Medical Management of Rheumatic Diseases

Diane Lacaille, Rheumatologist

ACE Workshop

April 23, 2018

Basic Approach/Goals

1) Symptom control:
   - Acetaminophen, NSAIDs, steroids (intraart, po)
2) Prevention of joint damage:
   - DMARDs (plaquenil, MTX, sulfasalazine, gold cyclosporine, leflunomide, biologics…)
3) Control of systemic vasculitis:
   - Immunosuppressants (steroids,azathioprine, cyclophosphamide, chlorambucil)

Acetaminophen

- Uses:
  - Very safe medication for pain control.
  - Ideal first line for non inflammatory conditions
    - eg. OA, mechanical back pain
  - Adjunct therapy for inflammatory conditions.
- Strategies of administration:
  - prn vs prophylactic before painful activities vs regular schedule for best continuous control.
- Disadvantage: frequent administration.
- Dose: up to 4gm/day (2 ES tylenol tabs 4 times a day or 2 “tylenol for arthritis” 3 times a day).
- Concern: liver disease if long term high dose.

Anti-inflammatories (NSAIDs)

- Need regular use for anti-inflammatory effect (vs prn)
- Efficacy and S/E: highly variable between individuals.
- Efficacy trial: maximum dose for 2 weeks
- Cox-2 specific inhibitors: less side-effects
  - Cox-1 mediates normal physiological functions
  - Cox-2 mediates inflammation
- Main S/E: GI upset, diarrhea, ulcer, renal failure, water retention (HBP, edema), platelet abn. (bleeding), CVD.
- Monitoring: BP, usu. no blood tests (hgb & Cr optional)
- Surgery: Discontinue 4 - 5 days prior.
- Topical NSAIDs: used on superficial joints & muscles

Steroids

- Very effective at controlling inflammation, but long term use has risk of side-effects.
- S/E risk increases with dose and duration, no known safe dose or duration. Dose < 7.5 mg/d physiological.
- Osteoporosis Prevention: on ≥ 7.5 mg/day for > 3 months
  - Ca (1200 mg/d), Vit D (800-2000 IU/d) and bisphosphonate
- Intra-articular injections good alternative. Can be repeated every 4-6 months. Rest joint for 24 hours.
- Short courses of low-dose prednisone (5-10 mg/day)
  - useful as bridging therapy, while waiting for DMARD effect
  - to control flare-ups.
- Useful for crystal arthritis (gout/pseudogout)

DMARDs

- Slow disease progression: reduce joint erosion, deformities, improve function.
- Onset of action is slow (av. 6-8 wks). Pts need support with measures for symptomatic relief.
- All have potentially serious S/E:
  - require close monitoring, i.e. regular blood tests
  - very rare and reversible (when monitored)
  - strategies exist to alleviate some S/E (eg.nausea)
  - generic info about S/E not always appropriate

Starting a DMARD

- No consensus on choice of agents, individualized.
- Various agents often needed over time

For mild RA, or for use in combination:

- Hydroxychloroquine:
  - max dose 5.0 mg/kg/day – single dose or BID
  - slow onset of action = 2 – 3 mos
- Sulfasalazine: 1gm BID (up to 1.5 or 2g BID).
  - start at 500 mg/d and gradually increase by 500 mg per week for less side-effects.
  - onset action 4 - 6 weeks.

Starting a DMARD

For moderate or severe RA:

- MTX = most common first choice.
  - Oral or SC injection
  - Up to 25 mg once weekly
  - Often combined with HCQ and/or Sulfasalazine
- Gold (10, 25 then 50 mg IM once weekly)
  - combination with MTX or an alternative when liver concerns
- Leflunomide / Cyclosporine: 2nd / 3rd line

Combination Therapy

- 2 or more DMARDs often used:
  - if poor prognostic factors or
  - if response is not optimal to single therapy.
- Common examples:
  - methotrexate + hydroxychloroquine + sulfasalazine
  - methotrexate + gold
  - methotrexate + leflunomide (some caution)
  - methotrexate + cyclorsporin
  - methotrexate + biologic medication

DMARDs - Monitoring

- Close monitoring is essential.
- All (except plaquenil) require regular blood tests
- MTX, sulfasalazine, leflunomide, cyclosporin: CBC, liver function tests (ALT), creatinine (monthly at first, then every 2 - 3 months).
- Gold: CBC & urine (protein) weekly initially, then q 2 - 4 weeks.
- Plaquenil: Regular eye testing for (q 12-18 mths).
- Leflunomide & cyclosporin: monitor BP

The ART of Methotrexate

- Consider starting at 15 mg/wk in moderately active RA, except in the elderly
- Go to a higher dose – 20 to 25 mg/wk
- Consider MTX SQ, if oral is not tolerated or with insufficient benefit at doses > 15 mg/wk (variable absorption)
- Always use folic acid 1 mg/day to prevent side-effects. May be increased up to 5 mg/day if needed.
- If MTX is not tolerated, consider folinic acid (5 mg po 10 hours post MTX dose) in lieu of folic acid

Newer DMARD

Tofacitnib (Xeljanz)

- Not a biologic (Small molecule, immunomodulator). JAK inhibitor.
- Indications: Approved for RA (mod-severe active RA, failed MTX) used in combination with MTX (unless intolerant).
- Dosing: 5-10 mg po BID
- Side-effects: little GI S/E, increased liver enzymes and lipids, infections (H Zoster), malignancy, CV events, decreased WBC (rare)

Newer DMARD - Apremilast (Otezla)

- DMARD for Psoriatic Arthritis & Psoriasis
- Not covered under pharmacare yet for arthritis
- Tablet of 30 mg taken twice daily
- **Side effects:** may include headache, nausea and diarrhea initially within the first 2 to 4 weeks, weight loss and possible risk of increased depression

Biologic DMARDs: Anti-TNF Agents

- Used when failure of DMARDs (10 -15% cases)
- SQ agents:
  - etanercept (Enbrel, Brenzys, Erelzi)
  - adalimumab (Humira)
  - golimumab (Simponi)
  - certolizumab (Cimzia).
- IV infusions: infliximab (Remicade, Inflectra)
- Best when used in combination with methotrexate
- Indication: all approved for RA, AS, Psoriatic Arthritis & Psoriasis. Some indicated for inflammatory eye & bowel disease

Biologic DMARDs: Anti-TNF Agents

Advantages:
- rapid onset (2 wks)
- very effective at reducing joint pain and swelling & improving fatigue & well-being
- prevents erosions (stops joint damage)

Concerns:
- infections (esp. TB & opportunistic, also bacterial)
- malignancies (skin, lymphoma)
- autoimmune antibodies
- multiple sclerosis
- psoriasis

Other Biologic DMARDs

Abatacept (Orencia):
- Prevents T cell activation (by inhibiting a co-stimulatory molecule on T cells)
- Indication: moderate to severe active RA, first line biologic or after failure of anti-TNF
- Used with or without methotrexate
- 30 min infusion every 4 weeks (except 0, 2, 4 wks)
- SQ injection (pre-filled syringe) weekly
- Side-effects: infusion reactions (rare), injections site reactions, allergic reactions, infections (especially viral), may increase cancer (lung and lymphoma)

Other Biologic DMARDs

Tocilizumab (Actemra):
- Anti-IL-6 (binds to IL-6 receptor)
- Indication: mod-severe active RA, as 1st biologic or after failure of anti-TNF
- Used with or without methotrexate
- Infusion every 4 weeks (4 – 8 mg/kg)
- SQ injection every 1-2 weeks
- Side-effects: infusion reactions (rare), injection site reactions, allergic reactions, headache, hypertension, increased liver enzymes, increased cholesterol, cytopenias, infections.

Other Biologic DMARDs

Rituximab (Rituxan):
- Antibody that depletes B cells (CD-20 +)
- Indication: RA, after failure ≥ 1 anti-TNF
- Used with methotrexate
- Two infusions 2 weeks apart
- Retreatment usually needed after 6-12 mths
- Side-effects: infusion reactions, infections, skin rash, rare brain infection (PML), cardiac

Other Biologic DMARDs

Ustekinumab (Stelara)

- Indications: Approved for PSO and PsA (also used in IBD and sarcoidosis)
- Used with or without methotrexate
- Fully human monoclonal antibody to p40 on IL-23 and IL-12 (prevents binding on T cells)
- SC dosing at 0, 4 weeks, then q12 weeks
- Side-effects: allergic reactions, injection site reactions, headaches, infections, malignancy

Other Biologic DMARDs

Secukinumab (Cosentyx)

- Approved for psoriasis, psoriatic arthritis and AS
- Blocks interleukin (IL-I7A)
- SC injection - preloaded pen or syringe, 4 doses weekly, then every 4 weeks.
- **onset of benefit:** 1 -2 weeks
- **possible side effects: i**nfections – nasopharyngeal, candida, headache, diarrhea (new or flare IBD).

Biosimilars Biologics

- Many different names
  - Canada: Biosimilars
  - USA: Follow-On Biologics
  - Europe: Biosimilar
  - WHO: Similar bio-therapeutic products
- Refers to a product that is structurally "similar to" an original product but "not identical".
- Production process cannot be replicated exactly (e.g. cell lines, manufacturing conditions).
- Not second generation biologic: Structurally different product meant to improve performance

Biosimilar Biologics

- Purpose: to reduce cost.
- Approved on the basis of extensive in vitro comparability testing but NOT clinical comparability testing, reducing approval costs.
- Some clinical trial testing is required to assess efficacy and safety.
- Concerns: Differences in production process and structure may change immunogenicity (allergic/infusion reactions, neutralizing Abs)
- Infliximab biosimilar: Inflectra (Hospira). Remsima (Celltrion),

Holding DMARDs or Biologics

Surgery:

- Hold biologic for approx. 2 weeks prior.
- Resume once healed with no open wounds and no post op infections, no high risk of infections (e.g. no tubes).
- Continue DMARDs until time of surgery.
- Hold MTX and leflunomide post op until healing well and no post-op infections.
- SSZ, gold and plaquenil can be continued.

For infections:

- May continue if a mild viral infection
- Hold until cleared if infection requires an antibiotic, or if a serious infection that requires hospitalization.

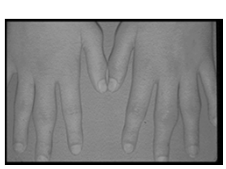
Current trends in RA treatment

1) Early is KEY

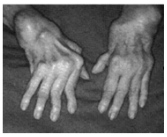
- Early diagnosis for early intervention
- Start DMARDs as soon as RA dx established
- before irreversible joint erosions which => joint damage => deformities => physical disability
- long term prognosis CAN be altered with DMARD therapy
- early patient education

Rationale for early DMARD tx

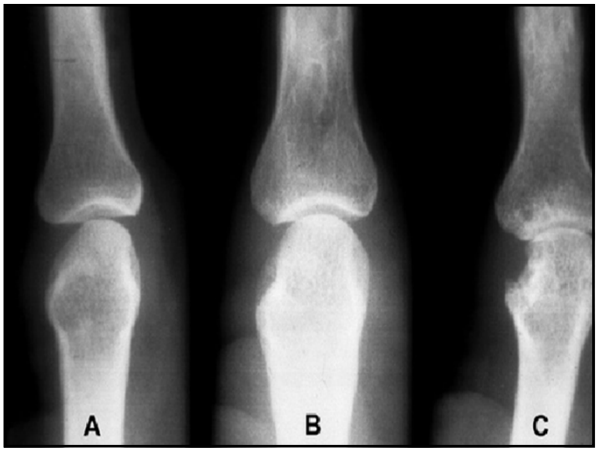
1. Persistent swelling leads to erosions which lead to joint deformities



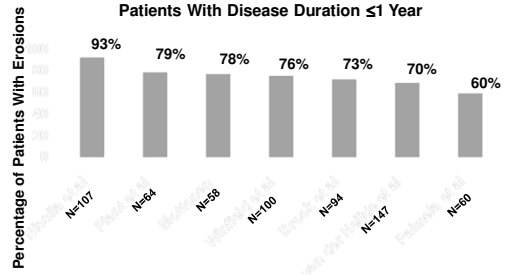
=>



2. Erosions develop early on



A Majority of Patients Develop Bone Erosions Within 1 Year

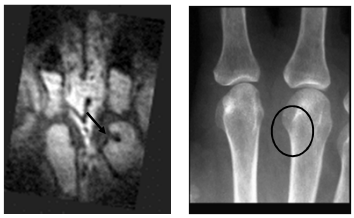


van der Heijde DM, et al. *Br J Rheumatol.* 1995;34(suppl 2):74-78.

Structural Damage Occurs Before It Is Visible on Radiograph

- MRI erosive lesion not evident on plain film
- Erosions can be detected by MRO within 4 months of onset

Distal aspect of the metacarpal on the right

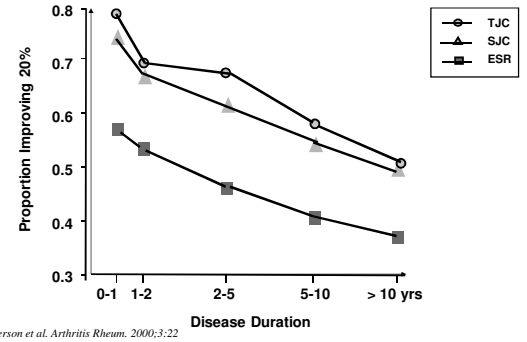


Images compliments of: O. Troum, MD, J. Crues, and Magna Vu.

3. There is likely a **window of opportunity** early in the course of RA, to successfully control inflammation and prevent radiographic erosions

** Boers et al. Arthritis Rheum 2003*

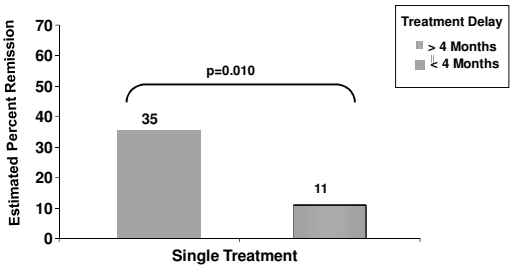
Response to treatment is better earlier in disease course



Anderson et al. Arthritis Rheum. 2000;3:22

Fin-RA Co Study

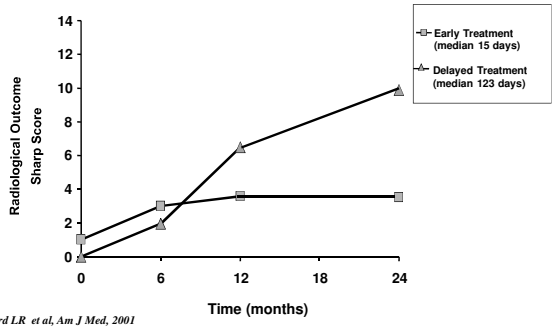
Earlier tx increases chances of remission @ 2 years



Mottonen et al, Arth Rheum 46: 894, 2002

Adjusted for age at BSL, sex, shared epitope, RF and ACR Criteria fulfilled

Brief Delay of Therapy Affects Radiographic Outcome



Lard LR et al, Am J Med, 2001

New trends in treatment of RA

2) Aggressive treatment:

- DMARDs in ALL with active inflammation
- continuous use of DMARDs
- increase to maximum tolerated or recommended dosage until benefit
- switch to another agent if no benefit
- frequent use of combination of agents

New trends in treatment of RA

3. Targeted approach to therapy.

Modify therapy until target is reached:

- no swollen joints,
- normal ESR,
- Little to no radiographic progression.

Aim is no longer simply to control symptoms, but to eradicate inflammation in order to prevent joint damage / physical disability.

**ACR guidelines for the management of RA. A&R 1996;39:713. 2002 Update: A&R 2002,46: 328. 2009 Update*

Key features of inflammatory arthritis:

- EMS > 1/2 hour, stiffness post immobility
- Pain worsens in AM & post immobility, improves with mild activity
- Fatigue and systemic symptoms
- Joint swelling
- Distribution of joint involvement. RA: small joints of hands (esp. MCPs) & wrists; feet (MTPs), symmetrical involvement.

Immunosuppressive agents

- Used to control the symptoms of systemic vasculitis (eg asso with RA) or systemic rheumatic diseases (eg. PMR, SLE, polymyositis).
- Steroids:
  - IV pulse, po, alternate days.
  - Prophylaxis for osteoporosis as soon as start.
  - Key to successful stopping is gradual taper.
  - Many side-effects, esp with long term use

Immunosuppressive agents

Other immunosuppressants:

- Azathioprine (Imuran)
- Methotrexate
- Cyclophosphamide
- Chlorambucil

May be used as "steroid-sparing" agents or as only immunosuppressant

Management of OA

- physio / exercise
- acetaminophen, NSAIDs
- capsaicin ointment, topical NSAIDs
- glucosamine
- intra-articular steroids
- Viscosupplementation
- Stem cell therapy
- joint replacement

Case study

- 37 yr old woman with recently dx RA
- prescribed MTX by rheumato. (15mg/wk).
- While PT visit, complains of nausea and asks if she should stop taking the drug: she wonders if she really needs it, bcse "it's not working", "arthritis is crippling anyways", and she has read about all the nasty S/E on the internet.

Thank you for your attention!

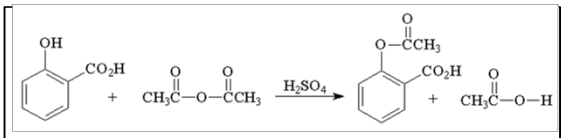
Additional slides for questions

SEBs are NOT Identical to Referent Product

SEBs can differ in at least three ways:

1. Primary amino acid sequence
   - This is usually proprietary and owned by the original manufacturer
2. Modification to amino acids
   - Glycosylation (addition of sugar moieties)
   - Addition of other side chains
3. Higher order structure
   - Protein folding
   - Protein-protein interactions

Synthesis of Small Molecules

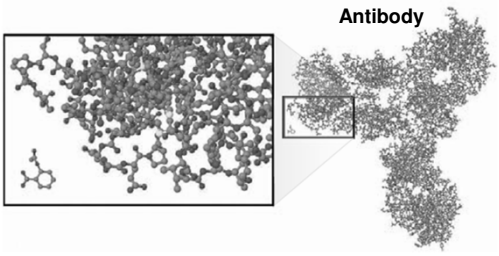


Salicylic acid **Acetic anhydride** **Acetyl salicylic acid ASPIRIN** **Acetic acid**

- Small Molecules like aspirin are made by a defined chemical processes

Adapated from: http://www.umsl.edu/~orglab/experiments/ASPIRIN.html.

Complexity of a Small Molecule Compared to an Antibody



The size and complexity of biologics precludes the use of a small molecule generic model for approval.

Kozlowski S. et al. *NEJM.* 2011;365(5):385-388.
Adapted from: http://www.chm.bris.ac.uk/motm/aspirin/aspirin.htm