Managing your disease - PM

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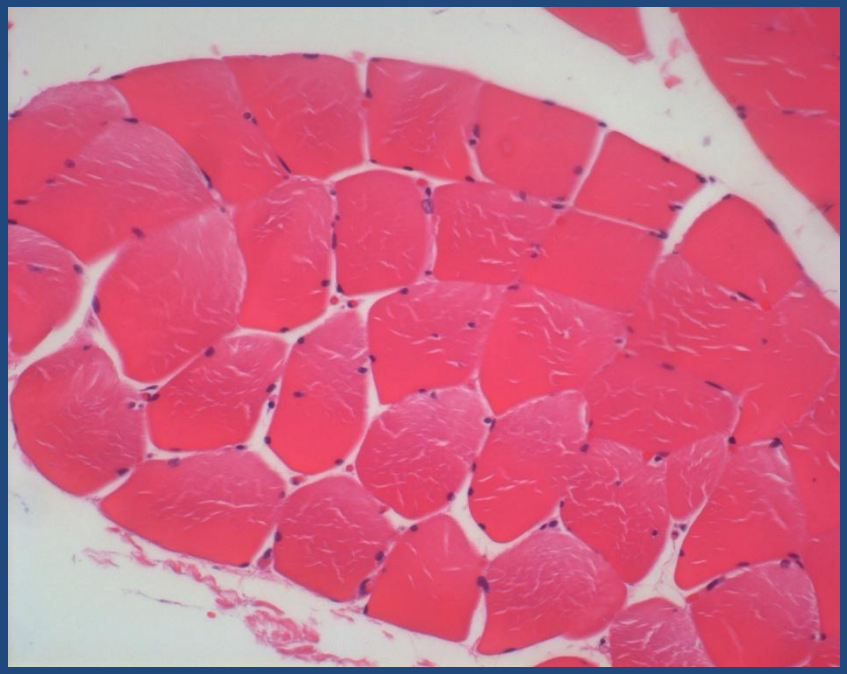
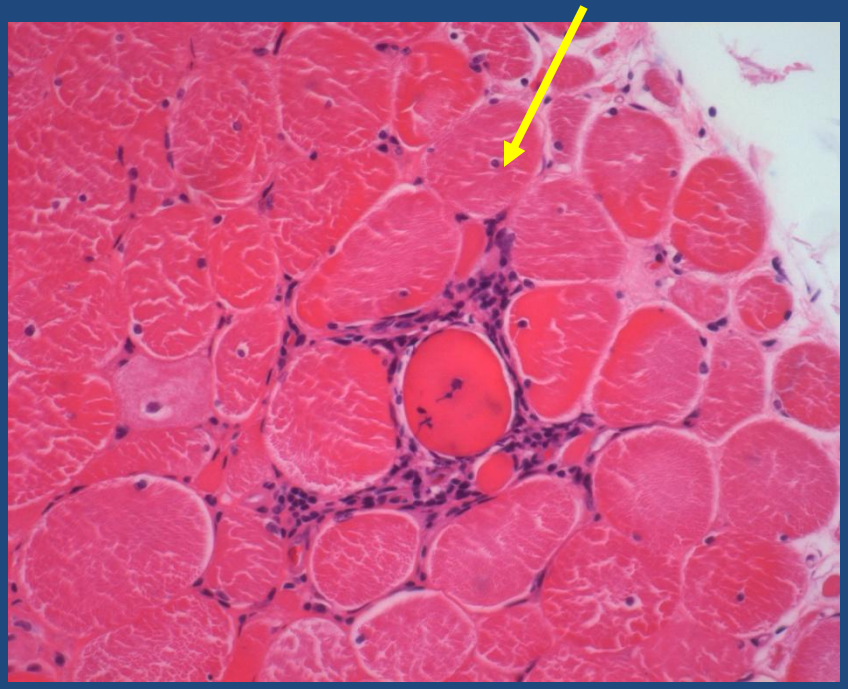
Polymyositis



Normal Muscle

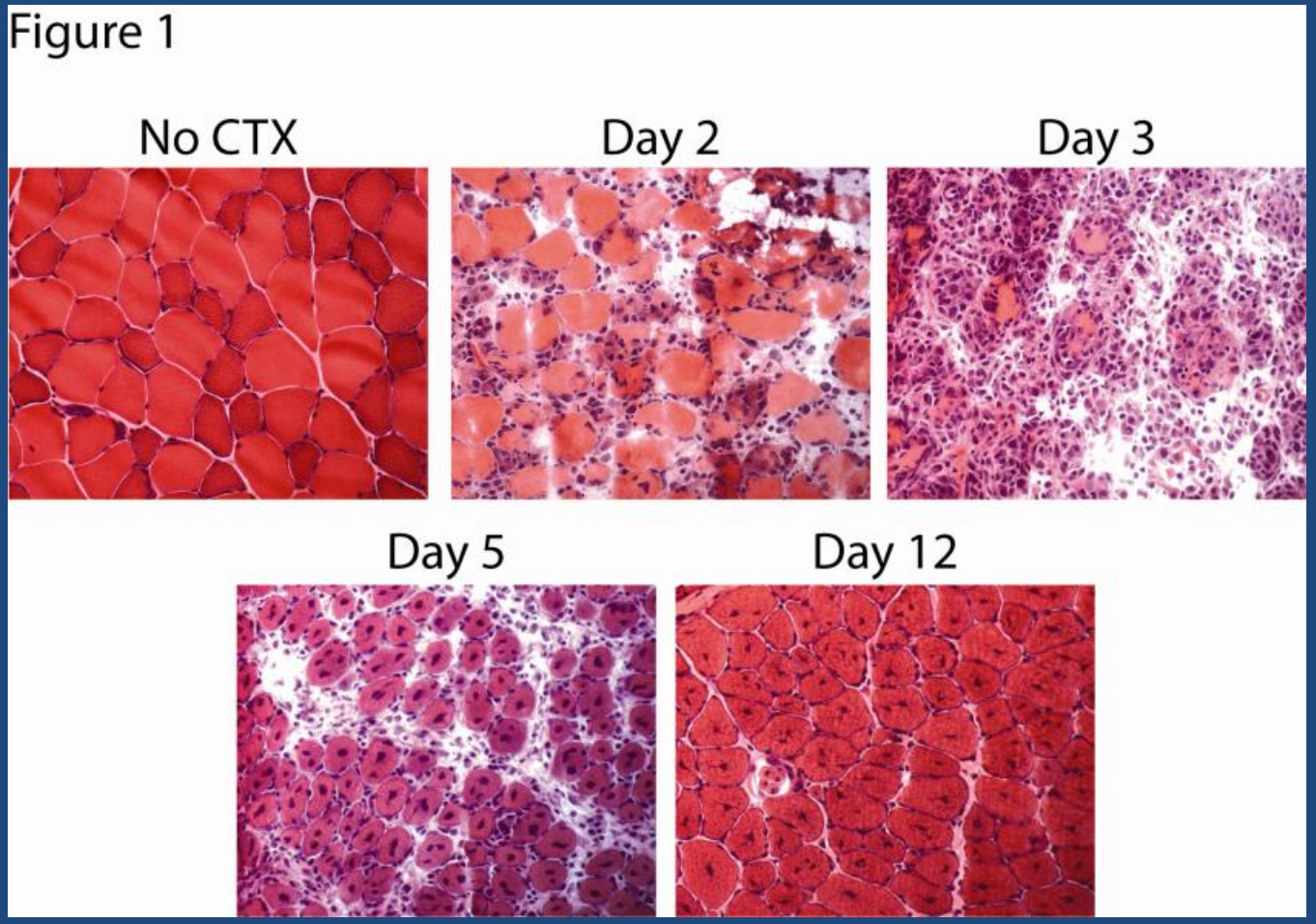


Myositis Muscle

Lymphocytes "attacking" normal muscle tissue

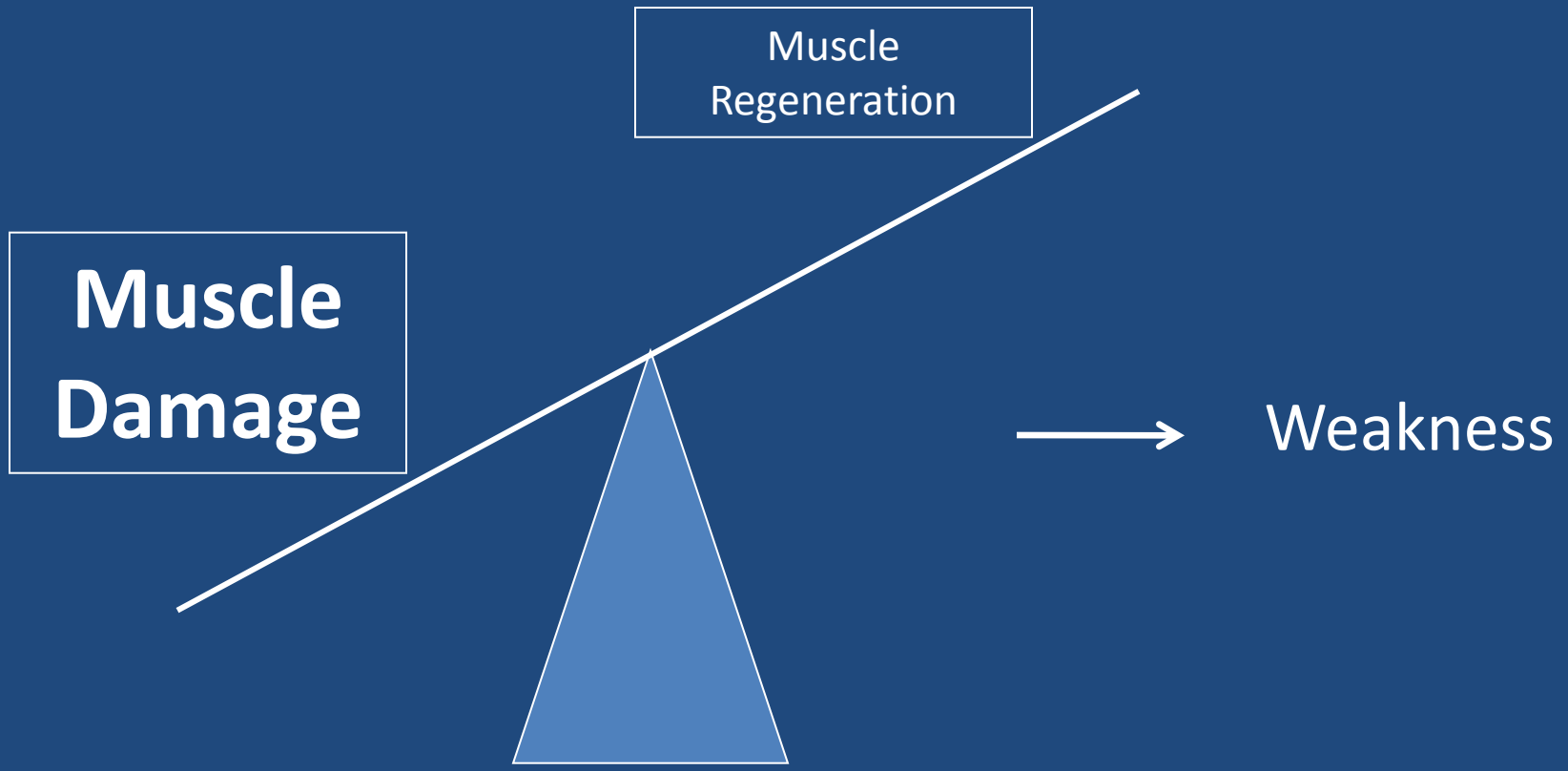
Result: muscle weakness

The other side of the equation: Damaged muscle can regenerate

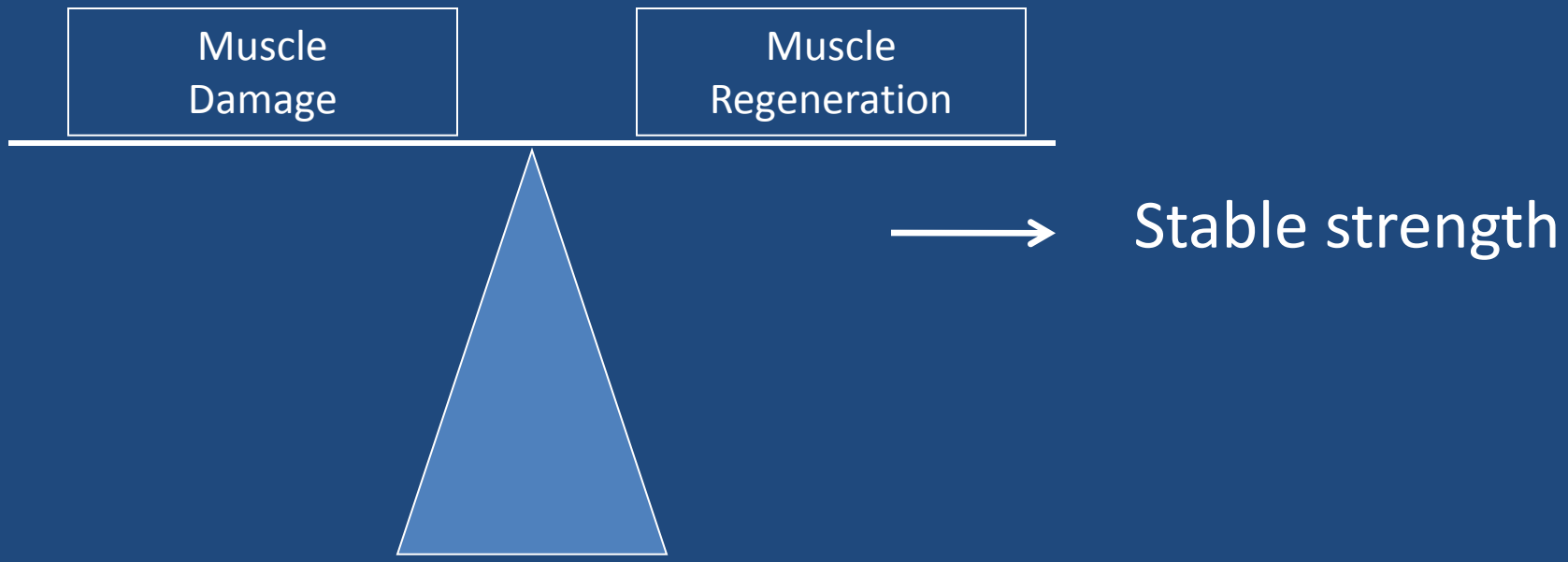


Cardiotoxin injected into a mouse leg muscle on day 0

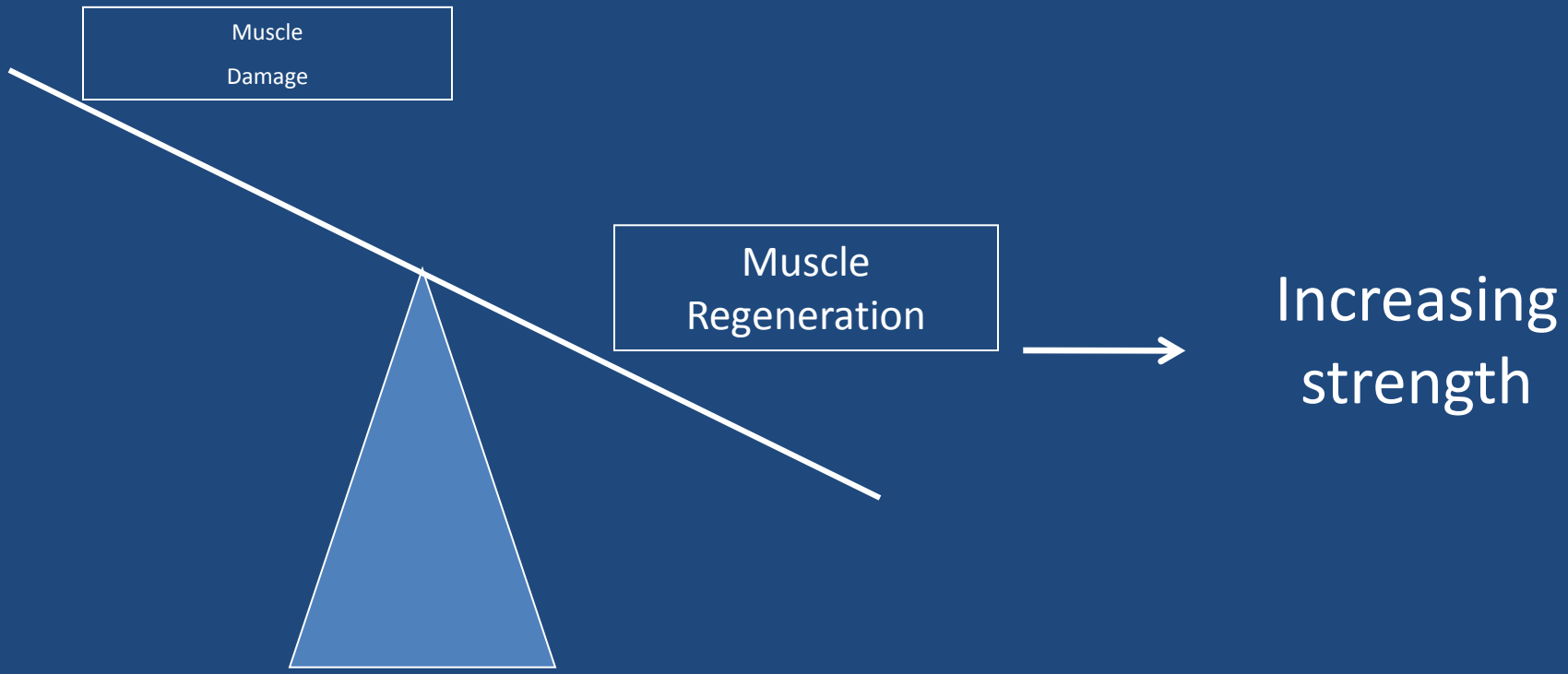
In myositis, weakness occurs when muscle damage outpaces muscle regeneration



Strength is stable when muscle damage and muscle regeneration are balanced



Strength increases when muscle regeneration is more efficient that muscle destruction



Treatment Approaches

- Reduce muscle destruction
  - Immunosuppression
- Increase muscle regeneration
  - Future therapies?
- Increase power of intact muscle
  - Excercise

Immunosuppression

- First Line
  - Steroids
- Steroid-sparing: first line
  - Methotrexate
  - Azathioprine (Imuran)
  - Mycophenolate mofetil (Cellcept)
- Steroid-sparing: second line
  - IVIg
  - Rituximab (Rituxan)
  - Etanercept (Enbrel)
  - Cytoxan
  - Cyclosporine
  - Others…

Prednisone – how it works

- Inhibits immune cells from entering muscle
- Interferes with mediators of inflammation
- Suppresses antibody formation
- Other anti-inflammatory properties

- Degree of effect is related to dose

Prednisone – adverse effects

Common

- Hypertension
- Weight gain
- Thinning of skin
- Poor wound healing
- Edema
- Gastritis, etc…
  - GI prophylaxis
- Increased risk of infection
  - Prophylactic antibiotics
- Osteoporosis
  - Calcium, Vit D, bisphosphonate
- Depression/Euphoria

Serious

- Diabetes
- Cushing's syndrome
  - "moon facies"
  - Buffalo hump
- Adrenal insufficiency
- Cataract
- Glaucoma
- Tuberculosis
- Avascular necrosis of hip

Prednisone

- Only drug FDA-approved for PM!
- Initial oral dose: ~ 1 mg/kg/day (60-100 mg/day)
- Usually tapered once disease controlled
- Tapering strategies vary
  - The faster the taper, the bigger the flare risk
  - The slower the taper, the bigger the side-effect risk
- Goal prednisone dose: < 10 mg/day
- Alternate day dosing may decrease side-effects

- May also be given in large doses by i.v. (e.g., 1 gram Solumedrol per day for 3 days)

Methotrexate – how it works

- Interferes with:
  - DNA synthesis
  - DNA repair
  - Replication of cells (e.g. immune cells)

- Other good features
  - Effective in treating arthritis

Methotrexate – adverse effects

Common

- Hair loss
- Rash
- Diarrhea
- Decreased appetite
- Nausea and vomiting
- Stomatitis (= inflammation of mouth mucous membranes)
- Increased infection risk

Serious

- Skin ulcer
- GI hemorrhage
- Myelosuppression
- Liver disease
  - Avoid if pre-existing liver disease
  - Liver enzymes must be monitored
  - No alcohol
- Lung disease
  - Cough and shortness of breath are symptoms
  - Some avoid if there is pre-existing lung disease (e.g. ILD)

Methotrexate

- Dosing
  - Usually given weekly by mouth or subcutaneously
    - SQ administration may lessen side-effects
  - Folate usually prescribed with MTX to decrease side-effects
  - Often started at a low dose (e.g., 10 mg/week) and increased to as high as 25 mg/week
  - Blood monitoring required
    - Liver function tests (LFTs)
    - Complete blood count (CBC)
    - Renal function

Azathioprine – how does it work?

- Exact immunosuppressive action unknown
- May inhibit
  - DNA synthesis
  - RNA synthesis
  - Protein synthesis
- Inhibits proliferation of immune cells

Azathioprine – adverse effects

Common

- Gastritis
- Nausea
- Vomiting

Serious

- Pancreatitis
- Decreased white blood cell count
- Anemia
- Decreased platelets
- Liver damage
- Infectious disease
- Increased risk of cancer with long-term use

Azathioprine

- Given after TPMT blood test performed
- Poor drug metabolism from low TPMT level results in increased risk of side-effects
  - Little or no TPMT (0.3%): use alternate drug
  - Low to intermediate TPMT (10%): reduced dose
  - Normal TPMT (90%): normal dose
- Typical dose – 1-2.5 mg/kg/day (start low and increase)
- Blood monitoring required
  - CBC weekly for one month, every other week for 8 weeks, then monthly
  - Liver function tests every 2 weeks for one month, then monthly

Mycophenolate Mofetil (Cellcept) – how does it work?

- Inhibits proliferation of immune cells
- Suppresses antibody formation
- May inhibit recruitment of immune cells to sites of inflammation

Mycophenolate mofetil (Cellcept) – Adverse Effects

Common

- Hypertension
- Edema
- Hypercholesterolemia
- GI (pain, constipation, diarrhea, nausea, etc..)
- Backache
- Headache
- Insomnia
- Tremor
- Kidney issues
- Cough
- Infection

Serious

- Gastric ulcer
- GI hemorrhage
- Decreased blood cell production
- Lymphoma, skin cancer
- Fatal brain infection (PML)
- Lung damage

Mycophenolate mofetil (Cellcept) -

- Dosing: usually start at a low dose and increase until receiving 1000-1500 mg by mouth twice each day
- Blood monitoring
  - CBC weekly for one month, then every other week for 8 weeks, then monthly for one year
  - Periodic tests of renal and liver function

IVIg – how does it work?

- It is a pool of antibodies from > 1000 individual donors
- Unclear how it suppresses the immune system
- May form an immune complex that is anti-inflammatory
- May stimulate removal of recipient's own antibodies
- May bind to and inhibit macrophages (a type of inflammatory cell)

Ivig – adverse effects

Common

- Headache,
- Muscle pain
- Fever
- Chills
- Backache
- Chest pain
- Nausea, vomiting

Serious

- Asceptic meningitis
- Kidney failure
- Increased blood clotting (heart attack, stroke)
- Red blood cell destruction
- Allergic/anaphylactic reaction

IVIG

- Usually not given to patients with history of heart attack or stroke
- Avoided in those with kidney problems
- IgA level checked (if absent, may have allergic reaction)
- Usually initiated as one infusion per day for 5 days
- If tolerated well, may get same dose over fewer days
- Given as inpatient, outpatient, or at home depending on the circumstances

Rituximab (Rituxan) – how does it work?

- This antibody targets antibody producing immune cells (B cells)
- Eliminates B cells from the body

Rituximab (Rituxan) – adverse effects

Common

- Itching
- Nausea, vomiting
- Dizzyness
- Headache
- Fever
- Shivering

Serious

- Chest pain
- Abnormal heart rhythm
- Severe skin reaction
- Bowel obstruction
- Decreased blood cells
- Hepatitis B
- Allergic reaction
- Fatal brain infection (PML)
- Kidney damage
- Lung damage

Rituximab (Rituxan)

- Administration
  - Intravenously
  - Various initial infusion strategies (e.g., two infusions two weeks apart)
  - Re-dosed when benefit wears off AND B cells return to circulation (monitor CD19 positive cells)

Etanercept (Enbrel) – how it works

- Inhibits tumor necrosis factor (TNF)
- TNF induces inflammation, so…

Etanercept (Enbrel) – adverse affects

Common

- Injection site reaction
- Abdominal pain
- Vomiting
- Headache
- infection

serious

- Skin cancer (basal cell)
- Severe skin rash
- Low blood cell counts
- liver disease (autoimmune)
- Lymphoma
- Tubeculosis
- Multiple sclerosis
- Other erious infections

Etanercept (Enbrel)

- Test for TB prior to starting
- Some needle caps contain latex derivative
- Dose: weekly subcutaneous injections (rotate sites)
- Blood work: occasional CBC and liver function tests

Pregnancy and PM drugs

Probably safest

- Prednisone – Class A
- Etanercept (Enbrel) – Class B
- IVIg – Class C

To be avoided/harmful

- Rituximab (Rituxan) – Class C
- Azathioprine (Imuran) – Class D
- Mycophenolate mofetil (Cellcept) – Class D
- Methotrexate – Class X

Most safe <----------> Most harmful

Class A > Class B > Class C > Class D > Class X

Is the treatment working?

- Following strength is the most important – if you aren't getting stronger the treatment isn't working!!

- Following CK levels may be helpful
- Muscle MRI may be useful
- EMG may occasionally play a role in monitoring disease activity

My basic approach to treatment

- Start with prednisone
- If myositis is severe/rapidly progressive, add second agent immediately
- Add second agent if disease flares during prednisone taper
- Increase second agent to effective or maximally tolerated dose
- Consider additional or alternative medications if required prednisone dose is too high

Everyone is different!

- Very difficult to say how well response to treatment will be at beginning of therapy
- A good initial response to prednisone usually bodes well
- The majority of patients require a second agent
- Some patients do not respond well
  - Is the diagnosis of PM correct?
  - Some patients diagnosed with “PM” actually have inclusion body myositis or another muscle disease

Excercise

- Very important!
- Proven to benefit patients with PM
- Should include muscle strengthening
- Creatine supplementation may provide additional “boost”
  - 20 grams/day for one week, then 3 grams/day