Making Sense of the Alphabet Soup: Vasculitis Medications

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Objectives

• Review (some of) the various medications used in the treatment of vasculitides
• Understand which toxicities to be aware of and how to minimize the risks of developing them
• What monitoring should be done prior to and while you are on medications
Med List

• Oral Medications:
  • Glucocorticoids (GC)
  • Methotrexate (MTX)
  • Azathioprine (AZA)

• Subcutaneous or Infusion medications:
  • Tocilizumab (TCZ)
  • Rituximab (RTX)
  • Cyclophosphamide (CYC)
Case Presentation

75-year-old WF complaining of ~3 weeks of new onset right sided headache

- Malaise, shoulder and hip girdle discomfort, 12 pound weight loss over the past 2 months
- Morning stiffness lasting 2 to 3 hours
- Difficulty with getting out of a chair and combing her hair due to pain
- Recent onset of jaw pain when eating, 1 transient episode of vision loss in the R eye but resolved after a few minutes
Case Presentation

Exam:
• Low grade fever
• CV exam normal with no bruits
• Proximal muscle tenderness without objective weakness
• No rashes or synovitis

Lab Results:
• Hgb 9.8; ESR 85; CK 32
• Remaining CBC/differential normal
• Basic metabolic panel, TSH normal
Case Presentation

• Diagnosis/Plan: Presumed giant cell arteritis
• Start IV steroids and order temporal artery ultrasound/TAB
• After 3 days of pulse steroids, switch to 1mg/kg oral prednisone daily
• Commonly, treatment for GCA must be continued for at least 2 years
Which of the following is NOT a side effect of prednisone?

A. Gastritis
B. Elevated glucose
C. Osteoporosis
D. Worsening kidney function
E. Hypertension
F. Avascular necrosis
Correct Answer: D

Worsening kidney function is not a side effect from prednisone use. In fact, steroids are often used to control inflammation in the kidneys to prevent kidney function deterioration.
Glucocorticoids (GC, prednisone, medrol, solumedrol)

- Used in almost every type of vasculitis to quickly control inflammation
- Often part of induction therapy given as “pulse dose” during acute hospitalization when organ threatening disease is present
- Goal is to minimize prednisone as much as possible and maintain disease control (often with the use of other immunosuppressive medications)
Prednisone

- Daily prednisone dose and duration of therapy are predictors of side effects (odds ratio [OR] = 4.5 for 5 to 10 mg and 32.3 for 10 to 15 mg)
- With the exception of cataracts, bone effects and atherosclerosis, many of the side effects are at least partially reversible with GC discontinuation.
- Overall, significantly less SE’s on doses <10mg/d

Waljee, BMJ 2017
Prednisone

• Skin: purpura, steroid acne, alopecia, bruising/skin thinning
  • Many features improve as steroids are lowered
  • Can try hair removal creams, topical acne medications
  • Bruising does not signify risk of internal bleeding

• GI: peptic ulcer disease/gastritis
  • Synergistic effects with NSAIDs (2x increased risk together)
  • Consider prophylaxis if using steroids with ASA or with other NSAIDs (can use a PPI, take steroids with food)

• CNS: Hypomania in 30% and depression in 10%, trouble sleeping
  • Partial loss of explicit memory
    • More in elderly patients—can be seen as early as 3 months after starting therapy
  • Psychosis (in doses >20mg/day)
Prednisone affects the bone

- Obtain DEXA scan if you have risk factors for osteoporosis within 6 months of starting steroids
- Women and men >40 at mod-high risk of fracture should take oral bisphosphonate

Optimize calcium intake (1,000–1,200 mg/day)* and vitamin D intake (600–800 IU/day) and lifestyle modifications (balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day) over no treatment or over any of these treatments alone.

Conditional recommendation because of indirect evidence on the impact of lifestyle modifications on fracture risk, low-quality evidence on the impact of calcium and vitamin D on fractures in GC users, and indirect evidence on the benefit of calcium and vitamin D on fracture risk in the general OP population.

Buckley, Arth Rheum 2017
Prednisone

• Cardiovascular: Atherosclerosis, elevated blood pressure, weight gain

• Elevated blood sugars
  • Even pts on <10mg/day have 1.9 fold increased risk of starting DM meds

• Infection
  • 1.5 fold increase in risk of infection at 10mg or less versus 8 fold in 40mg or higher (keep in mind that patients on higher doses are also usually more sick from underlying disease)
  • Use standard precautions, report signs of any developing infection early to your doctor
Interactive Case Presentation

- She does well on prednisone and her ESR normalizes to 20mm/hr. She has resolution of her headaches and jaw pain and feels well overall other than some fatigue. She does note frequent urination that has been making her get up many times at night to use the bathroom. You check her Hgb A1C and it is 8.2%. She has no prior history of diabetes and is currently on 35mg prednisone daily. Her father died from complications of diabetes and she is very scared about this new finding. She wants to know what her options are at this point.
Interactive Case Presentation

- Tocilizumab –blocks IL-6
- Approved for RA in the US in 2010
- Approved for GCA as a subcutaneous weekly injection 2017 → FDA granted breakthrough approval!
GIACTA: Major Trial for TCZ in GCA

- Sustained remission at week 52
  - Weekly tocilizumab → 56%
  - Every 2 weeks tocilizumab → 53%
  - Rapid steroid taper → 14%
  - Prolonged steroid taper → 17%

- Cumulative median steroid dose significantly lower in TCZ groups (P<0.0002) → steroid sparing

Stone, NEJM 2017
• Tocilizumab weekly and rapid prednisone taper patients had clinically meaningful improvement in SF-36 and FACIT-Fatigue scores compared with those receiving prednisone only.
TCZ and TAK

• TAKT study: did not meet primary endpoint, but results favored tocilizumab over placebo in refractory TAK

• Large multicenter French study showed that tocilizumab is efficient and may reduce the incidence of relapses in TAK

EULAR recommendations for the management of LVV—2018 update

6 Non-biologic disease modifying agents should be given in combination with GC in all patients with TAK. Tocilizumab or TNF-inhibitors can be considered in case of relapsing or refractory disease despite conventional DMARD therapy.

Nakaoka, ARD 2018
Mekinian, J Autoimmun 2018
Hellmich, ARD 2019
Tocilizumab

• Precautions
  • Anaphylaxis/hypersensitivity, Elevated LFTs (~20%), infectious risk
  • Caution in patients with increased risk for GI perforation, which is typically secondary to diverticulitis
  • Herpes zoster reactivation
  • Hyperlipidemia
  • Not recommended in those with hepatic impairment
  • Neutropenia: do not start in ANC <2k/mm³, discontinue if ANC drops to <500/mm³
Tocilizumab

• Monitoring
  • Signs and symptoms of infection
  • Latent TB screening before starting therapy
  • CBC with diff prior to and q4-8 wks during therapy
  • ALT/AST prior to and q4-8 wks during therapy
  • Additional liver tests as indicated
  • Fasting lipid profile prior to, at 4-8 wks, and q6 months
Med List

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  - Cyclophosphamide (CYC)
Case Presentation #2

• 63 yo WM presents to the ER with fevers, trouble breathing, coughing up blood, and leg swelling.

• Labs show anemia, elevated creatinine (worsened kidney function), and his urine has 4 grams of protein as well as blood. c-ANCA positive (+PR3)

• Infectious workup is negative. He is given a blood transfusion and kidney biopsy is performed

• Respiratory decompensation requiring intubation and dialysis initiated
Case Presentation #2

• In addition to pulse steroids, what medication(s) should be started?
  a) Cyclophosphamide
  b) Rituximab
  c) Methotrexate
  d) Plasmapheresis
  e) Azathioprine
• Induction: Putting out the fire
• What can we use?
  • Cyclophosphamide or Rituximab (rarely MTX in limited GPA)
• Maintenance: Keeping out the fire without causing a flood
• What can we use?
  • Rituximab, azathioprine, occasionally mycophenolate or methotrexate
Cyclophosphamide in AAV

Use of CYC and prednisone transformed AAV from a uniformly fatal disease to a chronic-relapsing disease with mortality of 20% at five years.

- **CYTOXAN**
  - 93% Remission
  - 50% side effects (within 5 years)

- **Complications**
  - Cystitis
  - Infertility
  - Bladder cancer
  - Lymphoma
  - Infection

Fauci, Ann Int Med, 1983
Hoffman, Ann Int Med, 1992
Jayne, NEJM, 2003
Booth, Am J Kid Dis, 2003
Cyclophosphamide

- Initially used as part of chemotherapeutic regimens in the treatment of cancers, but found in the 1950s to be effective in rheumatic diseases
- Used for induction in AAV. Also used in many other organ/life threatening vasculitides (PAN, cryoglobulinemic vasculitis, takayasus)
- Cyclophosphamide → phosphoramide mustard is active component. It disrupts nucleic acid binding resulting in impaired DNA synthesis, death of actively proliferating cells, and altered cellular function
Cyclophosphamide

• Established Major drug interactions
  • Live Vaccines

• Probable Major drug interactions
  • Allopurinol (increased CTX toxicity), cyclosporine (decreased Cyclo levels), etanercept (higher incidence of solid malignancies), St John’s Wort (decreased CTX effect), Tamoxifen (increased risk of thromboembolism), warfarin (increased INR)
Cyclophosphamide

• Higher cumulative CYC dose results in increased risk of toxicities (favors IV pulse dosing)

• In vasculitis, we used to treat with cyclophosphamide for many years before new agents were discovered for induction and maintenance→high levels of exposure

• Now, we treat for 3-6 months and then try and switch to alternative maintenance regimen
## Cyclophosphamide – Major Concerns

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Things To Note</th>
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</thead>
<tbody>
<tr>
<td>Bone Marrow Suppression</td>
<td>• Follow CBC regularly and dose adjust if needed based on WBC count</td>
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<td></td>
<td>• Nadir day 7-14 post IV dose</td>
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<tr>
<td>Gonadal Toxicity (ovaries and testes)</td>
<td>• Depends on age, sex and cumulative dose</td>
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<td></td>
<td>• Testicular injury after 7-9g of CYC</td>
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<td></td>
<td>• Women can develop amenorrhea, premature ovarian failure</td>
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<td></td>
<td>• Increased risks with older age (&gt;30) discuss egg and sperm banking options if possible</td>
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<tr>
<td>Infections (bacterial, opportunistic and viral)</td>
<td>• Increased risk with neutropenia and use of steroids</td>
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<td></td>
<td>• PJP prophylaxis with bactrim, get HPV vaccine (increased susceptibility/ reactivation)</td>
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Cyclophosphamide – Major Concerns

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<tr>
<td>Hemorrhagic cystitis/bladder cancer</td>
<td>• 2/2 metabolite of CYC → acrolein</td>
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<td></td>
<td>• Risk is highest (12-41% of GPA pts) with cumulative doses of 50-100g</td>
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<td></td>
<td>• Mesna for possible protection, tons of hydration</td>
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<tr>
<td>Malignancy</td>
<td>• Increased risk of leukemia, skin cancer and other malignancies</td>
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<td></td>
<td>• Duration of therapy is important risk factor → incidence greatest in pts treated for &gt;2-3 years</td>
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<tr>
<td></td>
<td>• MDS in up to 8% of pts with GPA after CYC and 13% if cumulative dose &gt;100g</td>
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</tbody>
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- Retrospective analysis of 1018 patients treated for autoimmune disease and vasculitis from 13 rheumatology centers → **median CYC dose was 9 g** (range 1.5 to 180g)
So......How about Rituximab?

- Rituximab was approved in 1997 for treatment of hematologic malignancies (CLL, NHL)
- Approved in 2006 for RA
- Approved in 2011 for induction in MPA/GPA and for maintenance in 2018
- Is also used in SLE, cryo, HSP, IgG4-RD
- Works by binding to CD20 on B cells
  - B cells make antibodies (such as ANCAs)
  - Also inhibits antigen presentation to Th cells
Rituximab

• Common reactions:
  • Pruritis, nausea/vomiting
  • Dizziness, HA, fever, shivering

• Concerning side effects:
  • Infusion reactions can be severe/fatal (ARDS, shock, hypotension, bronchospasm)
    • Usually (~80%) with first infusion
    • Pre-medicate and slow the infusion if needed
Rituximab

• Concerning side effects:
  • Progressive multifocal encephalopathy-
    • 92% of the population is JCV+
    • As of November 2015, there were nine confirmed PML cases among patients who had received rituximab for RA and two for GPA (more common in cancer patients)
    • There was no pattern of latency from time of rituximab initiation to PML development and no association of PML with the number of rituximab courses
    • Patients treated with rituximab carry a risk for HBV reactivation and should be screened for HBV prior to starting therapy
  • Severe mucocutaneous reactions (SJS, TEN)
  • Infections (monitor for late onset neutropenia and low immunoglobulins)

Berger, J Neurovirol 2018
Rituximab

• Some tests we check before (or during) treatment with RTX:
  • Hep panel and TB test
  • Lymphocyte subset count (CD19+ B cells)
  • CBC with diff (neutropenia)
  • Quantitative Immunoglobulins
  • ANCA titers
Rituximab

- Rituximab is being increasingly used in ANCA vasculitis due to its better overall safety profile, but of course, risks still exist.
- We are always trying to use enough medicine to control the disease, but as little as possible to avoid side effects.
- Recent trial comparing 4 weekly doses vs 2 weekly doses (375mg/m²) showed similar outcomes at 1 year.
- MAINRITSAN2 trial evaluated maintenance therapy with RTX to see if dosing based on lab and clinical parameters can be used rather than every 6 months.

Takakuwa, Clin Rheum 2019
Charles P, Ann Rheum Dis, 2018
Med List

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Brief Case

• Our 63 yo M was treated with pulse steroids and IV Cytoxan in the hospital. He was successfully extubated and had renal recovery. New baseline creatinine is 2.2 with mild low levels of protein in his urine. ANCA titers are now undetectable.

• He follows up in clinic and wants to know what the next steps are. You plan to continue IV Cytoxan for 3-6 months and then start:

  a) Rituximab
  b) Azathioprine
  c) Methotrexate
  d) Mycophenolate Mofetil
  e) Monitor for symptoms and re-treat if they develop
Azathioprine

- First used for kidney transplant by the British in the 1960s or earlier
- Used in IBD, RA, SLE, Takayasus, PAN, cutaneous vasculitis
- MOA: inhibits purine metabolism (affects DNA synthesis) and suppresses T>B cell function (increased T cell death)
  - TPMT testing?—mixed results—only present in 0.3% of population
- Start with 1 tablet and monitor counts while titrating to goal dose
Azathioprine

• Adverse Effects
  • Common
    • Anorexia, nausea, vomiting (up to 20%, usually soon after starting therapy)
    • Rare skin rash, muscle soreness
  • Serious
    • Bone marrow suppression (dose related leukopenia in ~25%)
    • Pancreatitis
    • Hepatotoxicity (5%) → does not progress to cirrhosis
    • Increased cancer risk (lymphoma/leukemia, skin cancer) — more problematic in transplant patients and studies with mixed results in autoimmune disease
    • Infections
Azathioprine: Interaction with other drugs

• **Established Major Drug Interactions**
  • Allopurinol, febuxostat—AZA toxicity (nausea/vomiting, leukopenia, anemia)
    • requires reduction to 1/3-1/4 AZA dose
  • Live vaccines
  • Captopril/enalapril—increased myelosuppression

• **Probable Major Drug Interactions**
  • Alfalfa—reduced immunosuppressive effectiveness
  • Warfarin—decreased anticoagulant effectiveness
Azathioprine Monitoring

• CBC weekly during first month and as dose is increased, twice monthly during 2nd-3rd months, then monthly
• LFTs every 2 weeks during first 1 month, then monthly thereafter
• If stable after 6 months, can consider spacing to every 3 months
Maintenance: AZA vs MTX

WEGENT: prospective, open label. MTX (25mg weekly) vs AZA (2mg/kg) after induction with IV CYC

Relapse rate 36% in AZA and 33% in MTX

DC maintenance

Relapse rate 36% in AZA and 33% in MTX

- Overall survival rate was 75-85% at 10 years
- MTX not safer than AZA with regards to SAEs, infections or malignancy

Pagnoux, NEJM 2008
Methotrexate

• Methotrexate has been used in multiple disease states including malignancy, rheumatoid arthritis, scleroderma, and vasculitis

• Doses used in rheumatic diseases are much lower dose than those used in malignancy (7.5mg-25mg weekly vs 1g cycles)
Methotrexate: Common Toxicities

- GI upset (nausea, stomach ache, loose stools)
  - Can use ranitidine or PPI evening before and after dose
- Fatigue/headache/malaise
  - GI and CNS issues usually occur within 24-48 hours after the dose
- Alopecia- usually not dose related
- Stomatitis (mouth sores)- more common at higher doses
  - Can improve with folic acid. Can increase doses from 1mg/d up to 5mg/day or consider leucovorin (~8 hours after MTX dose)
- Abnormal liver enzymes or low blood counts
  - Dose reduce and regular monitoring of LFTs and CBC
  - Avoid heavy alcohol use
  - Screen for hepatitis prior to starting MTX
  - Low blood counts more common with renal impairment (80-90% excreted via kidney)
Methotrexate

• Pulmonary Toxicity
  • Can be seen with both high or low dose and is usually seen in the first year of treatment
  • Baseline CXR, avoid if interstitial lung disease

• Teratogenic and abortifacient
  • Use contraception and stop therapy at least 3 months prior to conception

• Infections
Side Effects From Medications Used in Vasculitis

Increased risk of infections
Signs of Vasculitis

Increased risk of infections
Where Are We Going?

• Side effects of medications can have significant overlap with disease manifestations which can make management of vasculitis complicated
• With increased understanding of disease pathogenesis, we have been able to develop new drugs that are more targeted
• This helps us minimize risks and toxicities, but comes at a cost
• With newer drugs, we have less data on long term toxicities
• Price of rituximab or tocilizumab for 1 year is ~$36,000. Price of prednisone for 1 year is ~$120
• Many current trials are evaluating how fast we can safely stop/minimize some of these medications (TAPIR, MAINRITSAN3, MAINEPSAN, GIACTA)

Schmier, Clin Ther 2017
"The problem is that you're overmedicated. Luckily there are drugs that can help with that."