Update in GI and Hepatology

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Disclosure

- Bristol Meyers Squibb
  - Speaker Bureau

IBD Drugs

Ulcerative Colitis	Crohn's Disease
Azathioprine	Azathioprine
6-MP	6-MP
Infliximab Adalimumab	Methotrexate
Adalimumab	Infliximab
Golimumab	Adalimumab
Tofacitinib	Certolizumab Pegol
Vedolizumab	Vedolizumab
Ozanimod	Natalizumab
	Ustekinumab

Azathioprine and 6-MP

AZA is converted to 6 MP after absorption and 6 MP is metabolized to 6 TGN (the active metabolites).

Elevated 6 MMP (another 6 MP metabolite) leads to elevated AST/ALT, amylase and lipase level.

TPMT is the enzyme involved with 6 MMP formation.

Homozygous wild type TPMT 89% of pop

Heterozygous TPMT mut 11%

Homozygous TPMT mut 0.3%

Hetero and homozygous mut have decreased to absent TPMT activity and are at higher risk of leuopenia when treated with AZA and 6 MP.

If TPMT activity is normal, the target IBD tx dose is 2-3 mg/kg/day for AZA and 1.0-1.5 mg/kg/day for 6 MP.

If intermediate TPMT activity, the dose should be halved.

Low/absent TPMT activity should avoid these drugs altogether.

Slow onset of action (better for maintenance than induction).

SE: leukopenia, anemia, thrombocytopenia, elevated LFTs, nausea, 4-5 x increased risk for lymphoma and 2:1 higher risk in men than women with highest absolute risk in age >50 (1/354 person years of follow up). Increased non melanoma skin cancers.

In combination with biologics, fewer adverse events, less immunogenicity and higher biologic drug levels.

Methotrexate

Only for CD, 25 mg IM once a wk (subQ is as effective as IM but oral is not).

15 mg IM Q wk can maintain remission in those who achieved remission at 25 mg Q wkly.

Drug toxicity with nausea and diarrhea can be reduced with co-administration of folic acid 1 mg QD.

There is a potential for hepatic fibrosis so LFTs need to be periodically monitored.

Although not formally recommended, obtaining a liver bx after cumulative dose of 1.5 g in those with risk factors for liver disease or persistently elevated LFTs has been suggested by some investigators. The role of FibroScan is not clear in this context.

Can also prevent immunogenicity in pts on concurrent biologic therapy at a dose of 12.5-15 mg orally once a week.

Infliximab (anti TNF)

5 mg/kg at wks 0, 2, 6 and then every 8 wks

Can be increased to 10 mg/kg every 8 wks or 5 mg/kg every 4 wks in those with a loss of response

The combination of Infliximab and AZA in CD/UC is more effective than either therapy alone.

Abs to infliximab indicate a loss of response

Goal trough level of Infliximab is 5 micrograms/mL but in fistulizing CD can be 15 micrograms/mL or more.

Adalimumab (anti TNF)

Dosed every 2 wks starting with 160 mg at week 0, 80 mg at week 2, and 40 mg every other week thereafter

Dose escalation up to 40 mg Q wk or up to 80 mg Q wk

Suggested trough level of drug is 7.5 micrograms/mL or more

Certolizumab Pegol

Only for CD

Dosed every 4 wks at 400 mg at week 0, 2 and then every 4 wks thereafter

In those with loss of response, can increase the dose to 400 mg within 2 wks of the last dose to try to recapture the response

Does not cross the placenta so can be given throughout pregnancy

Less immunogenic than other anti-TNFs since it lacks Fc Ab component

Golimumab

Only for UC

Dosed sub Q 100 mg Q 4 wks after 200 mg at week 0 and then 100 mg at week 2

anti-TNF side effects/associations

Acute sinusitis, reactivation of TB and HEp B, pneumonia, fungal infections, acute infusion reactions, delayed hypersensitivity reactions, myalgias, arthralgias, fever (2-12 days after infusion), and formation of autoAbs (ANA and anti-dsDNA) which can lead to lupus-like reaction. Rare severe hepatic necrosis.

NHL has been associated (debatable small increased risk) but there is a HIGH risk of HSTCL when infliximab or adalimumab have been used with AZA and 6-MP in young males <35 YO (with AZA and 6-MP use at least 2 or more years).

There is also an increased risk of skin cancer, especially melanoma.

Natalizumab (anti-integrin alpha 4-beta 7)

Affect leukocyte adhesion/trafficking

Gut and brain action (alpha 4 beta 7 in gut and alpha 4 beta 1 in brain)

Also used in MS and for CD only

Dosed as 300 mg infusion at week 0, 4, 8 and then every 4 wks thereafter

The most serious risk is PML (caused by the reactivation of JC virus in the brain. This can have permanent and devastating neurological sequelae. Risk factors for PML include anti-JC virus positivity, prior use of IS, and increased duration of natalizumab use (over 2 yrs).

All pts should have baseline JC virus Ab testing and subsequent JC virus reconversion surveillance when using this agent.

This agent has been shown to delay surgery and improve outcomes in those with CD willing to undergo JC virus testing and receive the drug if Ab negative.

Vedolizumab (anti-integrin alpha 4-beta 7)

Affect leukocyte adhesion/trafficking

Gut action only (alpha 4 beta 7)

For both UC and CD

Does not increase risk of PML regardless of JC virus Ab status.

Dosed as 300 mg infusion over 30 minutes at wks 0, 2, and 6 followed by maintenance infusions every 8 wks

Can increase dose to 300 mg every 4-6 wks in those with loss of response

Most common side effect=nasopharyngitis

Ustekinumab (anti IL-12/23)

Targets and inhibits pro-inflammatory cytokines

IL-12 is important for Th1 cell development

Both IL-12 and 23 share a common p40 subunit which this agent targets

Can only used in CD as a one time, wt based infusion, followed by maintenance 90 mg sub Q injection Q 8 wks

Has also been used in psoriasis and psoriatic arthritis.

No increased risk of malignancy, lymphoma or infection.

Tofacitinib (Janus Kinase/JAK 1 and 3 inhibitor)

Only for UC

Targets intracellular tyrosine kinases that regulate inflammatory mediators via the JAK-STAT pathway which results in the suppression of T cells but without affecting the function of T regs.

Dosed as 10 mg BID for 8 wks then maintenance of 5 or 10 mg BID thereafter.

Is associated with increased risk of infection, especially non-systemic zoster and possibly lymphoma. Also associated with increases in total cholesterol, LDL and HDL.

Rapid onset of action within 3 days.

Ozanimod (sphingosine 1-phosphate receptor agonist)

Used in MS, only for UC

Once a day. Days 1-4: 0.23 mg PO QD. Days 5-7 0.46 mg PO QD. Day 8 and thereafter 0.92 mg QD.

Sequesters lymphocytes away from sites of chronic inflammation to peripheral lymphoid organs

Can cause a decrease in peripheral lymphocyte count for 14 days after tx discontinuation

Can cause elevated liver enzymes and bradycardia so baseline EKG should be checked. Can not be used in those with heart block or pacemaker. Can not be used in those with macular edema (also need vision test at baseline).

No increased risk of cancers like lymphoma.

Most common side effect is nasopharyngitis and HTN.

IBS drugs

Viberzi

Rifaximin

Linzess

Trulance

Amitiza

Motility drugs

Prucalopride/Motegrity

Gastric Pacers

Hepatitis Drugs

Chronic Hepatitis B treatment: Entecavir

0.5 mg QD

SE: lactic acidosis (decompensated cirrhosis only)

Monitoring on tx: Cr Cl at baseline; if at risk/renal impairment: Cr Cl, phosphate, urine glucose and protein at least annually; consider bone density at baseline and during tx in pts with hx of fracture or risks for osteopenia; lactic acid levels if thre is clinical concern; test for HIV before tx initiation

Chronic Hepatitis B treatment: Tenofovir Alafenamide

25 mg QD

SE: lactic acidosis

Monitoring on tx: Lactic acid levels if clinical concern; assess Cr, phosphorous, Cr Cl, urine glucose and protein before starting and during tx in all pts as clinically appropriate; test for HIV before tx initiation

Lower rates of bone and renal abnormalities; preferred in pts that have concern for renal or bone disease

Chronic Hepatitis B treatment: Tenofovir Disoproxyl Fumarate

300 mg QD

SE: neuropathy, Fanconi syndrome, osteomalacia, lactic acidosis

Monitoring on tx: eAg positive: monitor ALT and HBV DNA for evidence of resistance

Can be used in pregnant patients.

Hep C Treatment: Tx naive withOUT cirrhosis OR compensated cirrhosis

WHO IS ELIGIBLE FOR SIMPLIFIED TREATMENT

Adults with chronic hepatitis C (any genotype)
who do not have cirrhosis
and have not previously received hepatitis C treatment

WHO IS *NOT* ELIGIBLE FOR SIMPLIFIED TREATMENT

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
- End-stage renal disease (ie, eGFR <30 mL/min/m^2) (see Patients with Renal Impairment section)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

PRETREATMENT ASSESSMENT[A]

- **Calculate FIB-4 score.**
- **Cirrhosis assessment**: Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.
  - Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
  - Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
  - Prior liver biopsy showing cirrhosis
- **Medication reconciliation:** Record current medications, including over-the-counter drugs, and herbal/dietary supplements.
- **Potential drug-drug interaction assessment:** Drug-drug interactions can be assessed using the AASLD/IDSA guidance or the University of Liverpool drug interaction checker.
- **Education:** Educate the patient about proper administration of medications, adherence, and prevention of reinfection.

- **Pretreatment laboratory testing**

Within 6 months of initiating treatment:

  - Complete blood count (CBC)
  - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST])
  - Calculated glomerular filtration rate (eGFR)

Any time prior to starting antiviral therapy:

  - Quantitative HCV RNA (HCV viral load)
  - HIV antigen/antibody test
  - Hepatitis B surface antigen

Before initiating antiviral therapy:

  - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

Hep C Treatment: Tx naive withOUT cirrhosis OR compensated cirrhosis

[MAVYRET] [EPCLUSA]

RECOMMENDED REGIMENS*

Glecaprevir (300 mg) / pibrentasvir (120 mg)
taken with food for a duration of 8 weeks

Sofosbuvir (400 mg) / velpatasvir (100 mg)
for a duration of 12 weeks

ON-TREATMENT MONITORING

- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- No laboratory monitoring is required for other patients.
- An in-person or telehealth/phone visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

POST-TREATMENT ASSESSMENT OF CURE (SVR)

- Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.

FOLLOW-UP AFTER ACHIEVING VIROLOGIC CURE (SVR)

- No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR.
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin.
- Advise patients to avoid excess alcohol use.

FOLLOW-UP FOR PATIENTS WHO DO *NOT* ACHIEVE A VIROLOGIC CURE

- Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance.
- For patients unable to be retreated, assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended.
- Advise patients to avoid excess alcohol use.

AASLD

*More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment, including the treatment of patients with cirrhosis, can be found at www.hcvguidelines.org. Updated: December 10, 2019 © 2019 American Association for the Study of Liver Diseases and the Infectious Diseases Society of America

IDSA

Chronic Hepatitis C treatment: Harvoni

Tx naive g 1a/b, 4, 5, 6 non-cirrhotics: 12 wks

Tx naive g 1a/b, 4, 5, 6 cirrhotics: 12 wks

Chronic Hepatitis C treatment: Mavyret

G 1a/b, 2, 3, 4, 5, 6

Cirrhotic and non cirrhotic with CKD 4 or 5, post tx

Chronic Hepatitis C treatment: Epclusa

Cirrhotic and non cirrhotic g 1a/b, 2, 3, 4, 5, 6

Chronic Hepatitis C treatment: Vosevi

G 1, 2, 3, 4, 5, 6 or those previously treated with DAAs

Chronic Hepatitis C treatment: Zepatier

Tx naive non cirrhotics g 1a/b, 4: 12 wks

Tx naive cirrhotics g 1a/b, 4: 12 wks

Tx experienced compensated cirrhotics g 1a/b, 4

1,2, 4, 5, 6

Can be used in ESRD on HD

Do not use sofosbuvir in Cr Cl <30 or with amiodarone

All DAAs interact with statins except sofosbuvir

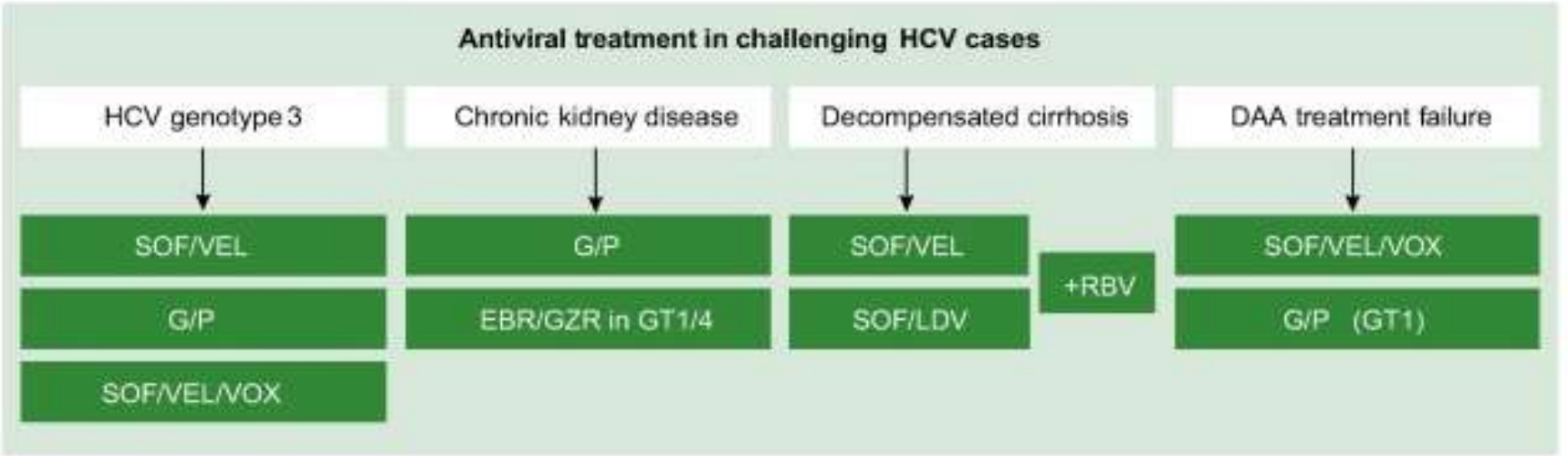
Do not use any protease inhibitors (--navirs) in cirrhotics

Prevent reactivation of Hep B in those who are s ag positive who will need steroids or B cell depleting chemotherapy or immunosuppression

Drug Drug Interactions with DAAs---PPIs and H2 Blockers

	GLE/PIB	EBR/GZR	SOF/LDV	SOF/VEL
Antacids	No interaction	No interaction	Separate by 4 hrs	Separate by 4 hrs
H_2 blockers	No interaction	No interaction	Together or 12 hrs apart; famotidine 40 mg BID	Together or 12 hrs apart; famotidine 40 mg BID
PPIs	No interaction	No interaction	Together with omeprazole 20 mg	With food, 4 hrs before omeprazole 20 mg

PPI, proton pump inhibitor.


Antiviral treatment in challenging HCV cases
HCV genotype 3
Chronic kidney disease
Decompensated cirrhosis
DAA treatment failure
SOF/VEL
G/P
SOF/VEL/VOX
G/P
EBR/GZR in GT1/4
SOF/VEL
SOF/LDV
+RBV
SOF/VEL/VOX
G/P (GT1)

Fibroscan

Non-invasive measurement of hepatic fibrosis and hepatic steatosis through sound waves directed in an US probe

Performed bedside

2 measurements: LSM and CAP score

Can give a falsely high fibrosis score if there is an acute elevation in LFTs, so check 3 months later once LFTs (acute hepatitis) has improved

Not accurate in those who have abdominal obesity, ascites, cardiac cirrhosis or on HD/PD

TIPS

Indications: refractory ascites, hepatic hydrothorax and variceal bleed. Also used to preserve vasculature in hepatic/portal vein bland thrombus for transplant surgery anatomical considerations/needs.

CI: hx of HE, TB>3 or MELD>18, tumor thrombus

Has been studied in 6 HD pts, they ended up having an irreversible hepatic enceophalopathy

New NAFLD drugs: Lira/Semaglutide

Pioglitazone

Liraglutide

Semaglutide

NSBB in variceal bleed prophylaxis

PBC drugs: Ursodiol

Dosed 13-15 mg/kg QD

Higher doses shown to have no benefit

PBC drugs: Ocaliva (Obeticholic Acid)

Do not use in those with severe pruritus as it worsens this, also can not be used in cirrhotics

Dose is

MELD 3.0

AI in Endo

EUS portal pressure measurements and fibrosis testing/liver bx

Question 1

Question 2

Question 3

Question 4

Question 5