Chronic Granulomatous Disease
Managing GI Issues

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Disclosures
Overall

- Inflammatory manifestations are difficult to treat
  - Inflammatory bowel disease, lung granulomas, genitourinary, ocular
  - No specific recommendations exist for treatment of inflammatory bowel disease (IBD) in CGD

- Treatment involves immunosuppressing an immunodeficient patient........
Colitis Treatment

Treatment of inflammatory bowel disease (IBD)

• Mainstay of treatment is immunosuppression
• Corticosteroids and tumor necrosis factor (TNF) inhibition common
CGD Associated Colitis Treatment

**TNF-α inhibitors in CGD**
- Works to dampen inflammatory response
- Leads to recurring problems with infection
- Time to first serious infection is 3-12 infusions
- Associated with deaths in 2 of 5 patients
- TNF-α inhibitors are profoundly dangerous and contraindicated in CGD
CGD Associated Colitis
Treatment

WELL WHAT DO
WE DO NOW?
Oral Glucocorticoids

- Often first line therapy for inflammatory manifestations
- Rapidly decrease symptoms and induce remission
- Burst and taper
  - 1 mg/kg/day burst typical
  - Looooooong taper (often 3-6 months)
  - Relapses common after cessation (up to 71%)
- One large cohort showed no steroid refractory cases
Oral Glucocorticoids

- Allows to control inflammation/symptoms while waiting for another medication to work
- Can remain on long term
  - Some require long term low dose prednisone (5-10 mg daily)
- Significant long term side effects
  - Infection, growth restriction, osteoporosis, weight gain, diabetes, adrenal suppression, mood disturbance, glaucoma, etc
CGD Associated Colitis Treatment

**Steroid sparing agents**

- Sulfasalazine and derivatives (mesalamine)
- 6-Mercaptopurine
- G-CSF—case reports
- Thalidomide—case reports
  - Difficult to use in the US
CGD Associated Colitis Treatment
CGD Associated Colitis Treatment

**Biologics**
- Vedolizumab
- $\alpha_4\beta_7$ inhibitor
Biologics

- Vedolizumab
  - 2 series—6 patients and 2 patients
    - All with improvement of symptoms and withdrawal of steroids
    - Only 1 patient with infection—pneumonia and inguinal adenopathy
  - Retrospective cohort at NIH
    - Promising results
    - May be limited by loss of response over time
CGD Associated Colitis Treatment

Biologics

- Ustekinumab
- Anti-IL-23—approved for psoriasis and psoriatic arthritis
Biologics

- Ustekinumab
  - Case report of IL-23 blockade in CGD colitis
  - Effective at treating colitis
  - Returned on cessation of therapy
  - Discontinued due to infection after 14 months
**IL-1β inhibition**

- Anakinra
- IL-1β is an inflammatory cytokine produced by inflammasome of innate immune system
- IL-1β blockade decreases inflammasome activation and restores autophagy in mice
  - Autophagy—normal process, maintains homeostasis by protein degradation and turnover of destroyed cell organelles for new cell formation
  - Macrophages in CGD→defect in autophagy→inflammasome activation and IL-1β release
- Mixed results so far in human case series
mTOR inhibition

- Rapamycin (mTOR inhibitor)—shown to be autophagy inducer
- Shown in vitro to increase autophagy and decrease IL-1β release
- Rapamycin could be a new therapeutic option
- Some in vitro data that anakinra and rapamycin may work synergistically

CGD Associated Colitis Treatment
Surgery

- Occasionally needed
- Indications include:
  - Small bowel obstruction
  - Gastric outlet obstruction
**Definitive treatment**

- Prednisone dependent IBD is indication for HSCT in CGD
- Preferred to get inflammation under control prior to transplant
- Has been shown to induce complete remission of inflammatory manifestations
CGD Associated Colitis Treatment

Are we causing it?

- Studies have shown colitis is unrelated/independent to bactrim, itraconazole or IFN-γ administration
CGD Associated Colitis Treatment

**Take home**

- Lesson learned from TNFα
  - We are using immunosuppressants in immunodeficient patients
  - Infections are very real risk
  - Close monitoring necessary
- Close collaboration between gastroenterology and immunology necessary
- Oral corticosteroids work—long term side effects
- Many options and more emerging options for treatment
- Difficult to treat
- HSCT and gene therapy are definitive treatments
Questions