The Office of Lifelong Learning, the Division of Rheumatology & the Physician Learning Program

Rheumatology Revealed 2.0: Advanced Insights and Evolving Best Practices for Family Physicians | Pearls for practice

Rheumatology Biologics in Primary Care Practice: Managing Risks, Interactions, and Patient Care

Dr. Anna Oswald

Introduction

- Arthritis Treatment approach: Medications & Non-medication
- Non-Medication: Physiotherapy, Occupational Therapy, Exercise, Education
- Medications:
  - Symptom control: NSAIDS, steroid injections, etc
  - Long term disease control achieved through Disease Modifying Antirheumatic Drugs (DMARD's) which can be Conventional or Biologic
- DMARD's prevent disease flares, disease progression, prevent extension of the disease into other organs (lungs, eyes, spleen, bone marrow and heart) but most importantly they prevent DEATH.
- Patients with RA who are well controlled with DMARD's have a life expectancy that is 21 to 26 years longer than those who are not on DMARD therapy.

Disease-Modifying Antirheumatic Drugs (DMARDs)

- Early aggressive therapy is the standard
  - window of opportunity for remission (6-12mo)
- Combinations work better than monotherapy
- Philosophy parallels that of cancer treatment
  - Hit rapidly dividing cells early and hard
- Goal = early remission, close follow up

Conventional Synthetic (csDMARDS)

- Methotrexate, hydroxychloroquine, sulfasalazine, leflunomide…
  - Cheap
  - Often slower (3-6 months for full effect)
  - More nuisance side effects (N/V, oral ulcers, malaise etc)
  - Fewer serious side effects
  - Often required to fail specific csDMARDs to access advanced therapies
- In RA triple csDMARDs = TNF inhibitor biologic + MTX
  O'Dell et al NEJM 2013;369(4):307-318

Disease-Modifying Antirheumatic Drugs (DMARDs)

- Conventional Synthetic "csDMARDs" e.g. MTX, HCQ…
  - Chemical structure
    - Developed for other purposes: Serendipitous discoveries
    - Generic forms available
- Targeted Synthetic "tsDMARDs" e.g. Janus Kinase inhibitors (JAKi) e.g. tofacitinib, upadacitinib
  - "nib" refers to small-molecule inhibitor of enzymes
  - "citinib" refers to JAK inhibitors
  - Chemical structure specifically designed to target or interfere with specific immune pathway
    - Generic forms available
- "mab" Biologic DMARDs e.g. adalimumab
  - Complex protein structure
    - Monoclonal antibodies designed for a specific target
    - Block the "action site" on the target immune cells
    - Biosimilar forms available
- "cept" Biologic DMARD e.g. etanercept
  - Complex protein Structure
    - soluble receptor designed for a specific target
    - Bind to the circulating antibodies to "mop" them up before they reach target
    - Biosimilar forms available

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Biologic & Targeted Synthetic (ts) DMARDS

- Designer drugs developed for specific immune targets
- Very few nuisance side effects
- Uncommon but more serious side effects
  - Infection risk
- Expensive!!
  - Innovator versions $20 000/year +
  - Biosimilar $11 000 - $16 000 /year +
- Strict rules to access and to continue advanced therapies

What are Biosimilars?

- Biologics are monoclonal antibodies or soluble receptors
  - = Large complex protein structures
- Can't make identical structures without the detailed "recipe"
  - Innovators not required to release "recipe" at patent end
- Biosimilars make the closest possible without actual "recipe"

- "Nocebo effect"
  - Initial unblinded studies: poorer efficacy
  - Subsequent double blind studies: equal efficacy & safety
- Required by all public and most private drug plans now

Pre- Biologics Screening

- TB: skin test or IGRA plus CXR
- Hep B (sAg, cAb, eAg) & Hep C Ab
- Vaccine review
- TNFi: ANA/ENA
- IL6 inhibitors: Lipids, Shingrix
- JAK: Shingrix

Biologic DMARDS- Examples

- Anti-TNF inhibitors (mAbs & Receptor blockers)
  - infliximab (Remicade/Inflectra), golimumab (Simponi)
  - etanercept (Enbrel/Erelzi/Brenzys)
  - adalimumab (Humira, +++ biosimilars), certolizumab…
- Interleukin inhibitors (mAbs):
  - IL-6 tocilizumab (Actemra)
  - IL-17 secukinumab (Cosentyx), Ixekizumab (Taltz)
  - IL-23 ustekinumab (Stelara)
- B-Cell Inhibitors: rituximab (Rituxan/biosimilars)
- Costimulation blockers: abatacept (Orencia)
- Targeted Synthetics (Small molecules)
  - JAK: tofacitinib (Xeljanz), Baricitinib, Upadacitinib (Rinvoq)
  - PDEi: apremilast (Otezla)

Contraindications to Biologics

- All Classes:
  - Active infection, Untreated Hep B/C, Latent TB
  - Live vaccines
  - Active cancer treatment
  - +/- Recurrent non-melanomatous skin cancers
- Anti-TNF
  - Class III/IV CHF, Multiple Sclerosis, Lupus
- IL-6 tocilizumab (tocilizumab)
  - Diverticulosis/itis, risk of bowel perforation, zoster
- JAK inhibitors
  - DVT/PE, zoster
  - Controversial: ??cardiovascular disease, ??cancer

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Common and serious adverse reactions

- Common
  - Infusion reactions for iv preparations
  - Injection site reactions (itchy hive like lesion)
- Less Common but serious
  - Bacterial infection: 1% risk/yr
    - MUST be assessed within 24-48h of symptom onset for consideration of antibiotics
    - Please fit them in!
    - Low threshold for antibiotics if suspicion of infection
    - MUST hold biologic during active infection for duration of antibiotic use, (? longer if high risk to ensure no recurrence)
  - Latent TBI activation
  - Non-melanomatous skin cancers
- Covid Considerations
  - TNFi: improved outcomes
  - Anti-IL6 and JAKi: probably improved as used in Covid Rx
  - Abatacept & rituximab: worse outcomes with COVID

RA and Cancer

- All RA patients have increased risk of heme malignancy (esp lymphoma, leukemia) and non-melanomatous skin cancer
- No increased risk in lymphoma in TNFi treated RA patients vs non TNFi treated RA patients!
  - Originally was thought to be true but several very large studies have since disproven this
- MTX & most biologics give small further increase in non-melanomatous skin cancers
- MTX might give very small increase risk of melanoma (controversial)

How to improve efficacy

- Encourage patients to continue their concurrent conventional DMARD therapy.
  - Patients who are on advanced therapies like biologics or targeted synthetic agents have 20% improved efficacy and outcomes when they are on methotrexate and the biologic
  - MTX suppresses the production of anti-drug antibodies (which are a cause of secondary failure)
  - Discourage Drug Holidays-it is a way for biologics to not work, it alerts the immune system & 25% will not recapture control if flare off drug requiring escalation to stronger DMARD
  - Encourage adherence
  - 1st biologic has best efficacy with decreasing chances of control with each switch
- Perioperative management
  - Biologics: Recommend holding 1-2 weeks prior (depends on severity of disease) and hold for a week after surgery (ensure no immediate post of infections)
  - Don't hold conventional synthetic DMARD's (infection risk is low) except MTX if risk for kidney injury