GI Pharmacology

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Mari Ikeguchi M.D.

Acid-Peptic Disease Therapies

- Anti-acid agents
  - Antacids
  - Histamine 2 Receptor Antagonists (H_2RA's)
  - Proton Pump Inhibitors (PPI's)
- Mucosal Protectants
  - Misoprostol
  - *Sucralfate*
  - *Bismuth Subsalicylate*
- Prokinetic Agents
  - *Cisapride - withdrawn*
  - *Metoclopramide / Domperidone*
- Antibiotics - H *pylori*
  - Amoxicillin
  - Clarithromycin
  - Metronidazole
  - Tetracycline

GI Pharmacology

- Acid-Peptic Diseases
- Anti-Emetics
- Inflammatory Bowel Disease Therapies
- Pancreatic Enzyme Supplements
- Bile Acid Therapy
- Chronic Viral Hepatitis

Antacids

- Aluminum hydroxide, Mg hydroxide *(Maalox, Mylanta) liquid*
- Calcium carbonate, Mg hydroxide *(Tums, Rolaids)*
- Sodium bicarbonate *(Alka Seltzer*, baking soda*)*
- Weak bases which act to locally neutralize acid, effective for symptom relief
- Place in Therapy
  - Effective (sometimes) in control of episodic GERD, dyspepsia
  - Are not for long term therapy in patients with moderate to severe disease

Acid Peptic Disease

- Dyspepsia: 'indigestion'
  - Defined as chronic or recurrent pain or discomfort centered in the upper abdomen
    - Common ailment, affecting up to 25% of the population over the course of a year, and accounts for 2-5% of visits to internists in the US
    - Nausea, burning, bloating, belching
  - There are 4 major causes of dyspepsia
    - Peptic ulcer disease (15-25%) -peptic ulcer, duodenal ulcers
    - GERD with or without esophagitis (15-25%)
    - Malignancy (2%)
    - Functional or nonulcer dyspepsia (NUD) (60%)

Antacids

- Rapid onset of action, generally short acting, one to two hours
- Side Effects
  - Osmotic Diarrhea-unabsorbed Mg salts
  - Constipation-Aluminum salts
  - Metabolic Alkalosis- absorption of unreacted alkali
  - Sodium overload- especially in patients with heart/renal failure
  - "Milk Alkali syndrome"- excess ingestion of calcium and soluble alkali-like antacids, especially sodium bicarbonate (baking soda) over a prolonged period of time (Rare)

Acid Peptic Disease Therapies

- Antacids
- H 2 Receptor Antagonists
- Proton Pump Inhibitors

Regulation of Acid Secretion

- Basal Acid secretion-variations by age, gender, H. pylori infection
- Food stimulated secretion
- The parietal cell is responsible for gastric acid secretion
- Parietal cell stimulation is mediated by:
  - Histamine (from ECL cells and possibly mast cells in the lamina propria)
  - Gastrin (from the antral/duodenal G-cells) major action is via the ECL cell
  - Acetylcholine (from vagal nerve endings)
- Parietal cell inhibition
  - Somatostatin inhibits acid secretion via inhibition of ECL cell histamine release and G-cell gastrin release
    - Release stimulated by hydrogen ions
    - Release inhibited by Ach

H2 Receptor Antagonists

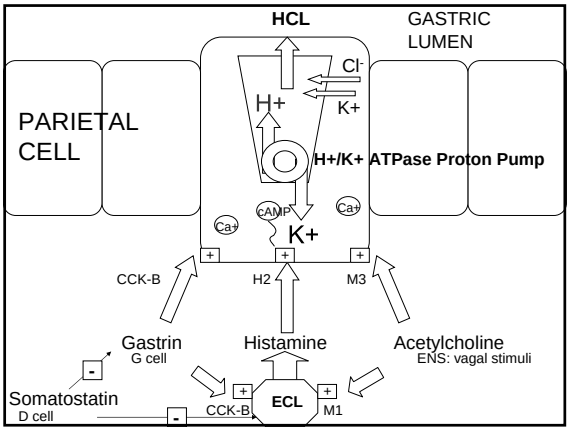
- Introduced in the 1970's, these were the most commonly prescribed drugs in the world
- Currently four in clinical use:
  - Cimetidine (*Tagamet*)
  - Famotidine (*Pepcid*)
  - Nizatidine (*Axid*)
  - Ranitidine (*Zantac*)
- Duration of action around 10 hours, hence BID dosing is commonly given to block 24 hour acid secretion

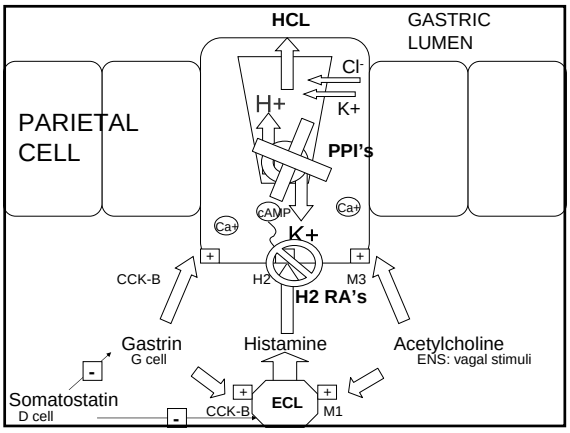
Regulation of Acid Secretion

- The parietal cell basolateral membrane has receptors for three stimulants:
  - Histamine (H2)
  - Acetylcholine (M3)
  - Gastrin (CCK-B/gastrin)
- Following binding, a second messenger is liberated (Ca+, cyclic AMP)
- This second messenger activates protein kinases which result in secretion of HCL whereby hydrogen ions are secreted into the lumen in exchange for potassium ions by action of the proton pump H+/K+ ATPase pump

H2 Receptor Antagonists

- Mechanism of Action: exhibit competitive inhibition of the parietal cell H2 receptor and suppress basal and meal stimulated acid secretion in a dose dependant manner
- They are particularly effective in blocking nocturnal acid secretion (which depends largely on histamine)
- Less effective than PPI's at blocking meal stimulated acid which is stimulated by gastrin, and Ach as well as histamine





Proton Pump Inhibitors

- Introduced in the late 1980's, PPI's are more potent than H2 blockers as suppressors of acid
- Mechanism of Action:
  - They accumulate in the acidic space of the actively secreting parietal cell where they are protonated into the active sulphenamide
  - The sulphenamide forms covalent irreversible disulphide bonds with the H+/K+ATPase pump

H2 Receptor Antagonists

- Place in Therapy
- GERD
- with mild symptoms fewer than 3 times per week / no proven pathology
- Routine uncomplicated ulcer healing (although largely replaced by PPI's)
- PUD in H pylori eradication regimens (Ranitidine-*(Zantac)*, bismuth citrate)
- NSAID induced duodenal ulcer prevention but <u>not</u> gastroprotection
- NUD - acid related, though benefit over placebo not clear
- Mild dyspepsia in general practice (OTC)
- Prevention of stress related gastritis - commonly used in ICU as a continuous infusion

Proton Pump Inhibitors

- Pharmacokinetics:
- Should be taken 30-60 minutes before meals, because they only bind to active proton pumps, and serum half life is short
- Duration of acid inhibition is up to 24 hours due to the irreversible inactivation of the proton pump
- Unlike H2 blockers, PPI's block the final common pathway of acid secretion, the proton pump itself
- They therefore inhibit *both* fasting and meal stimulated acid secretion well - up to 90-98% of 24 hour acid secretion

H2 Receptor Antagonists

- Side Effects
- considered extremely safe drugs
- <1 % and tend to be minor
  - diarrhea, headache, nausea, dizziness, myalgia, rashes
- Cimetidine <3% *(Tagamet)*
  - Confusion, mental status changes (elderly)
  - Anti-adrogenic effects: (increases serum prolactin, inhibits metabolism of estradiol), gynecomastia and impotence in men
- Crosses the placenta, though no known adverse effects on the fetus
- Drug Interactions
- Most reports are with Cimetidine
- Cimetidine Inhibits cytochrome P-450 enzyme system
- Potential to ↓ metabolism ∴ ↑ concentration and possibly toxicity of some drugs
- examples include
  - warfarin
  - phenytoin
  - theophylline
  - Cyclosporine
  - propranolol

Proton Pump Inhibitors

- Omeprazole: *(Prilosec)* 10, 20, 40mg PO/IV
- Lansoprazole: *(Prevacid)* 15, 30mg PO
- Rabeprazole: *(Aciphex)* 20mg PO
- Pantoprazole: *(Protonix)* 40mg PO/IV
- Esomeprazole: *(Nexium)* 20mg, 40mg PO/IV

- Only omeprazole available as a generic in US

Proton Pump Inhibitors

- Frequency of dose depends on indication
  - Once daily
    - PUD / GERD healing
    - initial symptom control
    - Maintenance
    - NSAID prophylaxis/gastroprotection
  - Twice daily
    - H *pylori* eradication regimens
    - severe / complicated GERD (med to long term)
    - severe / complicated PUD (short term)

Proton Pump Inhibitors

- Side Effects:
  - Generally well tolerated and safe as a class of drugs
  - Headache, diarrhea, abdominal pain, and nausea and constipation and bloating
  - Category B in pregnancy
- Interactions:
  - May inhibit cytochrome P-450 metabolism to various degrees
  - May interact with other medications by affecting the absorption of drugs which are dependent upon low gastric pH (e.g. iron, digoxin, and ketokonazole)
- Long term side effects:
- Gastric acid is an important barrier to colonization and infection of the stomach from ingested bacteria
- Hypochlorhydria with ↓'d acidity, may ↑ enteric infection risk (Salmonella, Shigella)
- Theoretical concerns regarding Hypergastrinemia
  - Gastric carcinoids
  - Not established

PPI's: Clinical Indications

- Place in Therapy:
- GERD:
  - Considered the most effective agents for both erosive and nonerosive reflux disease with respect to healing and for management of severe symptoms (i.e.-erosive esophagitis, strictures, Barretts
- PUD:
  - H pylori associated ulcers: Healing, and eradication of organism
  - Gastric prophylaxis in patients who continue to take NSAIDs and are high risk (elderly, prior PUD, etc.)
- NUD: modest efficacy (10-20%) over placebo

Mucosal Protective Agents

- Sucralfate: sulfated polysaccharide complexed with aluminum hydroxide *(Carafate)*
  - Acts locally by binding to erosions, ulcers to promote healing via angiogenesis and granulation tissue formation
  - Used in healing of gastroduodenal ulcers and prophylaxis of stress ulcers
- Misoprostil: prostaglandin analog (PGE1) *(Cytotec)*
  - Stimulates gastric mucosal blood flow
  - Used in prophylaxis of NSAID induced gastroduodenal ulcers
  - Contraindicated in pregnancy, stimulates uterine contractions
  - Causes diarrhea (common) and cramping abdominal pain
- Bismuth subsalicylate: *(Pepto Bismol)*
  - Bactericidal against H. pylori in combo with antibiotics
  - Acts locally to coat erosions, ulcers and provides a mechanical protective layer against acid
  - Stimulates gastric bicarbonate, mucous secretion
  - Turns stool black

PPI's: Clinical Indications

- Adjunct to Endoscopic therapy: in the prevention of re-bleeding in patients with acute GIB from peptic ulcers
  - Improvement in outcomes in upper GIB (coagulation improves with elevation pf pH)
    - Continuous Infusion: Complicated PUD where high risk of rebleed (vv, adherent clot) Lau et. al. Effect of IV omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. NEJM Aug 3 2000, 343;5:310-316
- Stress Ulcer prophylaxis
- Gastrinoma and other hypersecretory states, typical doses of Omeprazole are 60-120mg/d, and dosage is titrated to reduce basal acid output to less than 5-10meq/h

Anti-Emetics

- Nausea, Vomiting
- Five sources of input to the vomiting center
  - Chemoreceptor trigger zone-emetogenic stimuli in the blood or CSF
  - Vestibular system-motion sickness
  - Pharyngeal irritation - gag and retch response
  - Vagal and Enteric afferents - chemo, RT, infectious gastroenteritis, distension
  - Central nervous system-stress, psychiatric disorders, anticipatory vomiting due to chemo

Anti-Emetics

- Serotonin 5-HT3 Antagonists
  - Ondansetron – *(Zofran)*, Granisetron – *(Kytril)*, Dolasetron – *(Anzemet)*
  - Block peripheral and central 5HT-3 receptors
  - Useful in nausea associated with chemotherapy, post-op, and post-radiotherapy induced
  - Cause QT prolongation
- Phenothiazines-antipsychotic agents
  - Prochlorperazine – *(Compazine)*, Promethazine – (*Phenergan)*, Thiethylperazine
  - Block dopamine, histamine, and muscarinic receptors

IBD Drugs

- Anti-Inflammatory Medications
  - Aminosalicylates 5-ASA
- Glucocorticoids
- Purine Analogs
- Methotrexate
- Cyclosporine
- TNF-Inhibitors

Anti-Emetics

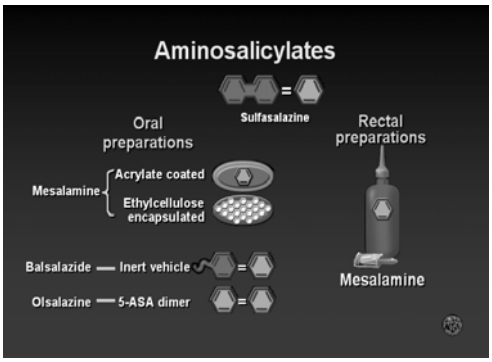
- Substituted Benzamides
  - Metoclopramide – (*Reglan)*, Trimethobenzamide – (*Tigan)*
  - Dopamine receptor blockade
  - Metoclopramide is also a prokinetic agent mediated through cholinergic stimulation
  - Extrapyramidal side effects - tardive dyskinesia which can be irreversible, Parkinsonian symptoms, restlessness limit their use

IBD Drugs

- Aminosalicylates (5-ASA) are the most commonly used initial medications for IBD
- 5-ASA: 5-amino-2 hydroxy benzoic acid
- Salicylate with an amino group at the 5-position
- Azo compounds
- Mesalamine
- Come in many forms including pills, enemas, or suppositories

Inflammatory Bowel Disease

- Ulcerative Colitis
- Crohn's Disease
- Chronic lifelong diseases with acute flares alternating with remission
- More than 1 million cases in the U.S.
- Prevalence: 100 cases per 100,000 population



IBD Drugs

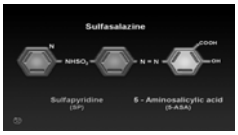
- Azo compounds: refers to 5-ASA bound by an azo bond (N=N) to another 5-ASA or to an inert compound
  - Oral: Sulfasalazine, Olsalazine, Balsalazide
- Mesalamine: refers to single molecule 5-ASA formulations packaged to deliver drug to different segments of the small or large intestine
  - Oral mesalamine: (*Asacol, Pentasa)*
  - Suppository mesalamine: (*Canasa)*
  - Enema mesalamine: (*Rowasa)*

Mesalamine compounds

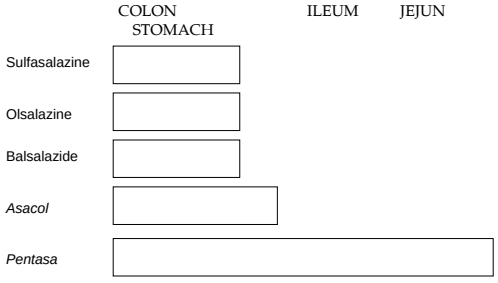
- Single molecule 5-ASA
- *(Asacol)*
  - 5-ASA capsule in a pH dependent polymer eudragit s-resin
  - Polymer dissolves at pH 7 in the terminal ileum and cecum
- *(Pentasa)*
  - 5-ASA in ethylcellulose coated granules allows for time and pH dependant release throughout the GI tract

Sulfasalazine

- Sulfasalazine: (*Azulfidine)* the first aminosalicylate used for IBD
  - A two part molecule with 5-ASA bound to sulfapyridine
  - It depends on bacterial cleavage of the azo bond in the colon to deliver locally acting 5-ASA
  - High incidence of side effects due mainly to the sulfapyridine molecule: up to 40% of patients cannot tolerate therapeutic doses
- Side Effects:
- GI upset, headaches, myalgias, bone marrow suppression, hypersensitivity reaction (due to sulfapyridine), pancreatitis
- Oligospermia (reversible)

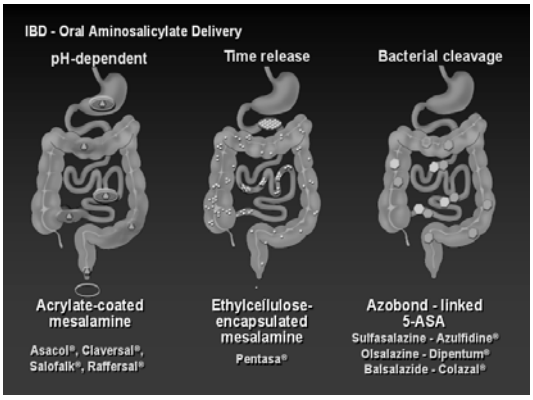


Location of 5-ASA Release



Azo compounds

- Sulfasalazine: *(Azulfidine)*
- Clinical use:
  - Ulcerative Colitis: used in induction of remission in mild to moderately active disease and for maintenance of remission
  - Crohn's Disease: use is limited to patients with mild to moderate colitis, ileocolitis,
    - maintenance of remission unproven
- Newer Azo compounds: deliver 5-ASA without the toxicity of the sulfapyridine moiety
  - Balsalazide: 5-ASA linked to an inert carrier *(Colazal)*
  - Olsalazine: 5-ASA dimer *(Dipentum)*
  - Olsalazine not used for active UC as it stimulates a secretory diarrhea

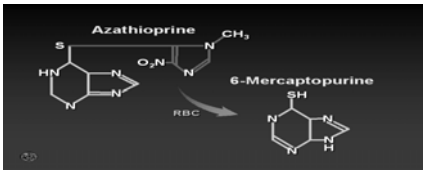


Glucocorticoids

- Are highly effective in the treatment of acute attacks of Ulcerative colitis and Crohn's
- Place in Therapy: Flares
  - Induction of remission of moderate to severely active UC and CD
- Can be given orally, intravenously, or topically (for distal colitis)
- Block inflammatory responses via inhibition of inflammatory cytokines and inhibit cellular functions of lymphocytes, macrophages

Purine Analogs

- Azathioprine is a prodrug that gets converted to 6-MP
- Active UC and CD, maintaining remission, and is steroid sparing



Glucocorticoids

- Short and long term adverse effects:
  - Moon facies, acne, HTN, hirsutism, psychosis
  - Diabetes, infection, cataracts, glaucoma, avascular necrosis
- Budesonide: *(Entocort)* FDA approved in 2001
  - newer oral steroid with 90% first pass metabolism in the liver (significantly fewer side effects)
  - mild to moderate ileo-cecal Crohn's disease (at least 3 controlled studies show benefit c/w placebo at the 9mg/d dose)
  - Is of value in maintenance therapy to prevent flares
- Formulations: oral, or rectal enema preparation for topical treatment of Ulcerative colitis

Purine Analogs

- Role of monitoring therapy
- Complete blood cell counts and hepatic enzymes every one to two weeks and then monthly
- Side Effects: Cause bone marrow depression, especially leukopenia, and hepatotoxicity

Purine Analogs

- Azathioprine: *(Imuran)*
- 6-Mercaptopurine: *(Purinethol)*
- Oral immunosuppresive agents, purine antimetabolites, used in concert with 5-ASA therapy to take patients off steroids, can help close CD fistula, and prevent relapse
- They interfere with nucleic acid synthesis in white blood cells, especially in T-lymphocytes which are important in the production of mediators of inflammation
- Onset of therapeutic benefit not seen for 4-6 weeks

Methotrexate

- Antimetabolite, it inhibits dihydrofolate reductase thus inhibiting productionof thymidine and purines
- Stimulates apoptosis of activated Tcells and may interfere with IL-1
- Clinical Indication: Patients with steroid refractory/dependant CD or patients who fail to respond or are intolerant of 6MP, Azathioprine
- Induction and maintenance of remission in CD
- Efficacy in UC uncertain
- Side effects: liver toxicity, bone marrow suppression, pulmonary fibrosis

Cyclosporine

- Immunosuppressive agent, inhibits production of IL-2 by T-lymphocytes
- Most useful in severe UC refractory to steroids
- Not useful for Crohn's Disease at low dose, and more patients worsened as compared to placebo, not effective for maintenance in CD/UC
- IV: 4mg/kg
- May delay surgical colectomy in cases of toxic megacolon, "bridge" therapy
- Side effects: Nephrotoxicity, neurotoxicity-headaches, tremors, paresthesias, seizures

TNF-Inhibitors

- Adalimumab: (*Humira)* A recombinant *humanized* IgG1 monoclonal antibody
- Human monoclonal antibodies (human anti-human antibodies HAHAs)are less immunogenic than chimeric monoclonal antibodies
- Administered subcutaneously

TNF-Inhibitors

- Infliximab: (*Remicade)* A chimeric IgG1 mouse-human monoclonal antibody to TNF-alpha
- It binds to soluble and membrane-bound TNF- with high affinity, impairing the binding of TNF- to its receptor
- Infliximab also kills cells that express TNF- through antibody-dependent and complement-dependent cytotoxicity
- It has been shown to be effective for patients with moderate to severe Crohn's disease and more recently for Ulcerative Colitis as well for both short and long term treatment

Pancreatobiliary

- Pancreatic Enzyme Supplements
  - Pancrealipase: lipase, amylase, protease, available in both non-enteric coated and enteric coated preparations
    - Non-enteric coated formulations (*Cotazym, Viokase*) - must be given with acid suppression to prevent destruction by gastric acid
    - Enteric coated formulations (*Creon, Pancrease, Ultrase*) taken with meals, snacks

Infliximab

- Drawbacks
- Infliximab is immunogenic
- Intermittent administration results in human anti-chimeric antibodies (HACAs, a.k.a-antibodies to infliximab ATI)
- Antibodies to Infliximab ultimately can lead to infusion reactions, delayed hypersensitivity reactions, and loss of efficacy
- Infection: reactivation of latent TB, patients must undergo PPD testing

Pancreatic Enzymes

- Place in Therapy:
  - Management of pain and malabsorption, steatorrhea
- Dosing:
  - Based on age and weight of patient, degree of pancreatic insufficiency, dietary fat intake
- Side effects: oral mucositis, abdominal pain, diarrhea, hyperuricosuria

Bile Acid Therapy

- Ursodeoxycholic Acid, UDCA *(Urso)*
- The most hydrophilic of all bile salts
- Least toxic of all bile salts
- Giving *Urso* reduces the overall toxicity of the bile salt pool
- Place in Therapy:
- Gallstone dissolution therapy
- Primary Biliary Cirrhosis
  - Changes the composition and cholesterol content of the existing bile acid pool
  - It decreases the biliary secretion of cholesterol and unsaturates bile
  - Can promote solubilization of cholesterol in liquid crystals promoting dissolution

Hepatitis B

- Interferon *(Roferon-A alpha 2a)* *(Intron-A alpha 2b)*
- Lamivudine *(Epivir)*
- Adefovir *(Hepsera)*

Viral Hepatitis

- Hepatitis B
- Hepatitis C
- Immunomodulators
- Nucleotide/Nucleoside Analogs
- Guanosine Analog

Hepatitis B Treatment

- Interferon alfa preparations
- Interferons were the first drugs approved for Hepatitis B treatment in the US
- Interferon: naturally occurring glycoprotein that is secreted by cells in response to viral infections
- It exerts its effects by binding to a membrane receptor which leads to expression of genes that induce target cell killing by lymphocytes and inhibition of viral replication

Hepatitis B

- Hepatitis B: 1-1.2 million carriers in the US, 400 million worldwide, 2 billion have been infected
- Patient Selection
  - Chronic Hepatitis B (sAg for at least 6 months)
  - Evidence of Active replication (HBeAg+ 'replicative,' or high levels of HBV DNA) and raised serum aminotransferases
- Goals of therapy
  - Suppression of viral replication
  - Hep BeAntigen seroconversion to HBeAb
  - Improvement in hepatic necroinflammation
  - Reduction in long-term sequela of HBV associated disease (cirrhosis, HCC)

Hepatitis B Treatment

- Interferon alfa preparations
  - IFN-alpha 2A *(Roferon)*
  - IFN-alpha 2B *(Intron)*
  - PEG-IFN alpha 2a (*Pegasys)*
- IFN alpha treatment
  - leads to normalization of serum aminotransferases, sustained histologic improvement, reduced risk of cirrhosis
- Antiviral, antiproliferative and immunomodulatory effects
- Administered by subcutaneous injection
- Treatment duration generally 16 weeks

Hepatitis B

- IFN Side Effects:
- The major side effect is flu-like symptoms within hours of each injection- fever, mylagias, chills, headache
- Other side effects: renal failure, depression, thrombocytopenia, neutropenia, cardiotoxicity, limits its use
- A flare in hepatitis will be seen in many patients as well with increases in serum aminotransferases seen
  - Felt to be due to an immunologically mediated attack on HBV infected hepatocytes
- Patients with decompensated cirrhosis and poor hepatic reserve are poor candidates for IFN and it is to be avoided

Hepatitis B

- Adefovir: Nucleotide analog (*Hepsera)*
- Competitively inhibits HBV DNA polymerase and results in chain termination
- Maintains activity against lamivudine resistant strains of HBV
- Resistance occurs at a rate of about 1-4%/year
- Renally excreted, dose reduction in renal insufficiency necessary
- Expensive
- Well tolerated with few side effects

Hepatitis B : Oral agents

- Lamivudine, Adefovir, Tenofovir, Entecavir
- Lamivudine: (3TC *Epivir*) orally administered nucleoside (cytosine) analogue
- Inhibits HBV reverse transcription and terminates the HBV nascent proviral DNA chain
- Dose: 100mg tablet daily and administered for one year or longer
- Results: hepatic necroinflammatory activity improves, serum ALT normalizes in 40-70% of patients, loss of HBV DNA, HBeAg conversion (minority)

Hepatitis B

- Tenofovir: nucleotide (adenosine) analogue *(Viread)*
- Entecavir: nucleoside analog (*Baraclude)* approved in early 2005 was shown to be superior to lamivudine in improvement of histology, viral load reduction, and normalization of ALT
- Future: Combination therapy for Hepatitis B; IFN + lamivudine or adefovir is under investigation

Hepatitis B : Oral agents

- Lamivudine:
- Drawbacks: Treatment is associated with the development of resistant strains
  - 15-50% by three years
- Well tolerated

Hepatitis C

- The most common cause of chronic viral hepatitis in the United States
- Genotype 1a and 1b account for 70-75% of HCV in the US
- By the 1990's chronic Hep C had become the single most common form of liver disease for which liver transplantation has been undertaken
- 75-85% of patients with acute HCV infection will progress to chronic infection

Hepatitis C

- Patient Selection:
  - HCV RNA positive
  - Elevated or Normal ALT level
  - Evidence of active inflammation on liver biopsy
- Goals of Therapy:
  - To eliminate detectable viral RNA from the blood, thereby eliminating infectivity
  - Decrease ongoing HCV induced liver injury
  - Reversing or interrupting hepatic fibrogenesis to prevent progression to end stage liver disease
  - Lack of detectable hepatitis C virus RNA from blood six months after completing therapy is known as a sustained viral response (SVR)
  - Studies suggest that a sustained response is equated with a very favorable prognosis and that it may be equivalent to a cure

Hepatitis C

- Ribavirin *(Rebetol)*
- Given orally in conjunction with subcutaneous IFN
- Guanosine analog it appears to interfere with viral RNA dependant polymerase
- Side effects: Dose dependent hemolytic anemia that may be dose limiting, depression, fatigue, pruritus, rash, insomnia
- Absolute contraindications: anemia, renal/cardiac failure, pregnancy

Hepatitis C

- Current Standard of care is Combination Therapy:
- Pegylated Interferon plus Ribavirin
- PEG-IFN:
- IFN with a polyethylene glycol (PEG) moiety attached by a covalent bond resulting in reduced clearance and increased half-life allowing for less frequent dosing (once weekly rather than three times per week)

Hepatitis C

- FDA Approved Therapies:
  - PEG-IFN + Ribavirin
- Efficacy of pegylated IFN superior to non-pegylated interferons
- Duration 6 months to a year depending on HCV genotype
- Genotype 1: appears more resistant and therefore one year of treatment recommended
- Genotypes 2,3: 6 months of therapy
- SVR: 45-85% of patients
- Failure to clear HCV RNA or induce a 2 log reduction by 12 weeks predicts non-responsiveness
  - "12 week stop rule"