Monitoring and Supporting Immune Function After Immunomodulation

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What is immunomodulation in autoimmune diseases?


  “immunosuppressive doses” considered to be:
  - ≥20 mg prednisone QD [or equivalent] for >14 days: US CDC
  - ≥40 mg prednisolone QD [or equivalent] for >7 days: UK Dept Health “Green Book”
  - Persists for at least 1 month after treatment discontinuation
  - May result in hypothalamic/pituitary/adrenal axis [HPA] suppression; requiring stress coverage
  - Monitor for weight gain, hyperglycemia, HTN, fluid retention/edema, cataracts and/or glaucoma, skin bruising or thinning, sleep disturbances, osteopenia/osteoporosis and associated fractures, osteonecrosis, muscle weakness, accelerated ASCVD

- Use of immunomodulators for treatment as well as “steroid sparing” effects
  - “Immunosuppressive effects” persist for at least 6 months after treatment discontinuation
  - Fewer concomitant treatments and overall immunosuppression than associated with transplantation
    - Lymphomas believed related to persistently active, poorly controlled underlying autoimmune disease rather than treatments, eg not post transplant lymphoproliferative disease [PTLD]
    - Lower incidence of viral infection reactivation: H zoster, CMV
    - Role of bacterial and viral microbiome

- Therapies used: indications, [off label use] many have not been adequately studied in randomized controlled trials in autoimmune diseases
  - Antiproliferative agents:
    - Methotrexate: RA, psoriasis: Ps, psoriatic arthritis: PsA, [SLE], [IIM]: inhibition of adenosine synthesis, tetrahydrofolate reductase; long T ½ of intracellular metabolites: 4 – 6 months
    - Leflunomide: RA, [PsA], [SLE]: dihydroorotate dehydrogenase [DHODH] inhibition of pyrimidine synthesis: T ½ of active metabolite 10 – 14 days; cholestyramine washout
    - Mycophenolate mofetil: [SLE], [IIM], [SSc], [vasculitides]; not effective in RA: inosine monophosphate dehydrogenase [IMPDH] inhibition of purine synthesis: T ½ of active metabolite 12 hours; cholestyramine washout
    - Azathioprine: RA, [SLE], [IIM], [Crohn’s]. [UC]: purine mimic antimetabolite; metabolized by thiopurine methyltransferase [TPMT] to 6-MP: T ½ ≈ 24 hours
  - JAK/STAT inhibitors:
    - Tofacitinib: RA: T ½ 3 hours; pharmacodynamic effects persist for 7 – 14 days
  - Cytotoxics:
    - Alkylation agents:
      - Cyclophosphamide [oral and IV]: [SLE], [vasculitides], [SSc]; T ½ 3 – 12 hours
    - Calcineurin inhibitors:
      - Cyclosporine [oral]: RA, Ps, [PsA], [SLE], [UC]; (non-modified): T ½: 19 hours [range: 10-27]; (modified): T ½: 8.4 hours [range: 5-18]
      - Tacrolimus: [oral and IV]: [SLE]; T ½ 23 – 46 hours
Use of biologic agents: ALL associated with varying degrees of immunogenicity; infusion reactions and/or injection site reactions
  o **TNF inhibitors**: SQ: T ½ generally 10 – 14 days except CZP: pegylated anti-F(ab)’
    ▪ Adalimumab: RA, PsA, AS, Crohn’s, ped Crohn’s, UC, Ps, JIA
    ▪ Certolizumab pegol: RA, PsA, AS, Crohn’s
    ▪ Etanercept: RA, PsA, AS, Ps, JIA
    ▪ Golimumab [IV and SQ]: RA, PsA, AS, UC
    ▪ Infliximab [IV]: RA, PsA, AS, Crohn’s, ped Crohn’s, UC, ped UC, Ps
  o **Co-stimulation inhibitors**:
    ▪ Abatacept [IV and SQ]: RA, JIA; SQ: T ½ 8 – 25 days
  o **B cell directed therapies**:
    ▪ Rituximab [IV]: CD20 depletion: RA, vasculitis: granulomatosis with polyangiitis, microscopic polyangiitis, CLL, NHL, [SLE], [PTLD]; mean T ½ 18 – 22 days [range 5 – 78]
    ▪ Belimumab [IV]: SLE; T ½ effects on B cells and Ig levels: 8 weeks; pharmacodynamic effects: 16 weeks
  o **IL-6 inhibitors**:
    ▪ Tocilizumab [IV and SQ]: RA, sysJIA: SQ: T ½ 11 – 13 days at steady state
  o **IL-1 inhibitors**:
    ▪ Anakinra [SQ]: (RA), Neonatal-onset multisystem inflammatory disease [NOMID] including cryopyrin associated periodic syndromes [CAPS]; T ½ 4 – 6 hours
    ▪ Rilonacept [SQ]: CAPS; T ½ 9 days
    ▪ Canakinumab [SQ]: CAPS, sysJIA; T ½ 26 days

How utilized?
  • Autoimmune diseases
    o Treatment
    o Steroid sparing
  • Background therapy with biologic agents
    o Decrease immunogenicity
    o Prolong half life of cytokine targeted mAbs: FcR mediated clearance mechanism
  • Combination therapy is a paradigm
    o Glucocorticoids + immunomodulators: SLE, Crohn’s, UC, IIM, vasculitides, RA [low dose CS]
    o Immunomodulators + Biologic Agents: RA, Ps, PsA, Crohn’s, UC, SLE
    o Glucocorticoids + Immunomodulators + Biologic Agents: SLE, Crohn’s, UC, vasculitides
    o Infections always increased with concomitant glucocorticoid use, regardless of dose

Issues with use:
  • Common AEs: nausea, dyspepsia, abdominal pain, diarrhea, oral ulcers, URI, nasopharyngitis
  • Skin effects: rash, reversible hair loss, alopecia
  • Cytopenias, bone marrow suppression: leukopenia, neutropenia, lymphopenia, anemia
  • Infections:
    o Viral especially with lymphopenia
      ▪ Herpes zoster [reactivation]
      ▪ CMV
      ▪ Hepatitis B and C
      ▪ JCV and PML: Rituximab, MMF, past use of others in SLE
    o Bacterial
    o Fungal including pneumocystis prophylaxis
o Other opportunistic infections: Tb, atypical mycobacterial, coccidiodomycosis, histoplasmosis, blastomycoses, cryptococcus
o GI: Pseudomembranous colitis with associated use of broad spectrum antibiotics
o Vaccinations: influenza, pneumococcal, Hepatitis A and B, Herpes zoster
  ▪ Generally effective but may need to check titer and re-administer pneumococcal, hepatitis vaccines
  ▪ Avoid live vaccines when possible while receiving immunosuppressants
  ▪ Administer H zoster vaccine if >60 years of age preferably before receiving biologic agent or tofacitinib; consider for >50 years of age although often not reimbursed

- Lymphomas
- Non hematologic malignancies
- Pregnancy

Specific to certain agents:
- Methotrexate: dysphoria, liver fibrosis, idiosyncratic pulmonary fibrosis, reversible renal failure; leukopenia
  o Monitor LFTs; limit alcohol use
  o Monitor U/A and creatinine; reversible renal failure with concomitant NSAIDs
  o CXR pre-treatment and yearly
  o Contraindicated in pregnancy and abortifacient
- Leflunomide: LFT elevations, BP increases, rash, reversible hair loss;
  o Contraindicated in pregnancy
- Mycophenolate Mofetil: leukopenia, neutropenia,
  o Viral infections including H zoster and CMV
  o Contraindicated in pregnancy
- Azathioprine: rare hepatitis, pancreatitis
  o Lymphoproliferative disorders
  o Recommendation to assay TPMT levels prior to treatment initiation: AD inheritance: genotyping and functional assays available
    ▪ Low levels: use contraindicated
    ▪ Intermediate levels: increased risk for myelosuppression: use at lower doses
    ▪ However low frequency of homozygous variants in Caucasians and most myelosuppression not related to TPMT levels; alternatively start low doses and monitor closely
- Tofacitinib:
  o Increased risk for serious and opportunistic infections, viral infections including H zoster
    ▪ Administer H zoster vaccine if >50 years of age prior to initiation of treatment
    ▪ Screen for latent Tb
  o Monitor lymphocyte counts as well as CBC; dose reductions or discontinuations for anemia, neutropenia and/or lymphopenia
  o Increases in LDL/HDL, creatinine; decreases in neutrophil counts related to baseline levels and improvements in elevated CRP
  o Monitor lipids 4 – 8 weeks post treatment initiation; treat according to guidelines
  o Malignancies including lymphoma; PTLD in transplant patients
• Cyclophosphamide: poor tolerability; cytopenias and reduction in immunoglobulins; alopecia
  o Serious and opportunistic infections: Prophylaxis for Pneumocystis jirovecii recommended; Tb screening pre treatment
  o Bladder toxicity including hemorrhagic cystitis and bladder cancer with oral administration; less with IV and use of Mesna
  o Contraindicated in pregnancy → infertility; pretreatment sperm and oocyte cryopreservation
• Cyclosporine: poor tolerability;
  o Dose related increases in BP: Require close monitoring
  o Dose related decreases in GFR: Require close monitoring
  o Anemia
  o Headaches, paresthesias
  o Viral, serious and opportunistic infections
  o Hirsutism, gingival hyperplasia
  o Hemolytic uremic syndrome [HUS]/thrombotic thrombocytopenic purpura [TTP]
    /thrombotic microangiopathy [TMA]
  o Numerous medication interactions including with methotrexate
  o Increased risk of skin malignancies and lymphomas
  o Contraindicated in pregnancy
• Tacrolimus:  
  o HTN, edema, chest pain
  o Tremor, new onset diabetes mellitus, renal impairment
  o Anemia
  o Serious and opportunistic infections
  o Hemolytic uremic syndrome [HUS]/thrombotic thrombocytopenic purpura [TTP]
    /thrombotic microangiopathy [TMA]
  o Numerous medication interactions
  o Malignancies
  o Contraindicated in pregnancy
• TNF inhibitors:  
  o Increased risk for infections especially in 1st 6 – 12 months of Rx: pre-screen for latent Tb
  o Contraindicated in severe CHF
  o Monitor as for background therapy with MTX, LEF
  o Demyelinating disorders
  o Non melanoma skin cancers increased
  o Hepatosplenic T cell lymphomas
  o Not recommended for use in pregnancy; certolizumab may be preferred as pegylated anti-F(ab)’2; does not cross placenta
• Abatacept:  
  o Pre-screen for latent Tb
  o Monitor as for background therapy with MTX, LEF
• Rituximab:  
  o B cell depletion and decreased IgG levels
  o Serious and opportunistic infections including PML; Pre-screen for latent Tb
  o Infusion reactions; concomitant use of high dose corticosteroids
  o Monitor as for background therapy with MTX, LEF, AZA
Belimumab:
- Decreases in B cell and immunoglobulin levels
- Serious infections
- Administration with other biologic agents or IV cyclophosphamide has not been studied

Tocilizumab:
- Serious and opportunistic infections; Pre-screen for latent Tb
- H zoster
- LFT elevations and increases in LDL/HDL levels
- Monitor as for background therapy with MTX, LEF including LFTs and lipids; treat according to guidelines
- Gastrointestinal perforations: avoid use in patients with history of diverticulitis
- Demyelinating disorders
- Drug interactions: lowers IL-6 and thus normalizes cytochrome levels, increasing metabolism of simvastatin (and other CYP450 metabolized agents)

IL-1 inhibitors
- Increased incidence of infections associated with neutropenia
- Malignancies
- LDL/HDL increases

Monitoring Guidelines:
- For all immunomodulators and biologic agents:
  - Pre-treatment:
    - CBC including platelets, electrolytes, BUN/Cr, LFTs
    - Screen for latent Tb, assure Hepatitis B and C negative
    - CXR for methotrexate, cyclophosphamide
    - Consider vaccinations including H zoster prior to administration
  - Monthly, bimonthly until stable then q 1–3 months except when cytopenias occur or dose increased:
    - CBC, LFTs, BUN/Cr
    - Drug levels are generally not monitored but can be employed with cyclosporine, tacrolimus, MMF
    - Immunogenicity generally not assessed except with intermittent use in Crohn’s, UC and Ps

Patient education re:
- Importance of regular monitoring and outpatient visits
- Risks for infection including MRSA
- Risks for non-melanoma skin cancers, other malignancies
- Use in pregnancy and breast feeding

Expectant monitoring including
- Vaccinations: influenza, pneumococcal, etc as indicated
- Prophylaxis for pneumocystis with intense immunosuppression