Management of Immune Related Adverse Events

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Why Do Immune AEs Occur ?

Immune check point inhibitors release a "natural brake" on the immune system causing

T-Lymphocyte activity

This can cause immune mediated inflammation of any organ system

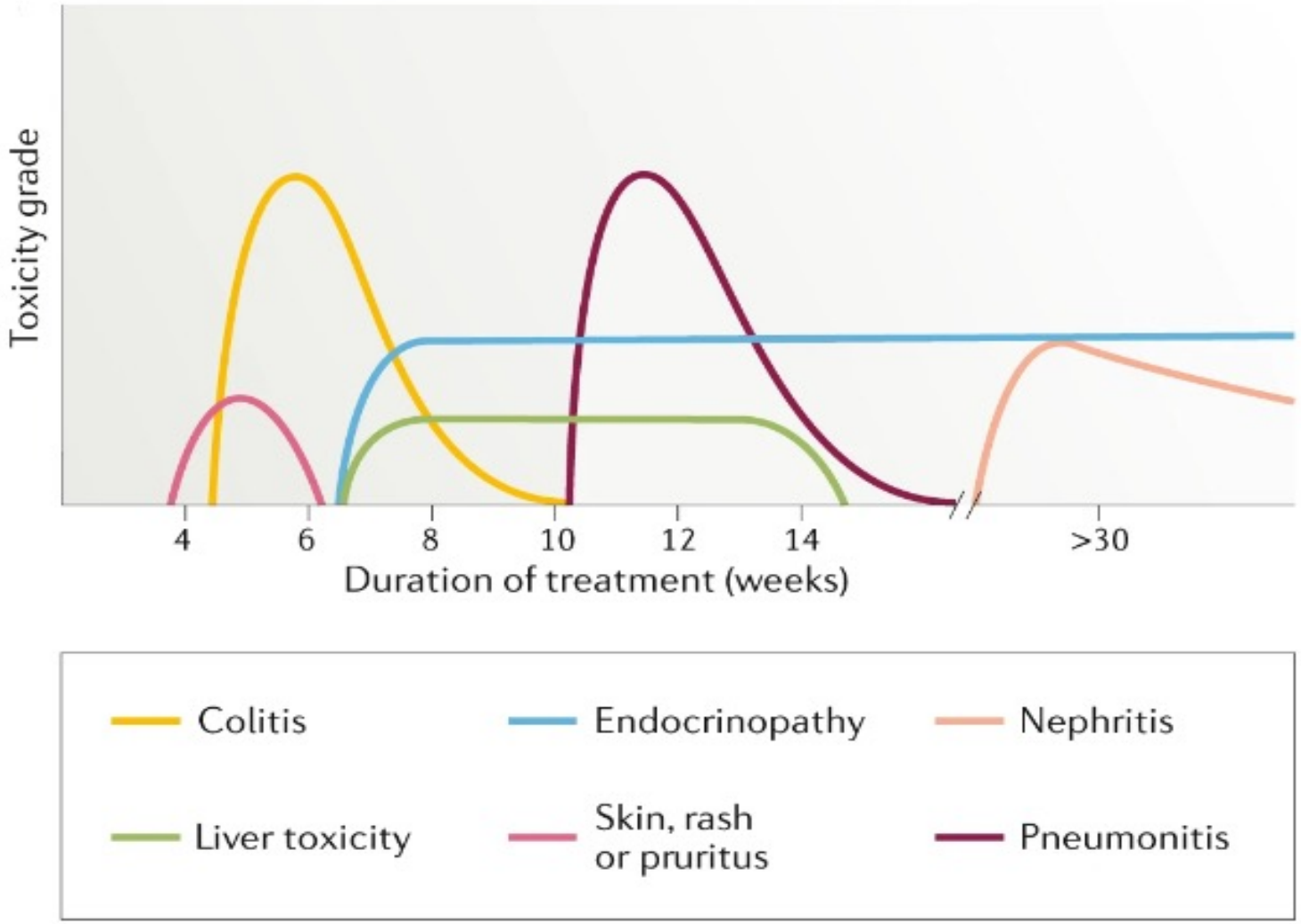
Organ Systems Affected

- Cutaneous – maculopapular rash, pruritis psoriasiform, lichenoid eruptions
- Musculoskeletal – myositis, inflammatory arthritis
- Cardiovascular – myocarditis, pericarditis, vasculitis, heart failure
- Gastrointestinal- diarrhea, colitis, megacolon, perforation
- Endocrine- hypophysitis, thyroid dysfunction hypoparathyroidism, insulin deficiency diabetes, primary adrenal insufficiency

Organ Systems Affected (continued)

- Neurologic - neuromuscular (myositis) and central (encephalitis, aseptic meningitis)
- Pulmonary – pneumonitis
- Renal – acute kidney injury, acute interstitial nephritis

Immune Related Adverse Events – Overview



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Systems affected to be addressed today include:

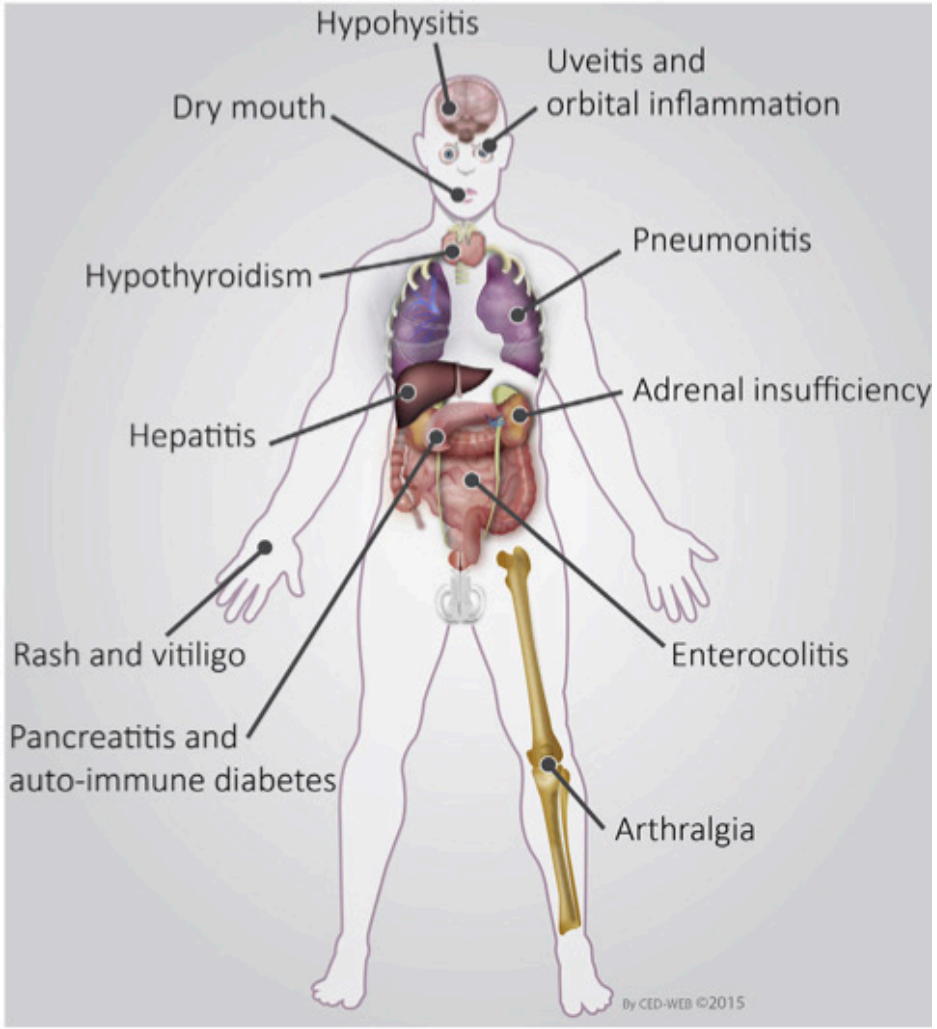
Cutaneous

Gastrointestinal

- **Colitis**
- **Hepatitis**

Pulmonary

Renal



CUTANEOUS

- Cutaneous toxicities including rash, pruritis, vitiligo are the most common reported toxicities and reported up to 71.5% of patients receiving immunotherapy treatment

- Grade 1 – Rash <10% BSA with/without pruritis
  - Continue treatment
  - Use of topical emollients +/- mild or moderate topical corticosteroids
  - Patient education: Avoid hot showers, avoid prolonged showers, use mild soaps, use emollients without fragrance/alcohol

CUTANEOUS (cont.)

- Grade 2 – Rash 10% - 30% BSA w/wo symptoms (pruritus, burning tightness)or limiting instrumental ADL or rash > 30% BSA w/wo mild symptoms
  - Consider holding and monitor weekly – if not improved over 4 weeks, then regard as Grade 3
  - Treatment with topical emollients, or oral antihistamines and medium to high potency topical corticosteroids
  - Consider initiating prednisone (or equivalent) 0.5 – 1 mg/kg, tapering over 4 weeks
  - If pruritus w/o rash – consider topical remedies (refrigerated menthol, pramoxine lotion)

CUTANEOUS (cont.)

- Grade 3 – Rash >30% BSA with moderate or severe symptoms or limiting self care ADL
  - Hold treatment and consult with dermatology
  - Treat with topical emollients, oral antihistamines and high potency topical corticosteroids, phototherapy may be used for severe pruritis.
  - Initiate oral prednisone or equivalent (1mg/kg) tapering over 4 weeks
  - When ≤ Grade 1 and prednisone (or equivalent) is below 10 mg/day may consider resuming with close monitoring and follow up with dermatology.
  - Pruritis without rash may be treated with gabapentin, pregabalin, aprepitant or dupilumab

CUTANEOUS (cont.)

- Grade 4 - Severe consequences requiring hospitalization or urgent intervention indicated or life-threatening consequences
  - Immediately hold treatment
  - Admission with consult to dermatology
  - Systemic steroid (IV methylprednisolone (or equivalent) 1-2 mg/kg with slow tapering when the toxicity resolves.
  - Consider alternative antineoplastic therapy over resuming immunotherapy if skin toxicity does not resolve to ≤ grade 1. If immunotherapy is the only option, consider restarting once side effects have resolved to Grade 1 with close dermatology follow up.

Gastrointestinal Toxicities: Colitis

- Frequency of colitis in the literature ranges from 8% - 27%, the incidence of diarrhea is as high as 54% in patients treated with anti-CTLA-4 antibodies, especially in patients receiving anti-CTLA-4 and PD-1 combination therapy. GI toxicity is less common with anti-PD-1 monotherapy with the incidence of diarrhea reported to be ≤ 19 %
  - Important to work up diarrhea first to rule out C-diff, parasites, CMV, other viral causes or infectious causes. Consider testing for fecal lactoferrin (for stratification to determine who needs more urgent endoscopy) and calprotectin (to follow up on disease activity)

Gastrointestinal Toxicities: Colitis (cont.)

- Grade 1 – Increase of < 4 stools per day over baseline or mild increase in ostomy output compared to baseline
  - Continue immunotherapy or may hold temporarily and resumed if toxicity does not exceed G1 or resolves
  - Supportive care may be given with loperamide – only if infection has been ruled out and without colitis related symptoms as a temporary measure.
  - Monitor patient every 3 days (phone call) until stabilized
  - Patient education: hydration, dietary changes
  - If prolonged G1 - obtain gastroenterology consult , possible endoscopy with biopsies.

Gastrointestinal Toxicities: Colitis (cont.)

- Grade 2 – Increase of 4-6 stools/day over baseline or moderate increase in ostomy output compared with baseline
  - Hold treatment until at least recovered to G1
  - May include supportive care with loperamide – only if infection ruled out; with diarrhea only and not colitis related symptoms as a temporary measure
  - Consider consult with gastroenterology
  - Administer corticosteroids 1 mg/kg /day prednisone or equivalent until symptoms improve to G1 - then start taper over 4-6 weeks

Gastrointestinal Toxicities: Colitis (G2 cont.)

- Endoscopic evaluation with EGD or colonoscopy is highly recommended for Grade ≥ 2 to stratify for early treatment of biologics based on endoscopic findings
- Consider addition of anti-tumor necrosis factor (infliximab) or anti-integrin (vedolizumab) antibody when colitis is corticosteroid refractory (if not decreased by one grade within 72 hours) or dependent or with high-risk endoscopic features on initial endoscopy.
- May consider resuming treatment after symptoms improve to ≤ G1 when steroid taper is completed, risk and benefits review if maintained on biologics and/or if endoscopic and histologic remission are achieved. Fecal calprotectin ≤ 116 ug/g may be considered a surrogate for endoscopic and histologic remission

Gastrointestinal Toxicities: Colitis (cont.)

- Grade 3 – Increase of ≥ 7 stools per day over baseline or incontinence, or hospitalization indicated or severe increase in ostomy output compared with baseline or limiting self-care ADL
  - Follow Grade 2 recommendations and add:
  - Consider hospitalization (dehydration, electrolyte imbalance)
  - Administer corticosteroid (initial dose of 1-2 mg/kg/day prednisone or equivalent) until symptoms improve to G1 then start taper over 4-6 weeks.
  - Consider IV methylprednisolone, especially if concern for concurrent upper GI inflammation

Gastrointestinal Toxicities: Colitis (G3 cont.)

- Consider early introduction of infliximab or vedolizumab in addition to steroids in patients with high-risk endoscopic features on initial endoscopy exam or inadequate response to steroids (persistent symptoms after 3 days)

Gastrointestinal Toxicities: Colitis (cont.)

- Grade 4 – Life-threatening consequences or urgent intervention indicated
  - Follow G2 – G3 recommendations with addition:
  - Permanently discontinue treatment
  - Provide inpatient care
  - Administer 1-2 mg/kg/day methylprednisolone or equivalent until symptoms improve to G1 and then start taper over 4-6 weeks
  - Consider early biologic (infliximab or vedolizumab) if inadequate response to steroids after 3 days.
  - Consider lower GI endoscopy if symptoms are refractory despite treatment or there is a concern for new infections

Gastrointestinal Toxicities: Hepatitis

- Hepatotoxicity has been reported in 2 %- 10% in monotherapies, and 25% - 30% for all grade hepatitis with combination immunotherapies, and approximately 15 % incidence of grade 3 toxicity

- Grade 1 Asymptomatic (AST or ALT > ULN to 3 X ULN and/or total bilirubin >ULN to 1.5 X ULN
  - Continue treatment – consider alternate etiologies
  - Consider monitoring labs 1- 2 times weekly

Gastrointestinal Toxicities: Hepatitis (cont.)

- Grade 2 - Asymptomatic (AST or ALT> 3 to ≤ 5 X ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN)
  - Temporarily hold treatment
  - Review and discontinue unnecessary medication and any known hepatoxic drugs and oncologic agents
  - May administer steroid (0.5 -1 mg/kg/day prednisone/equivalent) if no improvement seen after 3-5 days of holding treatment
  - Monitor labs every 3 days
  - If inadequate improvement after 3 days, consider adding mycophenolate mofetil
  - Taper steroid when symptoms improve to ≤ Grade1 and resume treatment when steroid is ≤ 10 mg/day (taper at least over 4 weeks)
  - Consider hepatology consult

Gastrointestinal Toxicities: Hepatitis (cont.)

- Grade 3 – AST or ALT 5 – 20 X ULN and /or total bilirubin 3 – 10 x ULN or symptomatic liver dysfunction, fibrosis by biopsy or compensated cirrhosis or reactivation of chronic hepatitis
  - Follow Grade 2 recommendations with the addition:
  - Consider permanently discontinuing treatment if asymptomatic
  - Consider inpatient admission
  - Permanently discontinue if symptomatic and start steroid 1 -2 mg/kg methylprednisolone or equivalent
  - If steroid refractory consider biopsy to rule out other causes – NASH, tumor, cholestatic variant, other drug related hepatic inflammation, infection other autoimmune entity.

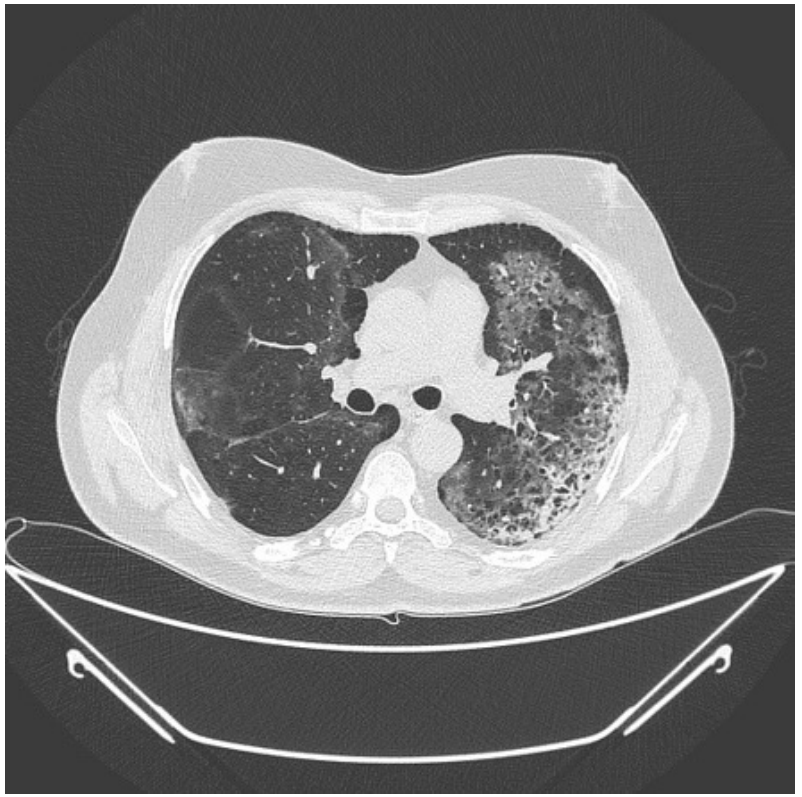
Gastrointestinal Toxicities: Hepatitis (G3 cont.)

- If infection ruled out consider adding azathioprine or mycophenolate
- Labs daily or every other day
- If no improvement achieved - refer to hepatologist for further pathologic evaluation
- Steroid taper can be attempted around 4 – 6 weeks when ≤ Grade 1
- Re-escalate steroids if needed
- Optimal steroid duration is unclear

Gastrointestinal Toxicities: Hepatitis (cont.)

- Grade 4 - Grade 4 – AST pr ALT > 20 x ULN and or total bilirubin > 10 x ULN or decompensated liver function (ascites, coagulopathy, encephalopathy and coma)
  - Follow Grade 3 recommendations with addition of:
  - Administer methylprednisolone or equivalent at 2 mg/kg/day

Immune Check Point Inhibitor Pneumonitis



Weerakkody Y, Bell D, Buemi F, et al. Immune checkpoint inhibitor therapy related pneumonitis. Reference article, Radiopaedia.org https://doi.org/10.53347/rID-76657

Lung: Pneumonitis

- Overall incidence 2.7 % (considered uncommon)

- Grade 1 – Asymptomatic or confined to one lobe of the lung or < 25% of lung parenchyma or clinical or diagnostic observations only
  - Hold treatment or proceed with close monitoring
  - Monitor patients weekly H&P, pulse oximetry, CXR, CT scan
  - Repeat chest imaging 3-4 weeks or sooner if patient becomes symptomatic
  - May resume treatment with radiographic evidence of improvement or resolution – if no improvement, should treat as Grade 2

Lung: Pneumonitis (Cont.)

- Grade 2 – Symptomatic or involves more than one lobe of the lung or 25% - 50 % of lung parenchyma or medical intervention indicated or limiting self care
  - Hold treatment until clinical improvement to G1
  - Prednisone 1 -2 mg/kg/day and taper over 4 – 6 weeks
  - Consider bronchoscopy with BAL w/wo transbronchial biopsy
  - Consider empiric antibiotics if infection remains in the differential diagnosis after workup
  - Monitor at least weekly, consider reimaging
  - If no improvement after 48 – 72 hours treat as Grade 3
  - Consider pulmonary and infection disease consults if necessary

Lung: Pneumonitis (Cont.)

- Grade 3 – Severe symptoms or hospitalization required or involves all lung lobes or > 50 % of lung parenchyma or limiting self care ADL or oxygen indicated

- Grade 4 – Life-threatening respiratory compromise or urgent intervention indicated (intubation)

  - Permanently discontinue treatment
  - Empiric antibiotics may be considered
  - Methylprednisolone IV 1- 2 mg/kg/day
  - If no improvement after 48 hours may add immunosuppressive agents (infliximab, mycophenolate mofetil, IVIG or cyclophosphamide).
  - Taper corticosteroids over 4 – 6 weeks
  - Pulmonary and infectious disease consults as needed
  - May consider bronchoscopy with BAL w/wo transbronchial biopsy if patient can tolerate

Renal: Nephritis and Acute Kidney Injury

- AKI considered an uncommon complication however the incidence has been reported as high as 10 % - 29%
- Presenting symptoms: urinary frequency, dark, cloudy urine, fluid retention of face abdomen and extremities, sudden weight gain, abdominal or pelvic pain, nausea/vomiting, high blood pressure and change in mental status
- Assess for concomitant medications – prescribed and OTC, NSAIDS, herbal, vitamin, nephrotoxic agent, or contrast media

Renal: Nephritis and Acute Kidney Injury (Cont.)

- Grade 1 – Creatinine level increased of > 0.3mg/dl or creatinine 1.5 – 2.0 x above baseline
  - Consider temporarily holding treatment and/or other potential contributing agents
  - Explore other potential alternative etiologies (recent IV contrast, fluid status, UTI, other combined treatment, concomitant medications)

Renal: Nephritis and Acute Kidney Injury (Cont.)

- Grade 2 - Creatinine 2-3 x above baseline
  - Hold treatment temporarily
  - Consult nephrology
  - Evaluate other causes and if ruled out administer Prednisone or equivalent 0.5 – 1 mg/kg/day
  - If worsening or no improvement after one week increase to 1 – 2 mg/kg/day prednisone or equivalent and permanently discontinue treatment
  - If improved to ≤ Grade 1 taper steroids over at least 4 weeks
  - If no recurrence of chronic renal insufficiency may resume treatment considering risk vs benefit and if patient agreeable
  - Resuming treatment can be considered once steroid has been tapered to ≤ 10 mg/day

Renal: Nephritis and Acute Kidney Injury (Cont.)

- Grade 3 – Creatinine > 3 x baseline or > 4.0 mg/dl or hospitalization indicated
- Grade 4 – Life-threatening consequences or dialysis indicated or creatinine 6 x above baseline
  - Permanently discontinue treatment if directly implicated in renal toxicity
  - Consult nephrology
  - Evaluate for other causes (recent IV contrast, medications, fluid status, UTI etc.)
  - Administer corticosteroids (initial dose of 1 – 2 mg/kg/day)

Treatment Options for Immune-mediated Reactions Refractory to Corticosteroids

- Azathioprine (immunosuppressant agent, anti-integrin)
  - Used for immune checkpoint inhibitor-induced autoimmune hepatitis, grade 3 or 4, steroid-refractory
    - **Oral:** 50 mg once daily, with subsequent incremental increases of 25 to 50 mg every 1 to 2 weeks up to a maximum of 2 mg/kg/day
- Infliximab (immunosuppressant agent; monoclonal antibody; anti-tumor necrosis factor)
  - Used for immune checkpoint inhibitor-induced Colitis (off-label use)
  - For grade 2, 3, or 4 colitis with either high-risk endoscopic features on initial endoscopy examination or with persistent symptoms despite 3 days of corticosteroid therapy
    - **IV:** 5 mg/kg at week 0, a second dose may be repeated 2 weeks later, and a third dose may be considered at 6 weeks if needed; use in combination with a corticosteroid
      - CONTRAINDICATED FOR IMMUNE-RELATED HEPATITIS

Treatment Options for Immune-mediated Reactions Refractory to Corticosteroids (cont.)

- Vedolizumab (monoclonal antibody)
  - Used for immune checkpoint inhibitor-induced colitis (off-label use)
    - For grade 2, 3, or 4 colitis with either high-risk endoscopic features on initial endoscopy examination or with persistent symptoms despite 3 days of corticosteroid therapy,
    - **IV:** 300 mg at 0, 2, and 6 weeks and then (if needed) once every 8 weeks thereafter; use in combination with a corticosteroid

- Mycophenolate mofetil (immunosuppressant agent)
  - May be used for the management of steroid-refractory cardiac, hematologic, hepatic, kidney, musculoskeletal, or pulmonary immune-mediated adverse events
    - Oral: 1 g twice daily in combination with a glucocorticoid

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