PHARMACOLOGIC MANAGEMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

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DISCLOSURE

I have no actual or potential conflict of interest

OBJECTIVES

- Brief overview of IBD
- Discuss symptoms and clinical features
- Outline diagnostic work-up
- Discuss the current aminosalicylate therapy in the management of IBD
- Discuss the current immunomodulators in the management of IBD
- Discuss the current biologic therapies in the management of IBD
- Discuss therapeutic drug monitoring

BRIEF OVERVIEW OF IBD

Ulcerative colitis

- Mucosal layer
- Rectum
- Proximal and continuous fashion

Crohn's disease

- Transmural
- Ileum and proximal colon
- Skip lesions

SYMPTOMS AND CLINICAL FEATURES

Extent and severity of inflammation

- Bloody diarrhea
- Abdominal pain
- Tenesmus
- Urgency
- Malnutrition
- Stricture
- Fistula
- Abscess
- Extraintestinal manifestation (aphthous ulcers, erythema nodosum, episcleritis, peripheral arthritis)

DIAGNOSTIC WORK-UP

Laboratory tests:

- Elevated WBC/PLT
- Low Hgb/HCT
- Low albumin
- Markers of inflammation (elevated CRP, ESR, fecal calprotectin)
- Rule out Clostridium Difficile

Radiographic tests:

- Small bowel follow through
- CT enterography
- MRI enterography
- Video capsule endoscopy

Colonoscopy

TREATMENT

Goals:

- Induce remission
- Maintain remission
- Prevent complications (disease-related and therapy-related)
- Maintain/restore nutrition
- Improve quality of life
- Minimize need for surgery

TREATMENT

- Aminosalicylates (5-ASA)
- Corticosteroids
- Antibiotics
- Immunomodulators
- Biologics
- Small molecule/JAK inhibitors

AMINOSALICYLATES (5-ASA)

AMINOSALICYLATES (5-ASA)

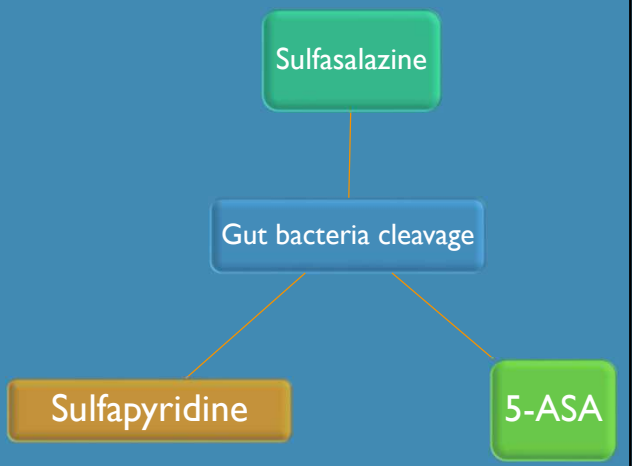
- Indication:
  - Induction of mild to moderate ulcerative colitis
  - Maintenance of mild to moderate ulcerative colitis
- Anti-inflammatory properties
- Formulations: oral and rectal
- Medication selection is based on delivery location matching disease location

5-ASA THERAPY

1. Sulfasalazine
2. Diazo-bonded 5-ASAs
3. Mesalamine

SULFASALAZINE

- Earliest form of the 5-ASA drugs
- Oral formulation only
- Burdensome side effect and allergy profile
- Mechanism of 5-ASA is not fully understood. It is thought to work on the anti-inflammatory cascade (cytokine inhibition, prostaglandin and leukotriene inhibition, free radical effect)
- Sulfapyridine: No therapeutic action



DIAZO-BONDED 5-ASAS

- Oral formulations only
  - Olsalazine = Two 5-ASA compounds linked by azo bond
  - Balsalazide = one 5-ASA compound linked by inert carrier
- Does not contain sulfa
- Bond cleaved by colonic bacteria
- 5-ASA released in colon

MESALAMINE

- Developed to avoid side effect profile of sulfasalazine
- Oral and rectal formulations
- Multiple delivery mechanisms
- Deliver active compound (5-ASA) to different parts of the bowel
- Favorable side effect profile

Mesalamine delivery location

MESALAMINE DELIVERY LOCATION

Canasa suppository	Rectum
Rowasa Enema	Sigmoid & Rectum
Lialda (delayed release, MMX), pH ≥7	Terminal ileum, colon
Apriso (extended release capsule), pH ≥6	Terminal ileum, colon
Asacol HD (delayed release), pH ≥7	Terminal ileum, colon
Delzicol (capsule containing delayed release enteric coated tablet), pH ≥7	Terminal ileum, colon
Pentasa (ethylcellulose-coated microgranule, moisure release)	Duodenum, jejunum, ileum, colon

MECHANISM OF ACTION OF 5-ASA

- Specific action unknown
- Modulates chemical mediators involved in the inflammatory response
- Possible inhibitor of TNF
- Block production of arachidonic acid metabolites
- Possible function as free radical scavengers
- Possible immunomodulation properties

TNF Tumor Necrosis Factor

DOSING

- Sulfasalazine: 500 mg PO q6h; Max:6g/day
- Olsalazine: 500 mg PO bid
- Balsalazide: 2.25 g PO tid
- Apriso: 1.5 g PO qam
- Asacol-HD: 1600 mg PO tid
- Delzicol: 800 mg PO tid x 6 weeks then 1600 mg/day PO divided bid-qid
- Lialda: 2.4-4.8 g PO qd x 8 weeks then 2.4 g PO qd
- Pentasa: 1000 mg PO qid

5-ASA

Special populations:

1. Liver: No dose adjustment, use with caution.
2. Renal: Avoid use in advanced renal impairment, close monitoring when used in mild impairment, renal toxicity has been shown in 5-ASAs
3. Pregnancy: No well controlled studies in pregnant women, animal models did not show fetal harm, use with caution
4. Lactation: Found in human milk in significant amounts, caution and monitoring advised

ADVERSE REACTIONS

- Common: nausea, vomiting, abdominal pain, headache
- Interferes with folate metabolism
- Worsening of colitis
- Mesalamine-induced hypersensitivity reactions: "-itis"

MONITORING

- Baseline renal function, CBC with differential, liver function test
- Periodic monitoring renal function, CBC with differential, liver function test

IMMUNOMODULATORS

IMMUNOMODULATORS

- Thiopurines
  - Azathioprine (AZA)
  - 6-mercaptopurine (6-MP)
- Methotrexate

INDICATIONS

Thiopurines

- Maintenance of corticosteroid induced remission of Crohn's disease and Ulcerative colitis
- Steroid sparing
- Combination therapy with biologics to potentiate effectiveness and reduce immunogenicity of biologics

Methotrexate

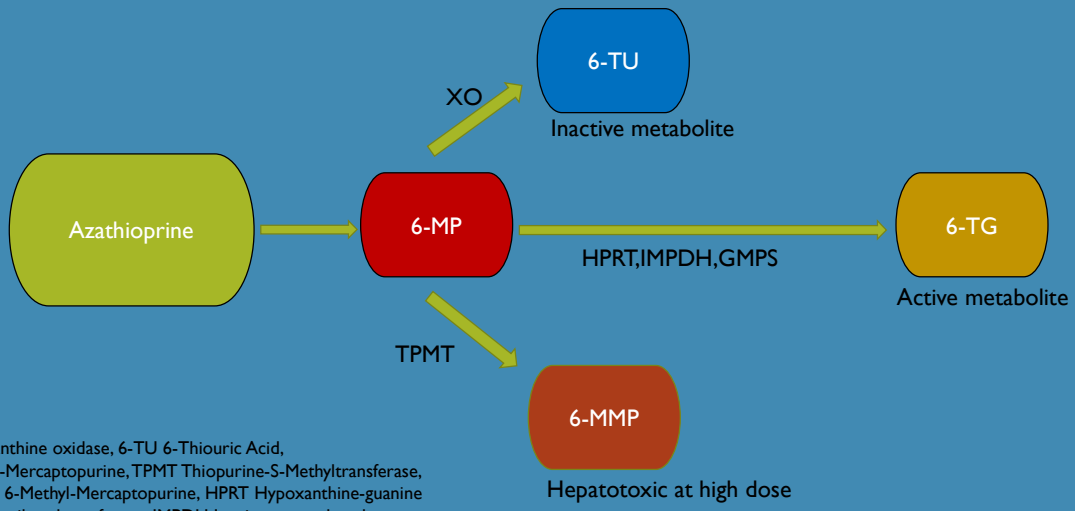
- Maintenance of corticosteroid-induced remission in Crohn's disease
- Steroid sparing
- Combination therapy with biologics to potentiate effectiveness and reduce immunogenicity of biologics

THIOPURINES

Mechanism of action

- **Slow onset of action up to 12 weeks**
- Inhibition of purine and protein synthesis in lymphocytes
- Inhibit lymphocyte proliferation
- Apoptosis of activated lymphocytes

THIOPURINE METABOLISM



XO Xanthine oxidase, 6-TU 6-Thiouric Acid, 6-MP 6-Mercaptopurine, TPMT Thiopurine-S-Methyltransferase, 6-MMP 6-Methyl-Mercaptopurine, HPRT Hypoxanthine-guanine phosphoribosyltransferase, IMPDH Inosine monophosphate dehydrogenase, GMPS Guanosine monophosphate synthetase, 6-TG 6-Thioguanine

DOSING

- Azathioprine: 100-250 mg PO qd; Max: 2.5mg/kg/day
- 6-MP: 75-125 mg PO qd; Max: 1.5 mg/kg/day

THIOPURINES

Special populations:

1. Liver: Caution advised
2. Renal: Dose adjustment depending on degree of impairment
3. Pregnancy: Low risk, fetus is protected- lacks the enzyme needed to convert AZA and 6MP to active metabolites.
4. Lactation: No absolute contraindication, minimal transfer, risk must be considered

THIOPURINES

Adverse effects:

- Common: Abdominal pain, nausea, vomiting, diarrhea, fatigue, arthralgia, rash, anemia, leukopenia.
- Uncommon: Serious infections, hepatotoxicity, pancreatitis, myelosuppression
- US Boxed warning: Malignancy

THIOPURINES

Monitoring:

- TPMT testing (enzymatic activity or genotype)
- Therapeutic goal:
  - 6-TG: 235-450
  - 6-MMP: <5700
- Prior to initiating therapy: CBC, BMP, LFT and TPMT
- Initiating treatment: CBC, and LFT every 1-2 weeks for 6-8 weeks. Thiopurine metabolites in 4-6 weeks.
- Dose escalation: CBC and LFT every 1-2 weeks
- Maintenance: CBC and LFT every 12 weeks

TPMT thiopurine methyltransferase

METHOTREXATE

- Folic acid antagonist
  - Interrupts DNA synthesis
  - Inhibits Interleukin
  - Suppress T-cell function
- Formulation
  - Subcutaneous and Oral
- Dosing
  - Induction: 25 mg once weekly
  - Maintenance: 15 mg once weekly
- Add folic acid 1 mg daily

METHOTREXATE

Adverse effects:

- Common: Nausea, increase in LFT
- Uncommon: hepatotoxicity, nephrotoxicity, fever, rash, malaise, vomiting, stomatitis, diarrhea, anemia, leukopenia, alopecia, opportunistic infections
- US Boxed warning: Malignancy, opportunistic infections, hepatotoxicity, impaired drug elimination in renal impaired patients, not recommended for use by women of childbearing age.

METHOTREXATE

Special populations:

1. Liver: Caution advised in hepatic impairment, contraindicated in chronic liver disease, evaluate for any per-existing liver disease before use
2. Renal:
   - CrCl 10-50: Dose reduce by 50%
   - CrCl <10: Avoid use
3. Pregnancy:
   - Contraindicated, teratogenic
   - Recommend 2 forms of birth control
   - Wait 3-6 months after d/c before conception
4. Lactation: Contraindicated
5. Male fertility:
   - Contraindicated
   - Oligospermia
   - Wait 3-6 months after d/c before conception

METHOTREXATE

Monitoring

- Prior to initiating therapy: CBC, BMP, LFT, Pregnancy test
- Initiating treatment: CBC, BUN/Cr, LFT every 2 weeks for 8 weeks
- Dose escalation: CBC, BUN/Cr, LFT every 1-2 weeks
- Maintenance: CBC, BUN/Cr, LFT every 12 weeks

BIOLOGICS

BIOLOGICS

1. Anti-TNF: Infliximab, Adalimumab, Certolizumab, Golimumab
2. Anti-Integrin: Vedolizumab
3. IL 12-23 Antagonist: Ustekinumab

TNF Tumor Necrosis Factor
IL Interleukin

BIOLOGICS: ANTI-TNF

Indication:

- Treats moderately to severely active Crohn's disease and Ulcerative Colitis

Mechanism of action:

- Infliximab is a chimeric monoclonal antibody. It binds to TNF-alpha and inhibits the binding of TNF-alpha to TNF receptor
- Adalimumab and golimumab are fully human monoclonal antibodies against TNF-alpha and, like infliximab, these antibodies bind to TNF-alpha and inhibit its binding to TNFR.
- Certolizumab is a humanized Fab fragment conjugated to polyethylene glycol (PEG)

DOSING

- Infliximab: 5 mg/kg/dose IVx1 on wk 0, 2, 6 then every q8wk
- Adalimumab:160 mg SCx1 on day1, then 80 mg SC x1on day 15, then 40 mg SC q2wk on day 29
- Certolizumab: 400 mg SCx1 on wk 0, 2, 4 then q4wk
- Golimumab: 200 mg SCx1, then 100 mg SCx1 in 2 wk, then 100 mg SC q4wk

BIOLOGICS: ANTI-TNF

Special populations:

1. Renal/hepatic impairment: No recommended dosage adjustments
2. Pregnancy: Risk of teratogenicity not expected
3. Lactation: May use while breastfeeding

BIOLOGICS: ANTI-TNF

Adverse effects:

- Common: Headache, abdominal pain, nausea, elevated liver enzymes, infections, antibody development, upper respiratory infections, sinusitis, infusion-related reaction, injection site reactions.

- US Boxed warning: Serious infections, malignancy.

BIOLOGICS: ANTI-TNF

Monitoring:

- Prior to initiation of therapy: Active and latent TB screening, HBV screening, CBC with Diff, liver and kidney function

- During maintenance therapy: Active and latent TB screening, CBC with Diff, liver and kidney function

BIOLOGICS: ANTI-INTEGRIN

Vedolizumab

Indications:

- Treats moderately to severely active Ulcerative colitis and Crohn's disease
- Formulation: Intravenous
- Dosing: 300 mg IVx1 on wk 0, 2, 6, then q8wk
- No boxed warning

Mechanism of Action:

- Humanized monoclonal antibody that binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MadCAM-1) and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue

BIOLOGICS: ANTI-INTEGRIN

Vedolizumab

Special populations:

1. Renal/hepatic impairment: No recommended dosage adjustments
2. Pregnancy: Caution advised
3. Lactation: No human data available

BIOLOGICS: IL 12-23 ANTAGONIST

Ustekinumab

Indication:

- Treats adults with moderately to severely active Crohn's disease and ulcerative colitis.
- Formulation:
  - Loading dose: one-time intravenous infusion
    - ❖ <55kg: 260 mg IV x1
    - ❖ 55-85kg: 390 mg IV x1
    - ❖ >85kg: 520 mg IV x1
  - Maintenance dose: subcutaneous injection; 90 mg SC q 8 wk

BIOLOGICS- IL 12-23 ANTAGONIST

Ustekinumab

Mechanism of action:

Ustekinumab is a human monoclonal antibody that binds to and interferes with IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses

BIOLOGICS- IL 12-23 ANTAGONIST

Ustekinumab

Special populations:

1. Renal/hepatic impairment: No recommended dosage adjustments
2. Pregnancy: No adverse events based on animal studies
3. Lactation: Unknown, no human data available

BIOLOGICS- IL 12-23 ANTAGONIST

Ustekinumab

Adverse effects:

- Common: Nasopharyngitis
- US Boxed warning: Serious infections, malignancy

Monitoring:

- Prior to initiation of therapy: Active and latent TB screening, HBV screening, CBC with Diff, liver and kidney function
- During maintenance therapy: Active and latent TB screening, CBC with Diff, liver and kidney function

SMALL MOLECULE/JAK INHIBITOR

JAK INHIBITOR

Tofacitinib

- **"JAK" stands for "Janus Kinase"**
- Indication: moderate to severe active ulcerative colitis who have had an inadequate response or who are intolerant to TNF blockers
- Dosing:

  10 mg PO BID x 8 wk, then 5 mg PO BID

  ER: 22 mg PO qd x 8 wk then 11 mg po qd
- Mechanism of action: small molecule, works intracellularly. Inhibits JAK1, 2, 3 leading to disruption of cytokine and growth factor signaling pathway
- Limitation: Use of Tofacitinib in combination with biological therapies or with potent immunosuppressants such as azathioprine is not recommended

JAK INHIBITOR

Tofacitinib

Special populations:

1. Liver:
   - Moderate impairment: 5 mg daily
   - Severe impairment: avoid use
2. Renal:
   - Moderate to severe impairment: reduce dose
   - HD: administer after dialysis
3. Pregnancy: Insufficient human data. Use effective contraception during treatment and for at least 4wk after d/c
4. Lactation: No human data available. Avoid breastfeeding during treatment and for at least 18 hours after last dose

JAK INHIBITOR

Tofacitinib

Adverse effects:

- Common: serious infection, opportunistic infection, Herpes zoster, malignancy, nonmelanoma skin cancer
- US Boxed warning: Serious infections, malignancy
- Recent safety alert: increased risk of thrombosis with 10 mg twice daily dosing

Monitoring:

- Prior to initiation: CBC with Diff, CMP, Hepatitis B, Hepatitis C, TB, lipid panel
- 4-6 weeks after initiation: repeat CBC with diff, CMP, lipid profile
- Labs every 3 months: CBC with diff, CMP

THERAPEUTIC DRUG MONITORING

Indication: if active IBD

Drug	Suggested trough
Infliximab	≥ 5
Adalimumab	≥ 7
Certolizumab	≥ 20

MEASUREMENT OF ANTI-TNF AND ANTI-DRUG ANTIBODIES (ADA)

Anti-drug Antibody (ADA)	**Subtherapeutic drug trough**	**Therapeutic drug trough**
Undetectable ADA	Shorten the dosing interval and/or increase drug dose, and/or add an immunomodulator	Switch to another class of drug
Detectable ADA	-Optimize if low level ADA -Switch to another drug in class and add immunomodulator	Switch to another class of drug and consider adding immunomodulator

Health Maintenance Checklist for Adult IBD Patients

CROHN'S & COLITIS FOUNDATION

Vaccine-Preventable Illnesses	Which Patients	How Often
Influenza (inactive)	All	Annually
Pneumococcal PCV13	If on/planning immunosuppression	Once[1]
Pneumococcal PPSV23	If on/planning immunosuppression	At baseline, repeat in 5 years and again after age 65
Tdap	All	Every 10 years
HPV	All aged 11–26 years	Once[1]
Meningococcal meningitis	All adult patients at risk of meningitis	Once[1]
Hepatitis A	If non-immune	Once[1]
Hepatitis B	If non-immune	Once[1]
MMR (live vaccine)	If non-immune[2]	Once[1]
Varicella (live vaccine)	If non-immune[2]	Once[1]
Herpes Zoster	All aged > 50 years[3]	Once[1]

Cancer Prevention	Which Patients	How Often
Cervical PAP smear	All on systemic immunosuppression[4]	Annual
Skin screen	All on systemic immunosuppression[4]	Annual
Colonoscopy	All with colonic disease for > 8 years	Every 1-3 years

Other Screenings	Which Patients	How Often
DEXA Scan	High risk; women with low BMI, post-menopausal, chronic steroid exposure	At least 2 years apart
PPD or IGRA	Prior to anti-TNF or anti-IL-12/23	Once (repeat if TB exposure)
Smoking status	All	Annual
Depression check	All	Annual

The evidence base for this checklist varies from "insufficient to assess benefits" to "moderate net benefits." Developed by the Crohn's & Colitis Foundation's Professional Education Committee Sub-Group: Alan Moss MD, Francis Farraye MD, MSc, Glenn Gordon MD, Raluca Vrabie MD • Approved by Committee Chairs: Millie Long MD, Samir Shah MD • V3_January_2018

1. Recommended timing and spacing of vaccines available in ACIP recommendation
2. Patients treated with systemic immunosuppressive therapy (steroids, thiopurines, anti-TNFs) should not receive live (attenuated) vaccines e.g. measles, mumps, rubella, nasal influenza, varicella, and yellow fever
3. The CDC's ACIP recommends the subunit vaccine (Shingrix) over the live vaccine (Zostavax), and that Shingrix can be administered to patients who have already received Zostavax. Patients receiving anti-TNFs, anti IL-12/23 or >20 mg prednisone should NOT be given the live zoster vaccine.
4. "Systemic immunopsuppression" currently includes azathioprine, mercaptopurine, methotrexate, anti-TNFs, anti-IL-12/23

ADDITIONAL INFORMATION

- ACG
- ACIP
- ACOG
- AGA
- NCI Skin Screen
- National Osteoporosis Foundation
- PHQ-9 Depression Survey
- US Preventive Services Task Force (USPSTF)

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POLL QUESTIONS

1. Which of the following medication causes worsening of colitis?

    a) Mesalamine
    b) 6-MP
    c) Ustekinumab

2. Which is an active metabolite of thiopurine?

    a) Azathioprine
    b) 6-TU
    c) 6-TG

3. Which of the following is a gut-specific biologic?

    a) Infliximab
    b) Vedolizumab
    c) Adalimumab

Questions ?