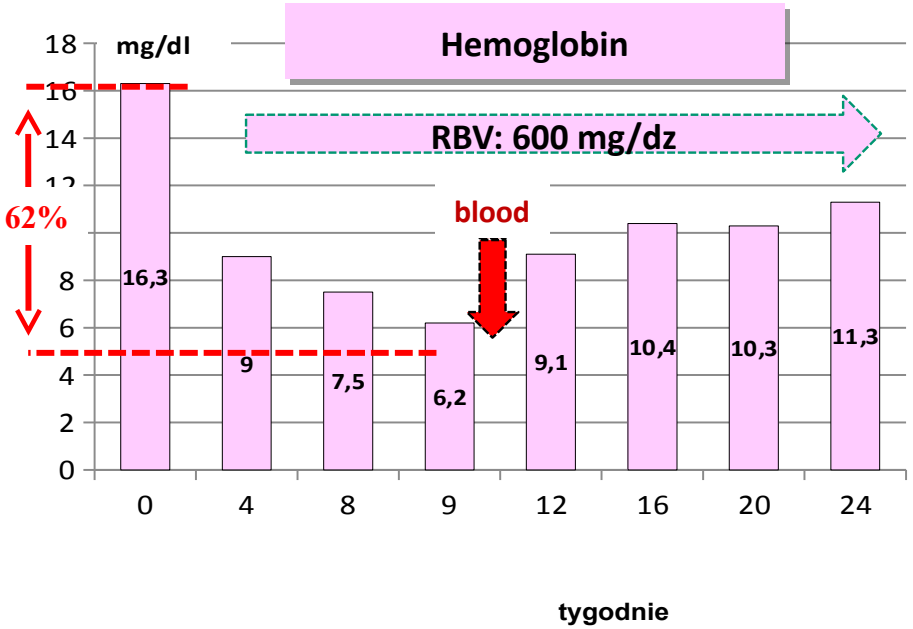
- PegIFNa2a: 180 mg/wk
- RBV: 1000 mg/day
- Telaprevir: 2250 mg/day

Week 4 - rash grade 2



Topical corticosteroids
Methylprednisolone aceponate (Advantan)





Cutaneous diseases strongly linked to HCV infection

Cutaneous diseases	Link to HCV infection
Mixed cryoglobulinemia	40-84% HCV-infected individuals produce cryoglobulins and 15% develop vasculitis, which is mostly cutaneous but can be systemic.
Porphyria cutanea tarda	HCV is the most common viral infection associated with PCT. Prevalence of HCV infection varies geographically.
Lichen planus	Strongly correlated with HCV infection in meta-analysis.

Cacoub P et al. J Hepatol 2012; 56: 455–63
Cacoub P et al. Arthritis Rheum 1999;42:2204–2212
Rebora A. Clin Dermatol 2010;28:489–496.
Lodi G et al. Oral Dis 2010;16:601–612.

Cutaneous reactions to interferon alpha and ribavirin

Reactions	
Localized	• Erythematous or eczematous dermatitis and psoriasis, • Localized alopecia associated with local cutaneous reactions to IFN, • Skin ulceration and necrosis, • Local infections and local allergic reactions to IFN injection,
Generalized	• Alopecia/hair growth anomalies, • Skin xerosis, dermatitis and pruritus, • Chronic inflammatory skin diseases (lichen planus or psoriasis), which may be induced or exacerbated by IFN, • Autoimmune and immune-mediated inflammatory disease (e.g. psoriasis and sarcoidosis)

Cacoub P et al. J Hepatol 2012; 56: 455–63
Lübbe J. Hot Topics in Viral Hepatitis 2008;9:29–35
Mistry N et al. Can J Gastroenterol 2009;23:677–683.
Lang AM et al. Arch Dermatol 1999;135:1126–1128.
Dalmau J et al. J Am Acad Dermatol 2005;53:62–66.
Lübbe J et al. Br J Dermatol 2005;153:1088–1090.
Quesada J, Gutterman J. Lancet 1986;1:1466–1468.
Fantini F et al. Dermatol Ther 2009;22:S1–S7.

Telaprevir or Boceprevir: safety findings in CUPIC study

Patients, n (% patients with at least one event)	Telaprevir n = 295	Boceprevir n = 190
Serious adverse events (SAEs)	535 in 160 patients (**54.2%**)	321 in 97 patients (**51.0%**)
Premature discont./due to SAE	139(**47.1%**) / 63(**21.3%**)	80(**42.1%**) / 27(**14.2%**)
Death **(3 septicemia, 1 pneumonia,1 variceal bleeding, 1 encephalopathy, 1 pulmonary neoplasia)**	7 (**2.4%**)	3 (**1.6%**)
Infection (Grade 3/4)	27 (**9.1%**)	8 (**4.2%**)
Hepatic decompensation (Grade 3/4)	15 (**5.1%**)	9 (**4.7%**)
Rash (grade 3/SCAR)	16 (**5.4%**) / 2 (**0.6%**)	2 (**1.0%**) / 0
Anemia (Grade 3/4: Hb <8 g/dL)	38 (**12.9%**)	19 (**10.0%**)
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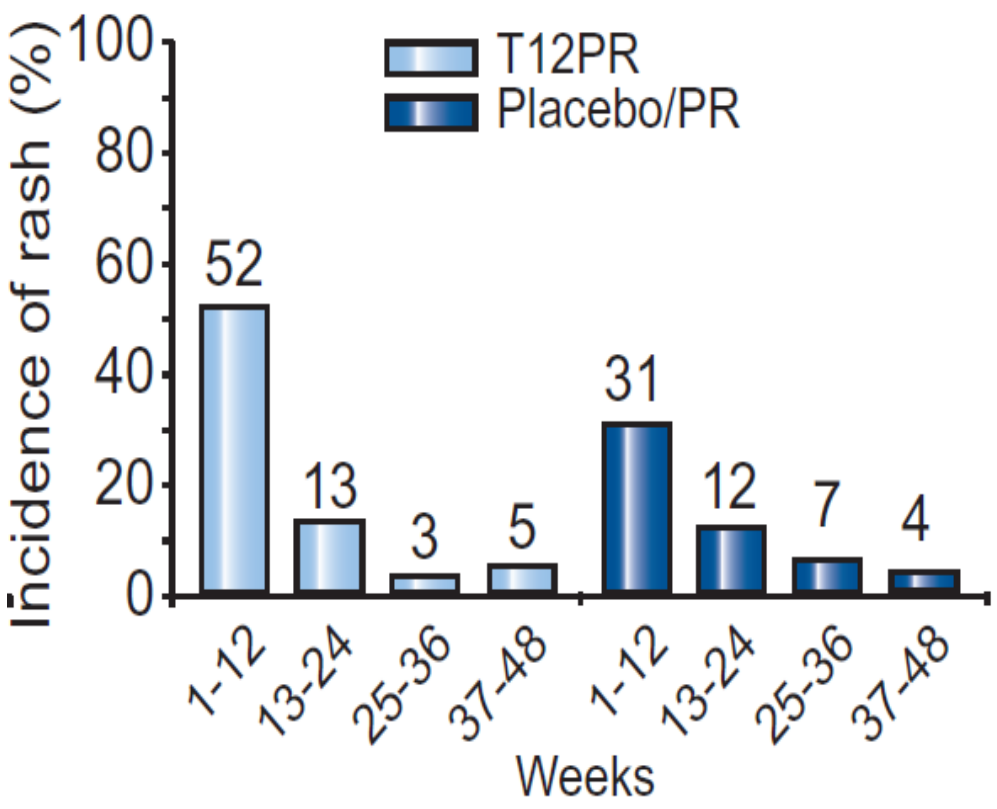
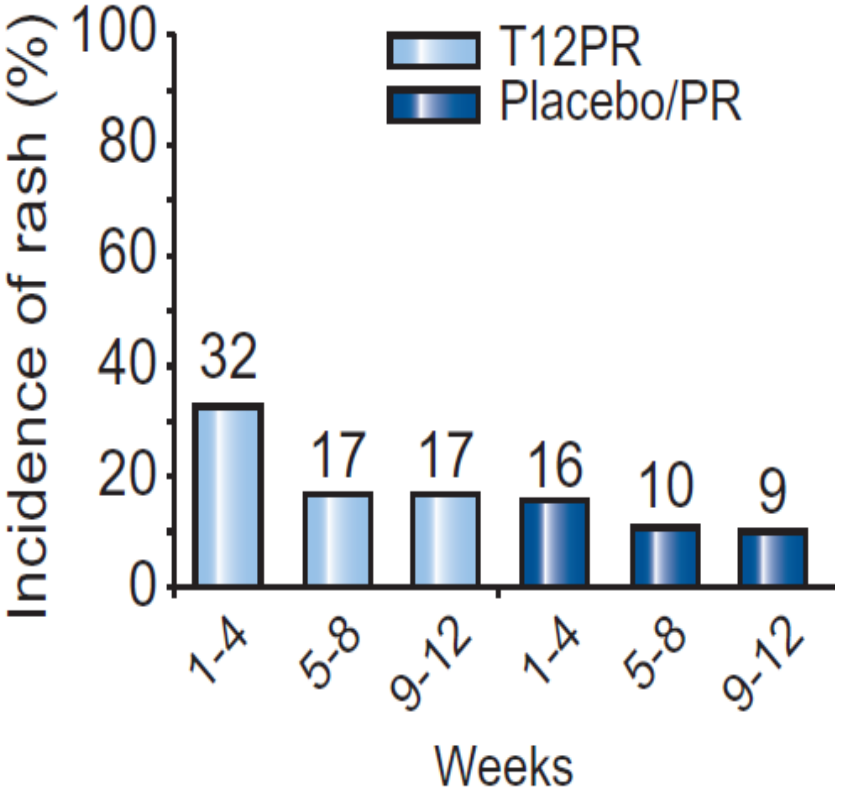
Fontaine H et al. EASL 2013

SCAR: severe cutaneous adverse reaction

Incidence of rash in TVR phase 2/3 by periods of treatment





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

Skin rashes in TVR phase III trials

	Patients, No (%)	
	TVR+PR n=1797	PLB+PR n=493
Adverse skin reaction	1009 (56)	168 (34)
Mild	725 (40)	143 (29)
Moderate	218 (12)	23 (5)
Severe	66 (4)	23 (<1)
Discontinuation TVR/PLB due to skin reaction	115 (6)	2 (<1)
Discontinuation all drugs due to skin reaction	15 (1)	2 (<1)

Prevalence of skin rashes and rate of discontinuations in BOC triple therapy is on the level similar to dual therapy

Roujeau et al. Arch Dermatol 2013

TVR triple therapy in F3/F4 naive and non-responders to dual therapy (AdvEx study)
rash related interventions

n (%)	naive	relapsers	part-resp	null-resp	ALL
	n=22	n=74	n=28	n=101	n=225
rash without need of intervention	**6 (27)**	**12 (16)**	**3 (11)**	**10 (10)**	**31 (14)**
local steroids and/or anti-histaminic	**5 (23)**	**14 (19)**	**11 (39)**	**22 (22)**	**52 (23)**
treatment discont. without SCAR*	**1 (5)**	**0**	**2 (7)**	**1 (1)**	**4 (2)**
SCAR*	**1 (5)**	**1 (1)**	**0**	**0**	**2 (1)**

*SCAR (Severe Cutaneous Adverse Reactions) = Steven Johnson Syndrome (SJS) or Drug Related Eruption with Systemic Syndrome (DRESS)

Zarebska-Michaluk D, Flisiak R, Janczewska E et al. submited to EASL 2014

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

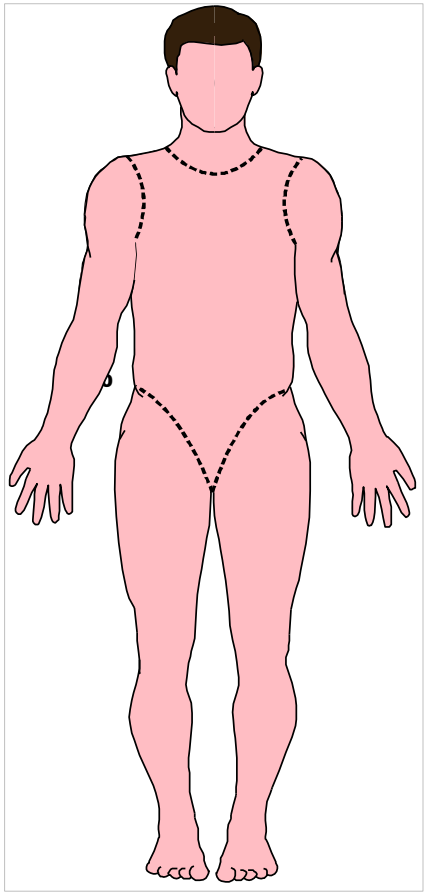
The TVR prescribing information does not suggest TVR discontinuation for grade 1 or 2 rash, which can be treated using emollients/moisturizers and topical corticosteroids.

For grade 3 rash, the prescribing information mandates immediate TVR discontinuation, with ribavirin interruption (with or without pegylated IFN-α) within 7 days of stopping TVR if there is no improvement (or sooner if it worsens).

In case of suspicion or confirmed diagnosis of SCAR, all medication must be discontinued.

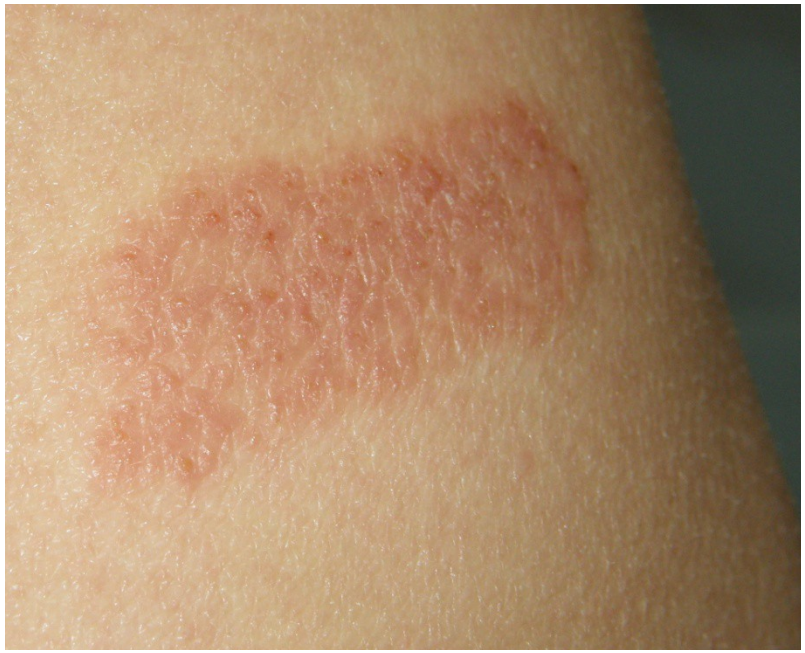
EASL Clinical Practice Guidelines: Management of hepatitis C virus infection Journal of Hepatology 2014; 60: 392–420.

Grading of skin eruption severity



- **Mild (grade 1):** localized skin eruption and/or a skin eruption with limited distribution (up to several isolated sites on the body)
- **Moderate (grade 2):** diffuse rash ≤50% of body surface area
- **Severe (grade 3):** Extent of rash >50% of body surface area or associated with significant systemic symptoms, mucous membrane ulceration, target lesions, epidermal detachment
- **SCAR (grade 4):** generalized bullous eruption, drug rash with eosinophilia and systemic symptoms, Stevens-Johnson Syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis, erythema multiforme

Management of mild rash (grade 1)



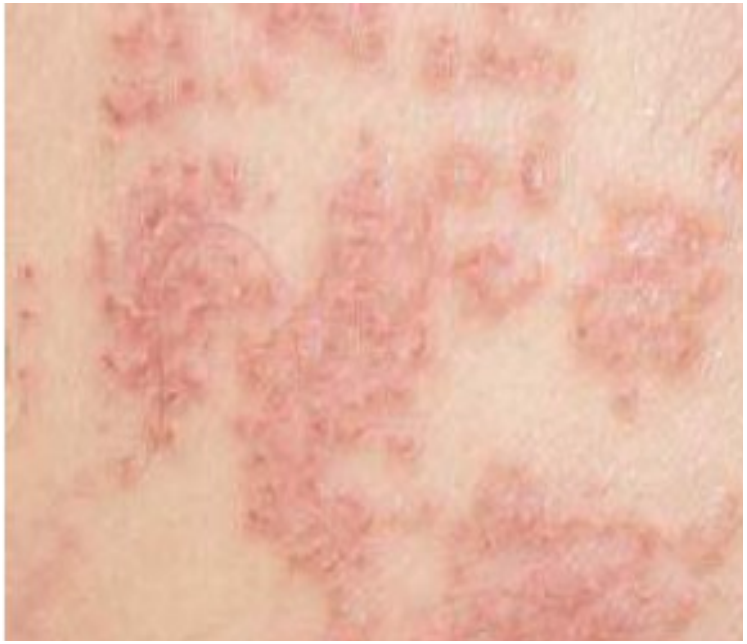
Localized skin eruption and/or a skin eruption with limited distribution, with or without associated pruritus.

- No treatment or topical ointments are necessary
- Monitor for progression or systemic symptoms until the rash is resolved

Telaprevir can be continued

Cacoub P, et al. J Hepatol 2012; 56: 455–63
Hezode C et al. Liver Int 2012; 32 suppl 1: 32-38

Management of moderate rash (grade 2)



Diffuse skin eruption involving <50% of body surface area with or without superficial skin peeling, pruritus, or mucous membrane involvement with no ulceration.

- ✓Topical treatment. Consider consultation with a dermatologist
- ✓Monitor for progression or systemic symptoms until the rash is resolved.
- ✓If moderate rash is progressing to severe (>50% bsa), TVR must be discontinued.
- ✓If no improvement within 7 days following TVR discontinuation, RBV should be interrupted. It may be required sooner if the rash worsens despite discontinuation of TVR. PEG-IFN may be continued.

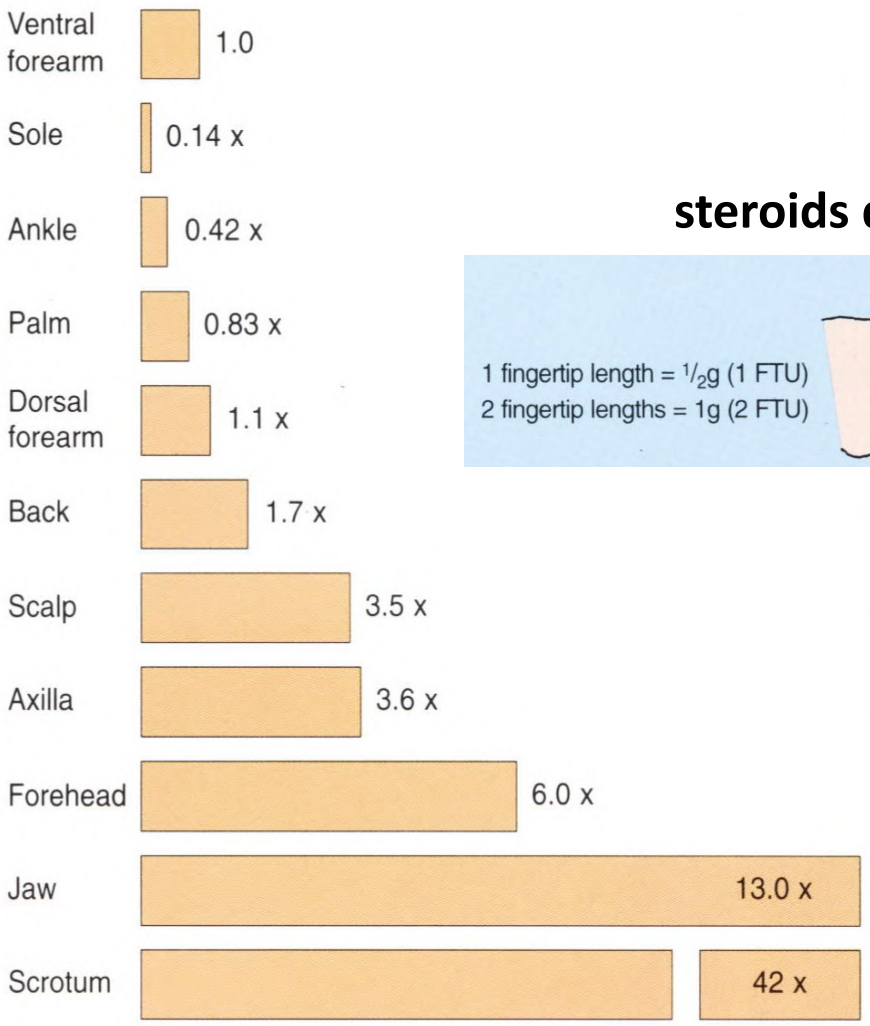
Cacoub P, et al. J Hepatol 2012; 56: 455–63
Hezode C et al. Liver Int 2012; 32 suppl 1: 32-38

Treatment of mild / moderate rash

- Moisturizing cream.
- Class 3 topical corticosteroid ointments:
  (european classification: 50-100 times as potent as hydrocortisone)
  - Betamethasone valerate - Beta Cream®, Betnovate®, Daivobet®, Fucicort®
  - Betamethasone dipropionate - Diprosone®, Diprovate®
  - Diflucortolone valerate - Nerisone C®
  - Hydrocortisone 17-butyrate - Locoid C®
  - Fluticasone propionate - Cutivate®
  - Methylprednisolone aceponate - Advantan®
  - Mometasone furoate - Elocom®
- In case of risk of laesions superinfection - ointments containing steroid and antibiotics and/or antifungal.
- Anti-histaminics for pruritus only (diphenhydramine, hydroxyzine, levocetirizine, and desloratadine) – no scientific evidences of efficacy.
- Limit exposure to sun/heat and wear loose-fitting clothes.

Dosage of topical steroids

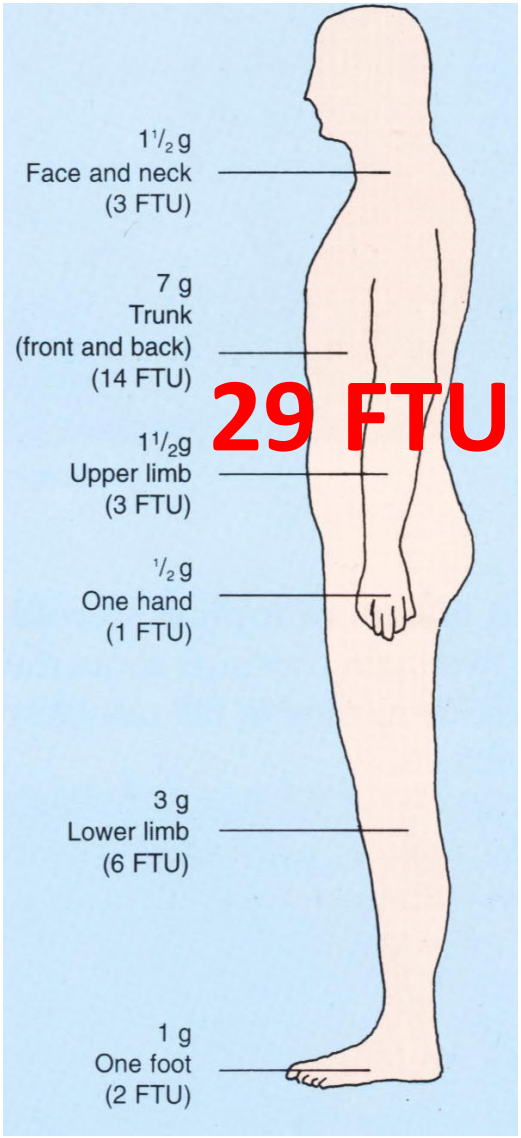
steroids absorption



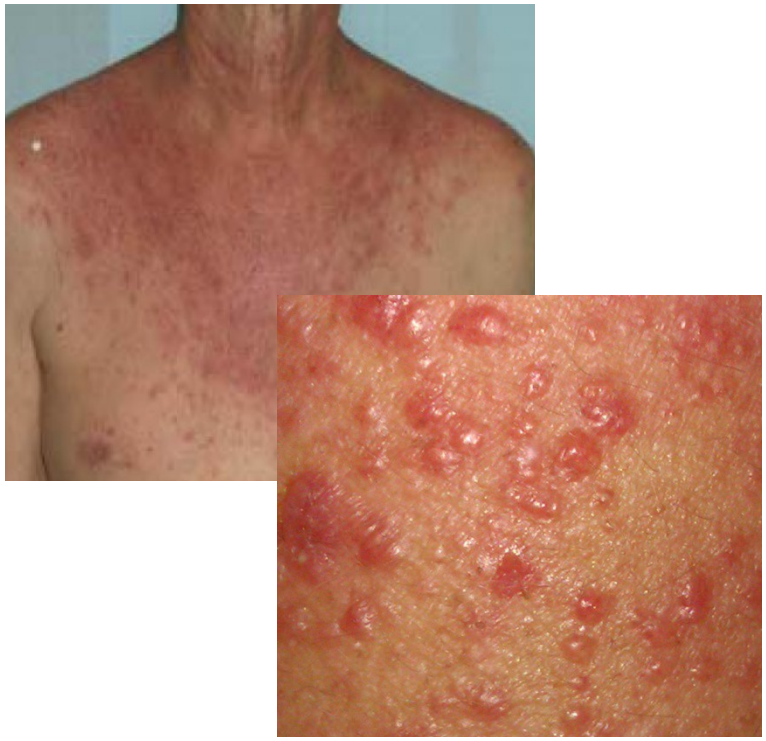
Skin on the head and genital region possesses the greatest absorption potential.

steroids dosage

steroid requirement for a single application



Management of severe rash (grade 3)



Generalized rash involving >50% of BSA

OR

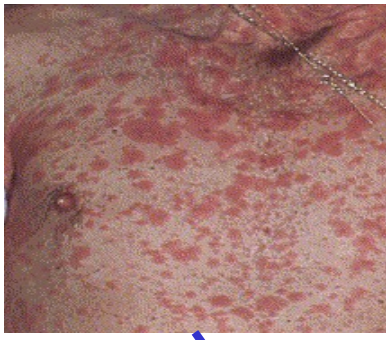
Rash presenting with any of the following:

- Vesicles or bullae
- Superficial ulceration of mucous membranes
- Epidermal detachment
- Atypical or typical target lesions
- Palpable purpura/non-blanching erythema

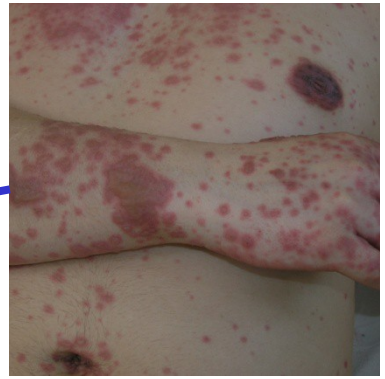
✓Permanently discontinue TVR immediately.
✓Consultation with a dermatologist.
✓Monitor for progression or systemic symptoms until the rash is resolved.
✓PEG-IFN and RBV may be continued. If improvement is not observed within 7 days of TVR discontinuation, or sooner if it worsens, interruption or discontinuation of RBV and/or PEG-IFN should be considered.

Cacoub P et al. J Hepatol 2012; 56: 455–63
Hezode C et al. Liver Int 2012; 32 suppl 1: 32-38

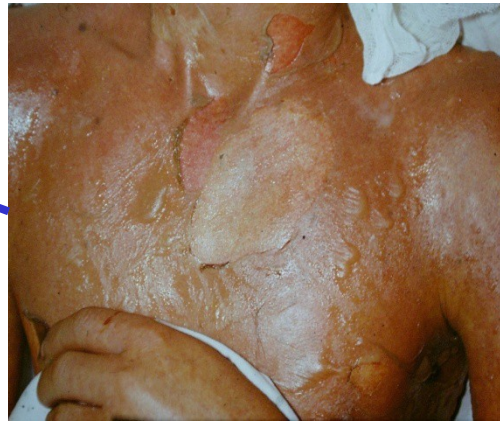
SCAR
serious cutaneous adverse reactions (grade 4)

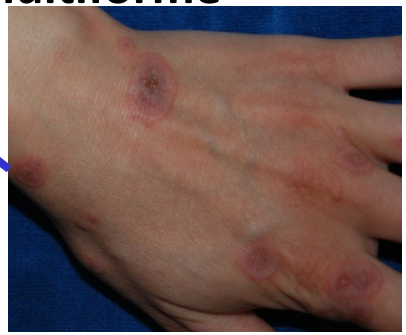


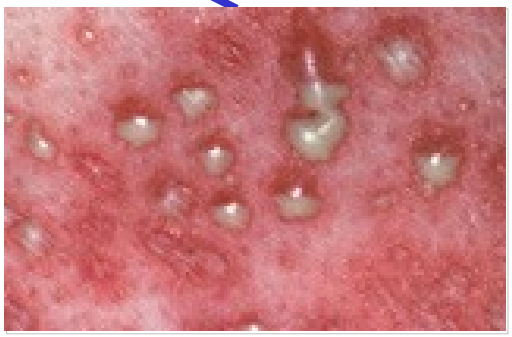
life-threatening or systemic reactions



- **DRESS – drug reaction with eosinophilia and systemic symptoms (drug-induced hypersensitivity syndrome - DHS)**
- **SJS – Stevens-Johnson syndrome**
- **TEN – toxic epidermal necrolysis**
- **AGEP – acute generalized exanthematous pustulosis**
- **EM - erythema multiforme***







Cacoub P et al. J Hepatol 2012; 56: 455–63
Hezode C et al. Liver Int 2012; 32 suppl 1: 32-38

*EM is not considered as a life threatening

SCAR diagnosis

When to suspect DRESS:

Alert criteria

1. Onset from 5-10 wk after dose
2. Rapidly progressing exanthema
3. Prolonged fever (>38.5 oC)
4. Facial edema

If any DRESS alert criteria are found, the patient should be assessed for the following

Confirmation criteria

1. Enlarged lymph node
2. Eosinophilia (≥700/µl or ≥10%)
3. Atypical lymphocytes
4. Rise in ALT, alkaline phosphatases (≥2 times upper limit of normal value)
5. Rise in creatinine (≥150% basal level)

If any DRESS confirmation criteria are also found, all treatment should be discontinued immediately and the patient should be referred to a dermatologist

When to suspect SJS or TEN:

1. Rapidly progressing exanthema
2. Skin pain
3. Mucosal involvement at ≥2 sites
4. Blisters or epidermal detachment (not only at PEG-IFN injection site)
5. Atypical/typical target lesions

If symptoms 3 or 4 are present, all treatment should be discontinued immediately and the patient should be referred to a dermatologist

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

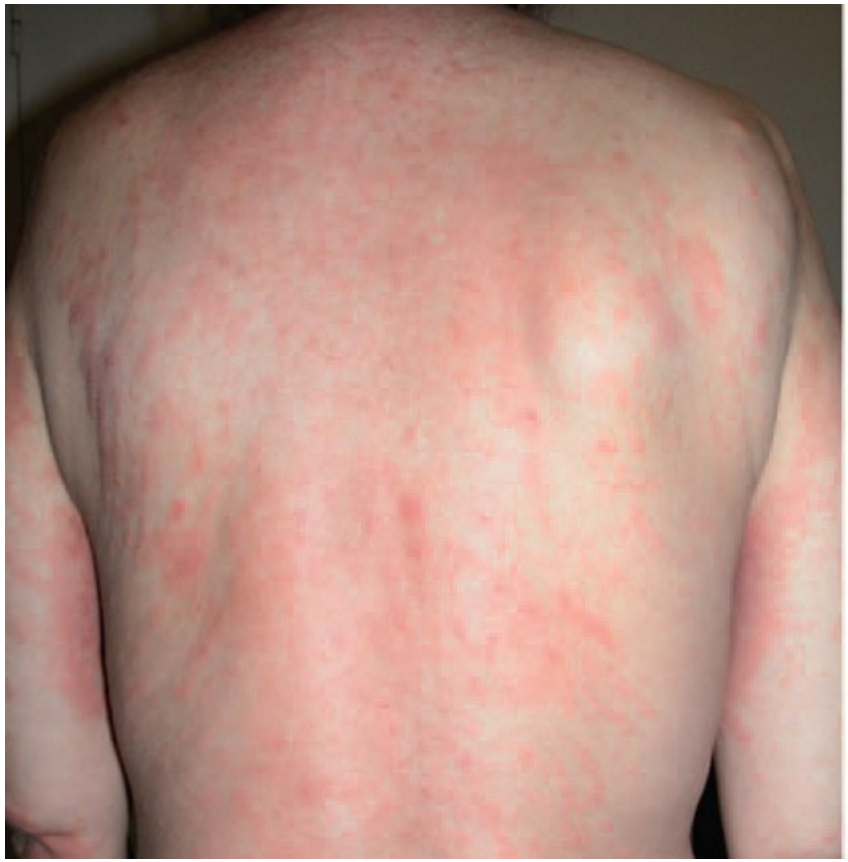
SCAR management

Suspected drug discontinuation

Referal to dermatologist (hospitalization)

- systemic corticosteroids
- iv. immunoglobilins
- cyclosporin A
- iv. supplementation of water and electrolytes

Severe skin rash in case of readministration of TVR in a patient who previously experienced a non severe rash



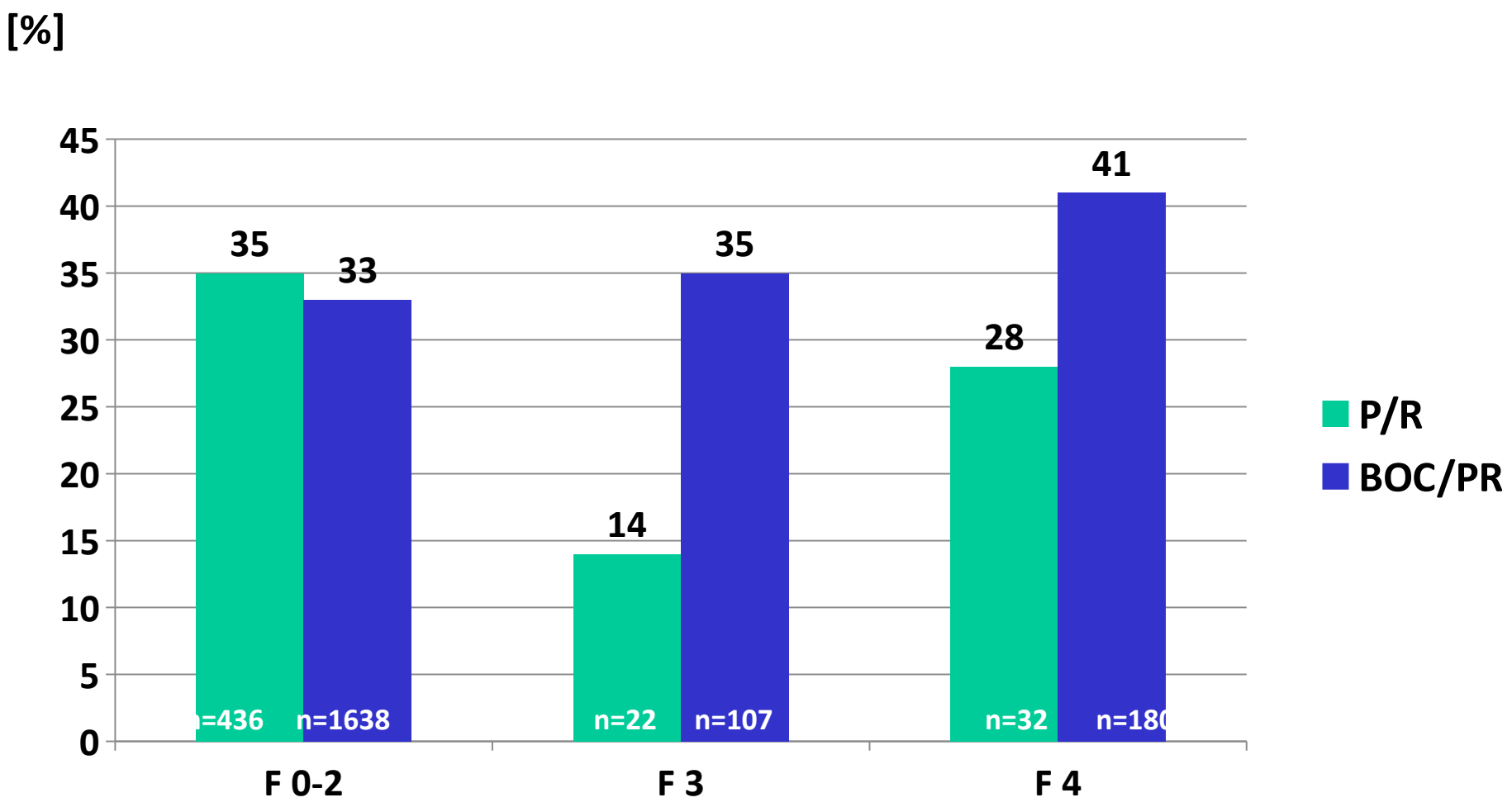
Eczematiform rash (grade 2) in a 61-year-old woman 10 weeks after the introduction of a combined treatment with Peg-IFN, RBV, and telaprevir.

Curtuasy of dr Nicolas Dupin
Dupin N, et al. Hepatol 2012; 55: 2042-3

Skin reactions - summary and conclusions

- Dermatological side effects with TVR-based triple therapy are more frequent than on dual therapy.
- More than 90% of dermatological side effects with TVR-based triple therapy were mild or moderate (grade 1/2), and in the majority of cases no progression was observed.
- In a small number of cases (6%), rash led to TVR discontinuation, whereupon symptoms commonly resolved. A few cases were classified as potentially life-threatening, severe cutaneous adverse reactions (SCAR).
- Mild or moderate dermatological reactions (grade 1/2) do not require treatment discontinuation, and can be primarily treated using class 3 topical corticosteroids.
- Severe (grade 3) reactions require immediate TVR discontinuation.
- In the case of an atypical cutaneous reaction (rapid progression, prolonged fever, mucosal involvement, blisters or epidermal detachment), a patient should be assessed for grade 4 reactions (SCAR) and all the treatment must be discontinued immediately.

Treatment-emergent infections: a meta-analysis of five phase 3 clinical trials with BOC-based therapy



Vierling JM et al. EASL 2013

Five died patients with hepatic decompensation or sepsis related to BOC-based therapy in a meta-analysis of five phase 3 clinical trials.

Patient ID (Study)	Baseline Data	Event	Treatment regimen (weeks of treatment)	Outcome
Cirrhotic Patients				
016301 (PROVIDE)	Male, 64 yo; F4 History of ascites Platelets, 108K Albumin, 3.7 g/L	**Decompensated cirrhosis with ascites and encephalopathy (confusion)**	BOC/P/R (TW6)	Discontinued treatment; events resolved
012072 (RESPOND-2)	Female, 51 yo; F4 Platelets, 170K Albumin, 3.5 g/L	**Bleeding esophageal varices and portal hypertension**	P/R (TW2)	Discontinued treatment; events resolved
000603 (PEG2a study)	Male, 48 yo; F4 Diabetic, IVDU Platelets, 135K Albumin, 3.8 g/L	**Multi-organ failure with total bilirubin peak 17.4 mg/dL** (*Staphylococcus* pneumonia, resulting in multi-organ failure)	BOC/P/R (TW12)	Died of multi-organ failure
Non-cirrhotic Patients				
000005 (PEG2a study)	Male, 52 yo; F2 Platelets, 280K Albumin, 4.2 g/L	**Possible urosepsis** (negative blood and urine cultures)	P/R (TW3)	Discontinued treatment; event resolved
001868 (SPRINT-2)	Male, 58 yo; F2 Platelets, 192K Albumin, 3.5 g/L	**Ascites** (Hospitalized with severe epiglottitis and neutropenia; developed acute renal failure; treatment discontinued; ascites and oedema noted 12 days later)	12 days after discontinuing BOC/P/R (TW12)	Discontinued treatment for other AEs; ascites resolved

Vierling JM et al. EASL 2013

Telaprevir or Boceprevir: severe infections in CUPIC study (week 16 data)

Severe infections were reported in 24 (4.8%) patients:

- pulmonary infection (n = 8),
- unidentified septicaemia (n = 7),
- acute pyelonephritis (n = 4),
- endocarditis (n = 2),
- food poisoning (n = 1),
- cutaneous infection (n = 2).

Bacteria were identified in 17 patients:

- Staphylococcus (n = 8),
- Escherichia coli (n = 5),
- Klebsiella (n = 1),
- Pyocyanic (n = 1),
- Bacteroides fragilis (n = 1)
- Pneumococcus (n = 1).

✓ Infectious complications occurred after a median duration of antiviral treatment of 8.6 weeks (2.3–15.9).

✓ PegIFN dose was reduced or discontinued in 13 patients (54.2%) before the occurrence of severe infection, and in an additional 6 patients (25%) after severe infection onset.

Hézode C & CUPIC Study Group. J Hepatol. 2013 Sep;59(3):434-41.

Telaprevir or Boceprevir: safety findings in CUPIC study (week 12 follow-up data), N=485

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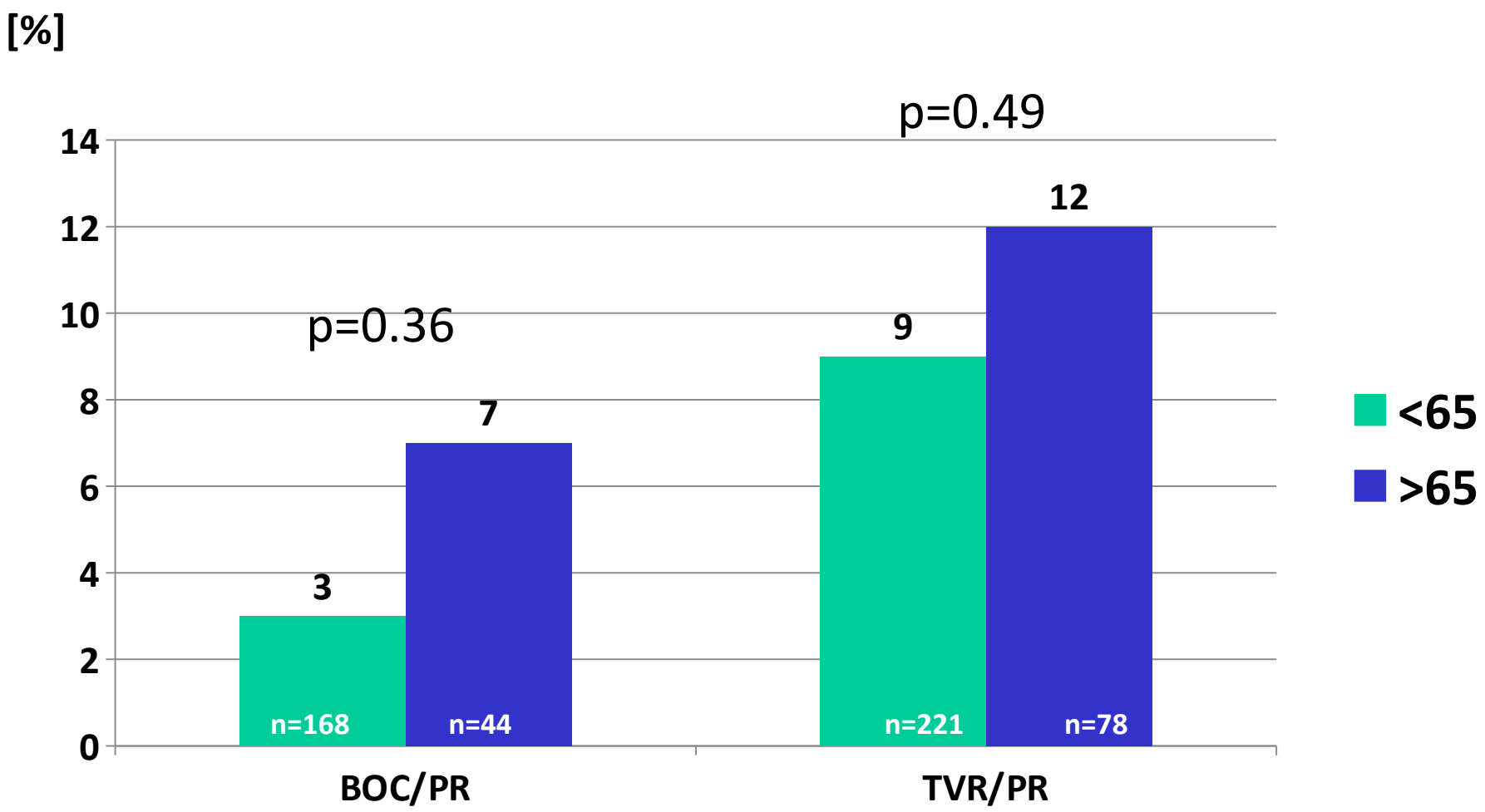
Fontaine H et al. EASL 2013

SCAR: severe cutaneous adverse reaction

Telaprevir or Boceprevir: age distribution of severe infections in CUPIC (week 12 follow-up data), N=511



Hézode C et al. AASLD 2013

Infections in some „real life" studies presented at the AASLD 2013

Study	Population	Infections
„PAN" cohort Mauss S et al.	N=205 BOC-45, TVR-159 cirrhosis-47%	5%
HCV-target Afdhal NH et al.	N=939 Cirrhosis (n=408) Non-Cirrhosis (n=531)	 25% 22%
von Wichmann MA et al.	N=86 TVR in HCV/HIV, F3/F4=20%/80%	13%
Callej J et al.	N=187 F4=80%	Infections - 30% (56) Grade 3/4 infections - 10% (17) Death to sepsis or pneumonia – 1% (2)
Maasoumy B et al.	N=86 BOC or TVR F3+F4=86%	SAE infections – 7% (6) 2 of 3 deaths due to sepsis
Guivarch M et al.	N=125 BOC or TVR, null/partial NR-63%/37% F3/F4=28%/72%	SAE infections – 6% (4)

Infections - summary and conclusions

- Severe bacterial infections are relatively frequent reason of SAE reporting in studies with BOC or TVR based therapy.
- Prevalence of infections during the triple therapy reach in some studies up to 30% and severe infections (grade 3/4) are usually reported in 4-10% treated patients.
- The most frequent clinical forms of severe infections are sepsis and pulmonary infection.
- Staphylococcus and Escherichia were the most frequently isolated ethiologic agents.
- No sufficient data on ethiology and clinical course of infections (including severe) were provided in publications from both clinical trials and postregistration studies.