Hepatitis C– New Directions, New Challenges

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Side Effect Management and Adherence Strategies

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Question for the audience.

Objectives

- Peglylated Interferon/Ribavirin / Telaprevir
- Pegylated Interferon/Ribavirin/Bocepravir

- Side effects of Pegylated interferon– review
- Side effects of Ribavirin– review
- Side effects of Telaprevir and their managment
- Side effects of Bocepravir and their management
- Adherence strategies in the new era of DAA's

Peg- IFN

- The package insert of interferon has lists of side effects, from more common to rare.

Pegylated Interferon

- **Boxed WARNINGS**
- **Alpha interferons, including PEGASYS, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping PEGASYS therapy.**

Pegylated Interferon

- 98 to 99 % of patients experienced one or more adverse events. For hepatitis C subjects, the most commonly reported adverse reactions were psychiatric reactions, including depression, insomnia, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache, and rigors. Other common reactions were anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.
- Package insert, peg-IFN alpha2a (pegasys)

HIV/CHC co-infection

- Serious adverse events occurred at a frequency of <1% and included: suicide, suicidal ideation, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (eg, hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, cerebral hemorrhage, thrombotic thrombocytopenic purpura, psychotic disorder, and hallucination.

Peg-Interferon

- The most common adverse reactions (incidence greater than 40%) are
- fatigue/asthenia, pyrexia, myalgia, and headache. (6.1)
- Screen patients prior to treatment initiation for depression and mental illness.

Management of neutropenia and thrombocytopenia

- **Laboratory Values Recommended Dose**
- ANC <750 cells/mm3 : reduce peg to 135mcg
- ANC <500 cells/mm3 : discontinue until ANC values return to >1000, restart at 90mcg and monitor
- Platelet <50,000 cells/mm3: reduce to 90 mcg
- Platelet <25,000 cells/mm3: discontinue treatment

Ribavirin

- **Ribavirin, may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.**
- **Counsel patient re: 2 forms of birth control during treatment and for the 6 months following treatment.**
- Package Insert, ribavirin

Anemia

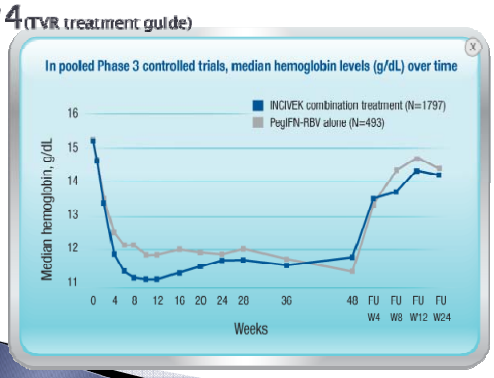
- Which drugs: Ribavirin, Telaprevir, Boceprevir.
- **Bocepravir:** Mechanism is likely the result of bone marrow suppression not due to hemolysis as with Ribavirin.
- Increased rates of anemia with triple therapy
- **Patients over the age of 50 need baseline stress test prior to treatment initiation**

DAA's: Telaprevir and Bocepravir

- 1. Dosing requirements, 375mg; 2 pills Every 8 hours!
  with 20grams of fat 30 minutes prior to dosing
- 2. Bocepravir: 200mg; 4 pills every 8 hours!

Only approved for HCV G1 and in combination with Peg Interferon and Ribavirin

Median hemoglobin values from baseline through follow up week 24 (TVR treatment guide)



Incidence rates of anemia Triple therapy with TVR compared to Peg-IFN /RBV

Hemoglobin values	Telaprevir + Peg-IFN and Ribavirin	Peg- IFN /Ribavirin
< or = 10 g/dL	36%	17%
<8.5 g/dL	14%	5%

Management of patients with Anemia – Ribavirin package insert , dose modification

Ribavirin package insert (ribapak)	CoPegus(brand) Package insert	Rebetrol , package insert
1. Reduce RBV to 600mg if Hg <10 g/dL or > or = 2g/dL decrease in hG during any 4 week period in patients with history if stable cardiac disease. 2. **Discontinue** if Hg < 8.5 g/dL in patients with history of stable cardiac disease	1. Reduce RBV to 600mg daily if Hg < 10 g/dL or decrease in Hg of < or = 2g/dL during any 4 week perios in patients with history of stable cardiac disease 2. **Discontinue** if Hg < 8.5 g/dL in patients with history of stable cardiac disease	1. Reduce RBV by 200mg daily in patients who are receiving 1000mg or 1200mg daily if <10 g/dL. If needed, an additional dose reduction by 400mg in patients receiving 1400mg daily. 2. History of stable cardiac disease: reduce RBV by 200mg daily if > 2g/dL decrease in Hg during any 4 week period. 3. Discontinue RBV if Hg is <12 after dose reduction.

Anemia Management Strategies with Triple Combination Therapy

1. There is no dose reduction for the protease inhibitors.
2. Modest dose reductions of ribavirin are recommended and acceptable. The use of epogen is off-label and is not first line therapy.
3. DAA 's should not be stopped and restarted due to risk of resistance.
4. No dose reductions of DAA's.
5. Epogen should not be used if hemoglobin is >or = 10 g/dl.
   Epo was not used in Telaprevir clinical trials.
   Epo was uses in Bocepravir clinical trials.

Anemia Management Strategies with Triple Combination Therapy (2)

- 1. Monitor closely: CBC baseline then weekly or every 2 weeks
- First: dose reduce Ribavirin
- If no improvement then consider Erythropoietin

- Peginterferon-alpha 2a package insert. Genentech, Inc. 2011

Telaprevir Side Effects

Most Common Adverse Drug Reactions with Telaprevir

Rash:	56%
Fatigue:	56%
Pruritis:	47%
Nausea:	39%
Anemia:	36%
Diarrhea:	26%
Anorectal discomfort:	11%
Dysguesia:	10%
Anal Pruritis:	6%

Anorectal management

- 1. Adequate fluid and fiber intake.
- 2. Avoidance of spicy foods, caffeine citrus that may aggravate symptoms.
- 3. Do not over bathe area, no soap, warm water only, Tucks pads.
- 4. Cold compresses may relieve itching
- 5. Sitz baths- four times daily.

Anorectal management (2)

- Pharmacotherapy

1. Hydrocortisone 2.5% suppositories or cream
2. Protective ointments, zinc oxide, diaper rash cream, A &D ointment
3. Topical lidocaine
4. Oral pain control, tylenol, ibuprofen
5. Stool softeners, colace, miralax
6. Referral to colo-rectal in the event of anal fissure

Most Common Adverse Drug Reactions with Telaprevir

	TVP combination therapy	Peg-IFN/RBV alone
Rash:	56%	
Fatigue:	56%	
Pruritis:	47%	
Nausea:	39%	
Anemia:	36%	
Diarrhea:		26%
Anorectal discomfort:	11%	
Dysguesia:	10%	
Anal Pruritis:	6%	

Most Common Adverse Drug Reactions with Telaprevir (TVR)

Adverse Drug Reaction	TVP combination therapy	Peg-IFN/RBV
Rash	56%	34%
Fatigue	56%	50%
Pruirits	47%	28%
Nausea	39%	28%
Anemia	36%	17%
Diarrhea	26%	17%
Vomiting	13%	8%
Hemorrhoids	12%	3%
Anorectal Discomfort	11%	3%
Dysguesia	10%	3%

TVR Rash

- Approximately 6% have discontinued therapy due to rash
- Approximately 4% have discontinued therapy due to anemia

Lab abnormalities observed during clinical trials

Lab	Lab abnormality	TVR combination therapy	Peg-IFN /RBV
Total WBC	< or = 1499	8%	5%
Lymphocytes	< or =499	15%	5%
Neutrophils	< or =749	12%	15%
Platelets	< or = 50 Between 50 and 90	3% 47%	1% 36%
Bilirubin	< or = 1.8 > or = 2.6 x ULN	41% 4%	28% 2%
Uric Acid	All grades > Or = 12.1 mg/ dL	73% 7%	29% 1%

RASH with TVR

- Occurred in 56% of patients, usually mild to moderate.
- Severe rash reported in < 5% of patients.
- Serious skin reactions including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens- Johnson's syndrome were reported in < 1 % of patients.

Rash- TVR

- Rash is most likely to occur during the first 4 weeks of therapy, however could occur at any time
- Improvement of rash occurs at discontinuation of TVR, though rash may take weeks to completely resolve.

Rash, what to do about it

- At your treatment teaching visit , discuss good skin practices

1. Apply moisturizers
2. Avoid alcohol based lotions
3. Drink water or other non caffeinated fluids
4. Wear loose fitting clothing
5. Use unscented laundry detergent, no fabric softeners, no dryer sheetsSUN: Stay out of it, wear sun screen
6. Avoid hot showers, use unscented soap

Rash, what to do about it

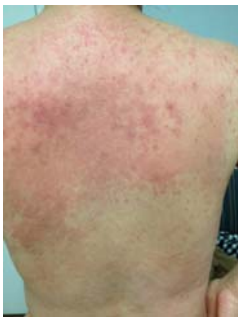
1. Topical steroids use the level of potency necessary to control rash, if accompanied by pruritis, use antihistamine, diphenhydramine or hydroxizine.
2. Non-sedating antihistamine during the day and diphenhydramine or hydroxazine at bedtime
3. Topical lidocaine, calamine lotion

-Telaprevir Full prescribing Information

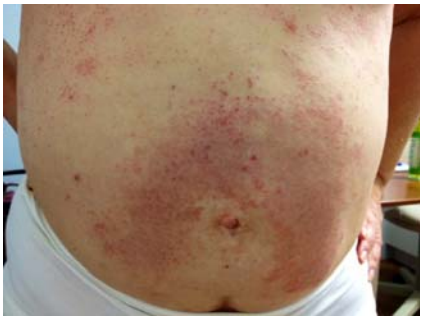
Rash

- 1. Mild: localized and with limited distribution
- 2. Moderate: Diffuse rash, with our without superficial skin peeling or mucous membrane involvement, no ulceration
- 3. Severe: Generalized rash or with vesicles, bullae or ulcerations (DISCONTINUE TVR, MAY OR MAY NOT CONTINUE PEG-IFN/RBV)
- **if TVR is discontinued due to rash it should not be restarted or reduced**

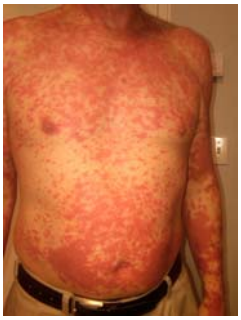
Rash photos



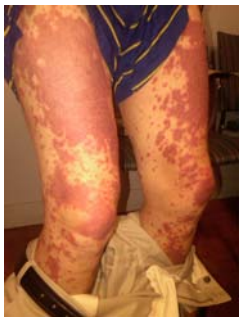
Telaprevir – rash , abdomen



Telaprevir–severe rash



Telaprevir– severe rash



Bocepravir: side effects

1. Anemia
2. Fatigue
3. Nausea
4. Headache
5. Dysguesia
6. Neutropenia

Side effects of Bocepravir in Naïve patients (SPRINT-1 & SPRINT-2)

Fatigue	**58%**
Anemia	50%
Neutropenia	25%
Nausea	46%
Dysguesia	35%
Vomiting	20%

Side effects of Bocepravir in previously treated patients (RESPOND-2)

Fatigue	**55%**
Anemia	45%
Neutropenia	14%
Nausea	43%
Dysguesia	44%
Vomiting	20%

Side effect Management

- Anemia--→dose reduction of ribavirin, Epogen (off label)
- Nausea-→Ondansatron, small meals throughout the day, ginger based drinks, citrus candy. If refractory: trial of benzodiazapine (i.e lorazapam)

--Though nausea and vomiting are reported as side effects, if this is refractory other causes must be investigated

- Neutropenia-→Dose reduction of peg interferon, neupogen (off label)

Side Effect Management-Bocepravir

- Dysguesia: Keep mouth hydrated with fluids and products for dry mouth.

Adherence, Why do we care?

- 1. Will lower rates of adherence effect treatment outcome?
- 2. Is resistance and issue?

Adherence Data

- Adherence to antiretrovirals has been extensively studies in HIV disease over the past 15 years, this is not true in Hepatitis C.
- Wagner et al (2011). 72 HIV-HCV co-infected patients treated for HCV, and just under 30% reported problems with missed doses of Peg/RBV which is similar to reports in other studies of Peg/RBV.

Adherence

- Poor adherence can affect treatment outcome.
- Adherence to ribavirin has been shown to be lower than adherence to peg-IFN

--pill burden, average daily divided dose of ribavirin is 1000mg (5 pills) or 1200mg (6 pills)

- In HIV treatment the association between high pill burden , lower adherence rates and incomplete viral suppression has been well demonstrated
  - Alam, I et al (2010), Cacoub,P et al (2008), Weiss, JJ et al (2008).

Adherence

- Relationship between adherence and EVR(early sustained viral response) and SVR(sustained viral response) in the co-infected patient.
- Cohort study: n=333, patients who took Peg/rbv from 2001-2006.
- Adherence was calculated using pharmacy refills and it declined over time but more for ribavirin.
  - Lo Re, V et al 2012 AIDS Behavior

Adherence data

- Retrospecitve analysis of Bocepravir Phase III data showed that completion of >80% significantly influced SVR rates.
- In addition, taking the Bocepravir every 7-9 hours at noted in package insert did not have effect on SVR.

Jacobson, IM et al (2012) J Hepatology

Adherence: the future

- Currently, resistance is not as much of a concern as it is with HIV antiretrovirals as it is thought that resistance to either Telaprevir or Bocepravir disappears within 2 years and does not archive.
- With the approval of the DAA's last year and many more oral therapies in the pipeline, adherence in HCV and HCV-co infection will receive more attention.

Adherence

- Package Insert: doses are every 7-9 hours.

Real life recommendation EVERY 8 HOURS.

TVR- 20 grams of fat 30 minutes prior to each dose

BOC- take with food

Adherence Challenges and Strategies

- TID dosing
- Higher pill burden
- Adverse Events
- Resistance

Osterberg, L., Blaschke, T., NEJM 2005.

- Identify potential adherence issues prior to treatment initiation
- Simplify the regimen
- Customize regimen to patient's life, take the time up front
- Use every opportunity to reinforce importance of adherence , ASK at every patient interaction

Adherence Strategies

- 1. Ribapak(blister pak of ribavirin in divided dose of 2 pills)
- – for example: 1000mg total daily dose= 400mg tab and 600mg tab of ribavirin

Adherence: the future

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