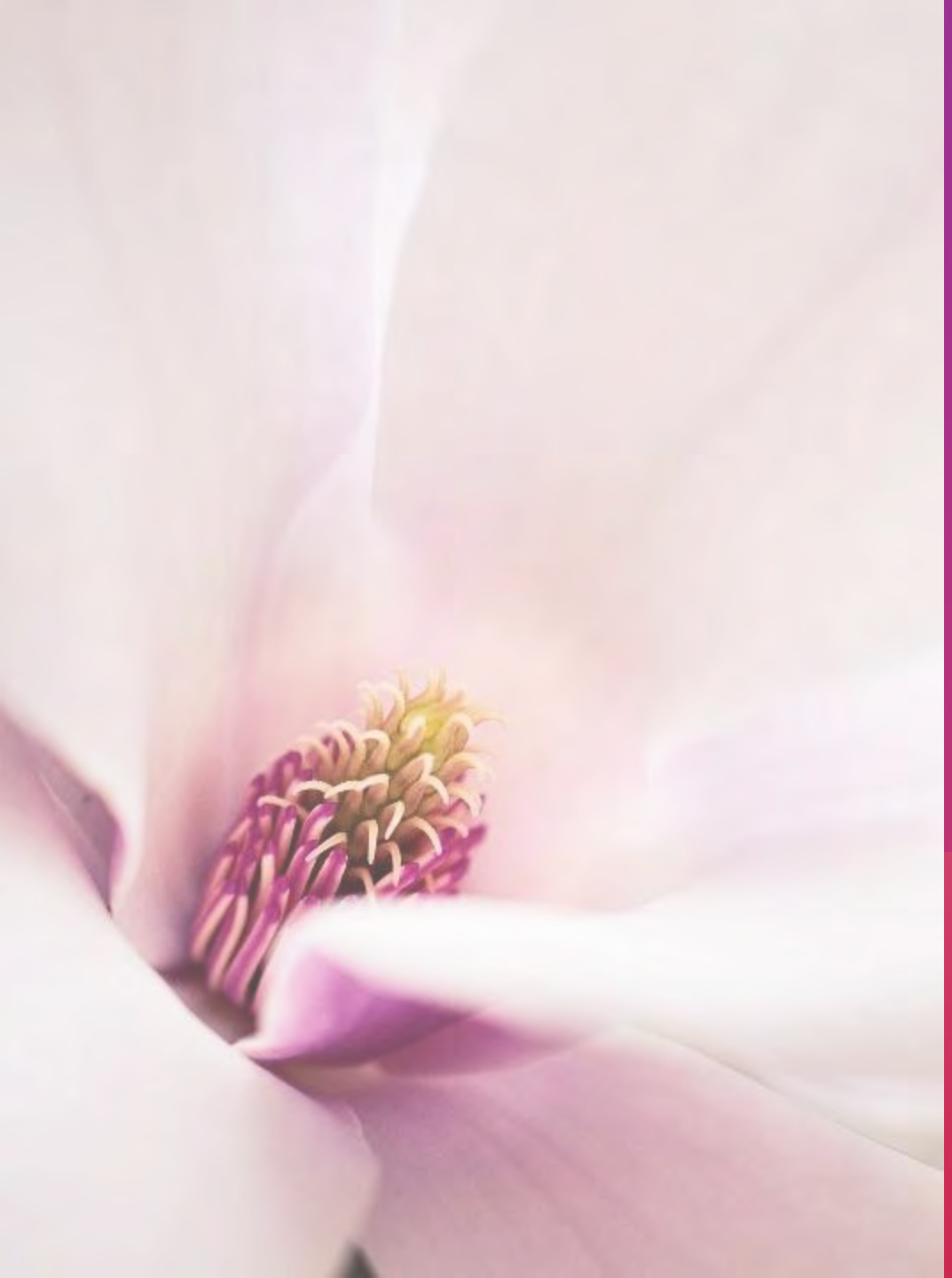


CONVENTIONAL THERAPY IN INFLAMMATORY BOWEL DISEASE(IBD)

DR MIDHUN THOMAS JOHN

CHARLOTTE MAXEKE ACADEMIC HOSPITAL

CONVENTIONAL THERAPIES OF IBD

- Aminosalicylates
- Glucocorticoids
- Immunomodulators
  - Thiopurines
  - Methotrexate
  - Cyclosporin
  - Tacrolimus

TARGETS FOR THERAPY

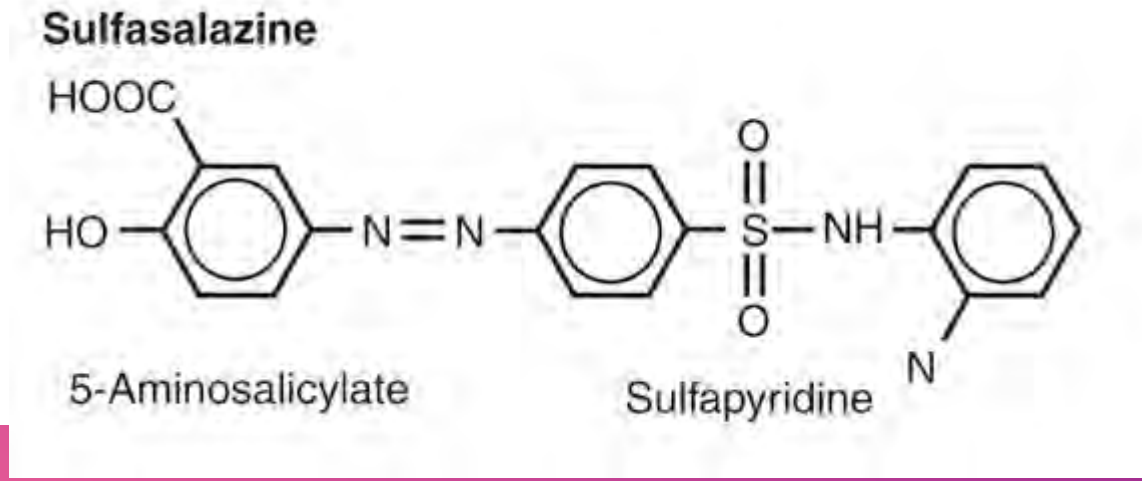
General Principles of IBD

- Endoscopic Healing
- Clinical Response
- Biochemical Response
- Radiological/Transmural Healing

Turner et al. Stride-II. An update on selecting therapeutic targets in IBD

AMINOSALICYLATES (ASA)

- Sulfasalazine (parent compound of all ASA), was developed by Swedish physician-Nanna Svartz in 1938 to 1939 for treatment of Rheumatoid Arthritis
- She was the first female professor at a public university in Sweden and focussed research of GI diseases and rheumatology
- 1941-1942: found that whilst treating arthropathy, colitis improved
- SFZ-comprises of ASA and Sulfapyridine (prevent absorption of ASA in the small intestine but causes most adverse events



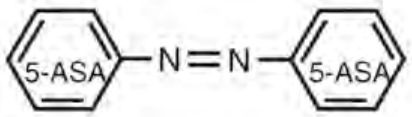
Sleisenger et al. Management of IBD

AMINOSALICYLATES (ASA)

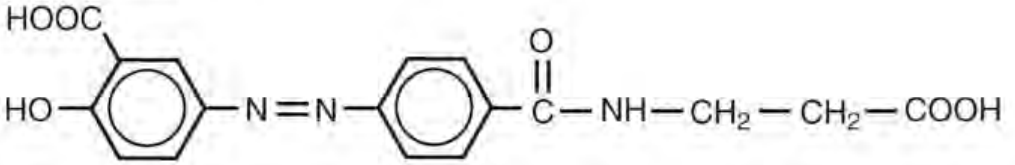
- Dr Azad Khan
  - 1977: a classic experiment that revealed that the active metabolite was the ASA and not the sulfapyridine
  - 90% absorbed in colon and small amount in small intestine
  - Upon reaching colon-azoreductase enzyme from anaerobic bacteria: cleaves the azo bond to ASA
  - 5 ASA then acts topically and some absorbed
  - Other drugs like Olsalazine and Balsalazide-also with azo bond linkage

- Adverse events of Sulfasalazine
  - Fever, rash, nausea, vomiting and headache
  - Other-hypersensitivity reactions, reversible sperm abnormalit (therefore provide folate supplementation)

Olsalazine



Balsalazide



Sleisenger et al. Management of IBD

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Drug	Formulation	Site of delivery
Prodrugs		
Balsalazide	4-aminobenzoyl β-alanine + 5-ASA	Colon
Olsalazine	5-ASA dimer	Colon
Sulfasalazine	Sulfapyridine + 5-ASA	Colon
Mesalamine Preparations		
Asacol, Claversal, Delzicol Salofalk/Apriso	pH sensitive, resin-coated; delayed release	Distal ileum, colon
Canasa	Suppository	Rectum
Lialda	pH sensitive, multi-matrix and polymethacrylate coated; delayed and slow release	Distal ileum, colon
Pentasa	Ethylcellulose-coated microgranules; controlled release	Duodenum to colon
Rowasa	Enema	Distal colon

AMINOSALICYLATE (ASA)

- Crohn's disease
  - Limited data supporting role of ASA
  - Most studies show Sulfasalazine to be superior to placebo in inducing remission in active CD (when the colon is the primary site affected)

  - BSG-not recommended for induction and maintenance

  - CONCLUSION: Not effective and excluded from recent evidence based treatment algorithms; individual case by case use

AMINOSALICYLATE (ASA)

- Ulcerative Colitis
  - Demonstrated efficacy for induction and maintenance of remission in mild to moderately active UC
  - At dose 3 to 6 g/day-induces remission in 39% to 62% of patients (twice the remission rate of placebo)
  - Cochrane reviews: ASA induction and remission of 53 studies with 8548 patients→ 29% of ASA entered clinical remission compared to placebo 17%
  - BD/TDS dosing compared to daily dosing showed no difference

  - ASCEND I and II trials
  - ASCEND III and Lialda trials
  - Momentum trial

AMINOSALICYLATE (ASA)

Rectally-Administered Therapies

- 5 ASA enemas, 5-ASA suppositories and 5-ASA foam
- Delivers drug up to the splenic flexure in 95% of patients
- Treats inflammation at around 15-20 cm from anal verge
- May use for Ulcerative Proctitis or left sided colitis; or as an adjunctive to oral therapy
- Standard dose-1 to 4 g of 5-ASA enema per night OR mesalamine suppositories 1-1.5 g daily or divided doses
- Preferred over topical glucocorticoids in distal UC
- Combination with oral mesalamine-more effective

AMINOSALICYLATE (ASA) and BSG 2025

Ulcerative Colitis

- Proctitis treated with topical 5-ASA therapy
  - If no response then add oral 5-ASA or topical corticosteroids
- Entry treatment for mild to moderate
- 5-ASA dose of >/= to 2g/day for induction and maintenance of remission (conventional doses of 1.5-2.4g/day)
- No RCT for higher doses (3-4.8g/day) but if severe disease or no response, then to use
- Combining oral and topical has better efficacy

GLUCOCORTICOIDS

- Effective and rapid induction of clinical improvement BUT prolonged use and repeated use→ adverse events
- Infectious risk is increased on higher doses of >40mg daily
- Not recommended for long term use
- Budesonide, with high hepatic first pass metabolism, low systemic steroid exposure and fewer adverse events → appealing

GLUCOCORTICOIDS

- Principles of use:
  - Use and effective dose (40-60 mg daily)
  - Do not overdose (more than 60mg daily often has no added benefit)
  - Do not treat for excessively long periods
  - Anticipate side effects-use adjunctive therapies

GLUCOCORTICOIDS

Crohn's Disease

- Favourable according to NCCDS in the short term (0.5 to 0.75 mg/kg/day) for initial treatment of active disease with dose adjustment according to CDAI
- ECCDS in short term reports 48mg/day in the first week, tapered by 12mg by week 6 and held at 8 mg for remission up to 2 years
- Usually patients with mild to moderate active disease treated initially with 40 mg to 60 mg of prednisone then tapered over 6 to 12 weeks→ response rate approximately 80% by the end of the first month
- When doses are pushed to 1 mg/kg/day for up to 7 weeks, 92% of patients can achieve clinical remission
- Not effective for long term therapy and can lead to glucocorticoid dependence

GLUCOCORTICOIDS

Systemic corticosteroids are suggested for induction of remission in patients with moderate to severe Crohn's disease.
Budesonide is suggested for the induction of remission in patients with mild ileocaecal Crohn's disease with treatment for not more than 12.
Corticosteroids are not recommended for maintenance of remission in patients with Crohn's disease.

Crohn's Disease

- Budesonide is structurally different from prednisone-90% first pass metabolism in the liver and erythrocytes and is converted to metabolites that have little biologic activity→ low systemic bioavailability = less toxicity
- Entocort:
  - Controlled ileal release oral budesonide preparation with Eudragit L 100 coated microgranules with an internal ethyl cellulose component
  - Releases at pH >5.5 and 50-80% absorbed in the ileocaecal region
  - Studies show 9 mg/day is superior to placebo and mesalamine; 15% less effective than prednisolone in achieving remission BUT with fewer side effects
  - RCT compared 6 mg to 9 mg at 12 months→ showed low relapse rates (24% and 119% respectively)
  - Meta-analysis showed that active luminal CD was superior over placebo in inducing remission BUT not in preventing relapse
- Overall→ Use only with induction with an immunomodulator or biologic agent; do not use for more than 12 weeks

GLUCOCORTICOIDS

Ulcerative Colitis

- 40-60 mg/day is used for moderately to severe UC
- Budesonide for induction of remission where ASA failed or not tolerated, and to avoid more potent adverse events
- Higher doses associated with adverse events without any significant benefit
- Not many studies comparing oral to parenteral; however parenteral used for severe cases
- In a double blind study-continuous infusion was no better than divided doses
- No maintenance benefits
- Rectally-Administered:
  - Liquid and foam formulations are effective short term therapy for active UC distal to splenic flexure
  - Foam is easier to retain and tolerated
  - Topical mesalamine and steroids have been more efficacious together then alone in distal UC

GLUCOCORTICOIDS AND BSG 2025

Ulcerative Colitis

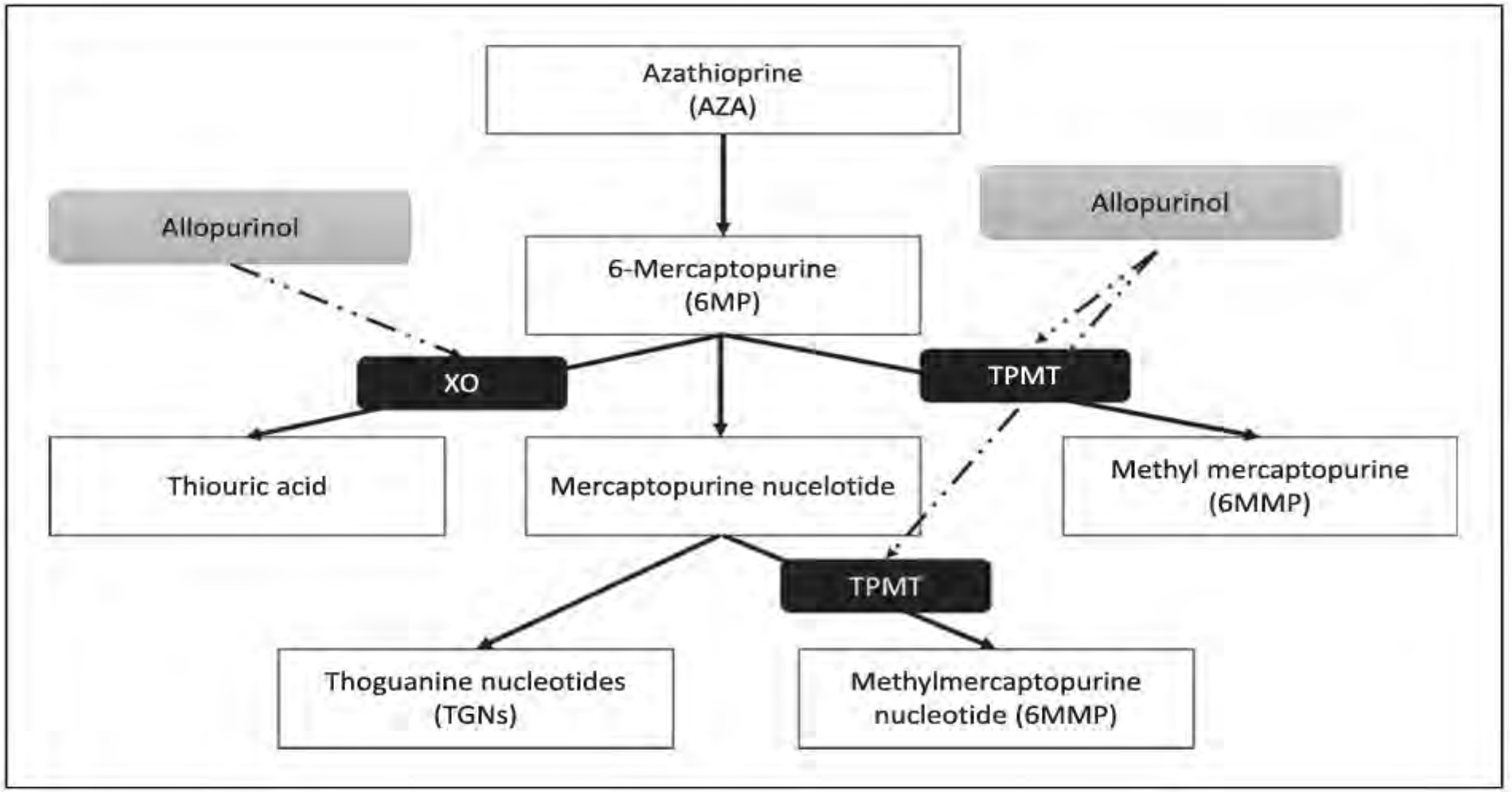
- Prednisolone is recommended for induction of remission in moderate to severe UC
- Lack of trial data-optimal dose starts at 40 mg then dose reduction of 5 mg per week to 0 mg
- Once daily recommended with morning and food to prevent sleep disturbances and mitigate dyspepsia
- Calcium and Vitamin D recommended unless contraindicated
- Concomitant supportive therapies can be started like PPI
- Beclomethansone dipropionate and MMX is suggested for induction of remission in patients with UC where 5-ASA therapy failed or not tolerated; and wish to avoid side effects of systemic steroids

THIOPURINES

- 1951- Introduced by Elion and Hitching: cytotoxic and immunosuppressive effect
- 1960s-Brooke and Bowen: Effective in refractory IBD patients
- 1980- placebo controlled trial showed superiority in induction and maintenance of remission
- 1993- 20 year clinical trial: over 60% on thiopurine therapy were in steroid free remission

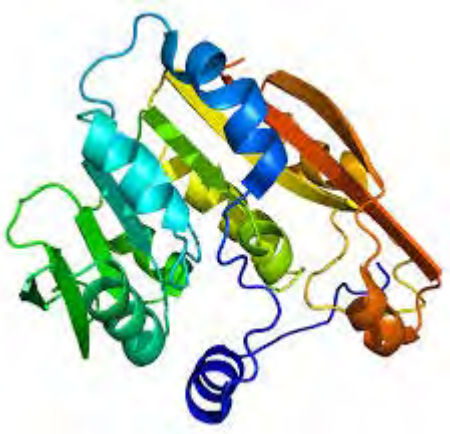
- Most widely used immunomodulator-Azathioprine (AZA) and 6-mercaptopurine (6-MP)
- Purine analogs that interfere with nucleic acid metabolism and cell growth→ exerts cytotoxic effects on lymphoid cells

THIOPURINES



THIOPURINES

- Monotherapy-not recommended due to the slow onset of action
- Use in induction of remission with a faster acting efficacious drug like corticosteroids (CS)
- Always check TPMT
- Recently associations with Asian ancestry-NUD15 genetic polymorphism-early myelosuppression
- Considered:
  - CS-dependant patients
  - Post-operative prophylaxis of CD recurrence
  - Maintenance strategy after cyclosporine rescue therapy
  - Concomitant immunosuppression during biological therapy



THIOPURINES

- Standard dosing:
  - 2-2.5 mg/kg daily
  - Steady state 14 days
- Therapeutic drug monitoring:
  - Recommended
  - Concentrations of 6-thioguanine above 250 pmol/8x10^8 red blood cells correlate with therapeutic efficacy in both CD/UC
- Adverse reactions: (rare)
  - Leukopenia, myelotoxicity, hepatotoxicity and acute pancreatitis
  - Low TPMT: myelosuppression and High TPMT: hepatotoxicity
  - Nonmelanoma skin cancer

THIOPURINES

- Malignancy Risk
  - Non-Hodgkin Lymphoma, hepatosplenic T-cell lymphoma and primary lymphoproliferative intestinal disorders, non-melanoma skin cancers and urinary tract cancers
  - Increased risk (therefore use is discouraged)
    - Age >65
    - Young patients with negative IgG serology to EBV

- Pregnancy and Lactation
  - Low risk drug and to be continued if used as a monotherapy
  - If used with anti-TNF, then rather advisable to stopping (individualised)

THIOPURINES

Thiopurines in Crohn's Disease

- Cochrane analysis of AZA and 6-MP in CD
  - Active disease-remission rate of 47% vs placebo 37%
  - Odds ratio for response increased after 17 weeks of treatment
  - Overall- 50% of patients may responds to thiopurine therapy. Once in remission, about 50% tp 66% of patients will maintain that response
- If not responding to thiopurines after 3-4 months then useful to measure metabolite levels
- SONIC Trial
- BSG- not suggested for use as monotherapy in induction and maintenance of remission in moderate to severe CD

THIOPURINES

Thiopurines in UC

- Not much data to support efficacy of AZA
- 4 RCT's noted but they were small studies and reached different conclusions
- One subset of patients with severe active UC who maintain remission with induction of cyclosporin→ studies showed that maintenance therapy with AZA reported to decrease colectomy rates

- BSG:
  - Purine analogues not suggested for induction of remission; but are suggested for maintenance of remission in patients with moderate to severe UC-once remission is achieved
  - Withdrawal of purine analagoues as monotherapy or combination therapy has a risk of relapse

METHOTREXATE

- Cytotoxic effect due to inhibition of dihydrofolate reductase, inhibition of pro-inflammatory cytokines and increased production of regulatory cytokines
- CD
  - Large RCT compared MTX SC to placebo with tapering steroids-overall 39.4% of patients assigned to MTX achieved remission off prednisone compared to 19.1% of placebo
  - Follow up study to RCT-lower dose of MTX given and at week 40, 65% still in remission. Therefore MTX beneficial at inducing and maintaining remission
  - MTX given with folic acid; not suitable for pregnancy
- UC
  - Lacked data to prove efficacy for treatment of active UC
  - METEOR trial-compared steroid dependant UC with MTX vs placebo with no statistic significance in steroid free remission or endoscopic healing
  - However patients more likely to be in clinical remission on MTX vs placebo
  - MERIT-UC trial further proved no difference in active treatment and placebo
  - BSG guidelines-not suggested in moderate to severe UC

METHOTREXATE AND BSG 2025

Crohn's Disease

- Not for monotherapy treatment for induction and maintenance of remission for moderate to severe CD

Ulcerative Colitis

- Not suggested for induction and maintenance of remission in patients with moderate to severe UC

CALCINEURIN INHIBITORS

- Cyclosporine:
  - Potent inhibitor of cell mediated immunity
  - Its use is mainly in acute severe, steroid refractory UC-covered in talk of management to ASUC
  - Little role in CD

- Tacrolimus:
  - Absorbed more reliably from the intestine than cyclosporine
  - Concern is the toxicity and its associated side effects
  - Only one RCT of tacrolimus in UC with 63 Japanese patients-patients with higher trough tacrolimus levels had better response and nonsignificantly higher rate of remission compared to placebo
  - Another RCT showed efficacy of healing in perianal fistulas in CD

ALTERNATIVE IMMUNIMODULATORS

- MMF
  - Pilot study compared chronic active UC receiving prednisone on AZA vs MMF. AZA superior with better remission rates
  - Concern for adverse events as well

- Thalidomide
  - Downregulation of TNF alpha and inhibition of NFKB activity
  - Shown to be effective in small studies in patients naïve to biologics and in whom thiopurines, MTX and anti-TNF have failed

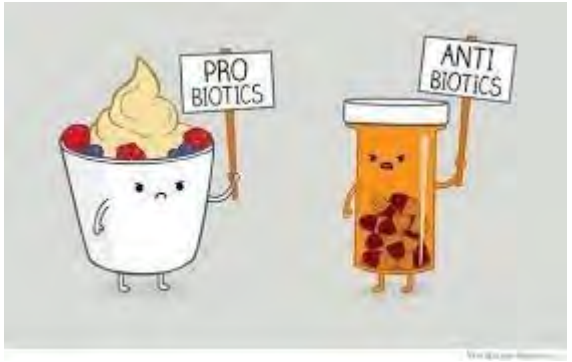
ADJUNCTIVE THERAPIES

- Antidiarrheal and anticholinergic agents to alleviate diarrhoea and cramping
- Patients with ileal disease/resection-vitamin B12 supplementation or addition of cholestyramine or colesevelam to control bile salt diarrhoea
- Iron supplementation

ANTIBIOTICS AND PROBIOTICS

- Antibiotics:
  - Clear role in treating pyogenic complications of CD
  - Treat perineal disease, fistulas and active luminal disease
  - Metronidazole, ciprofloxacillin, rifaximin
  - Limited use in UC

- Probiotics:
  - Not much clinical benefit



NUTRITIONAL THERAPY

- UC:
  - TPN has no role as primary therapy
  - Bowel rest in combination with IV steroids were no more effective than steroids alone

- CD:
  - TPN proven effective as short term therapy for severe luminal or perinal disease in combination with bowel rest

CONCLUSION

- Wide variety of drugs that prove to still be effective
- Large efforts taken to validate each of the drugs used
- Looking forward to the advanced therapies and how conventional therapy will integrate or disintegrate

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