Welcome!

Initial Therapy: Glucocorticoids and NSAIDs

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DISCLOSURES

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Disclosure Statement

Planners Jennifer Mandal, MD, Leslie Dexheimer Gleason, RN, and Tabitha Carroway, MPH have stated they have no relationships to disclose. Speaker Wendy Grant, MD has stated she has no relationships to disclose.

NSAIDs: The Basics

NSAIDs - Key Points

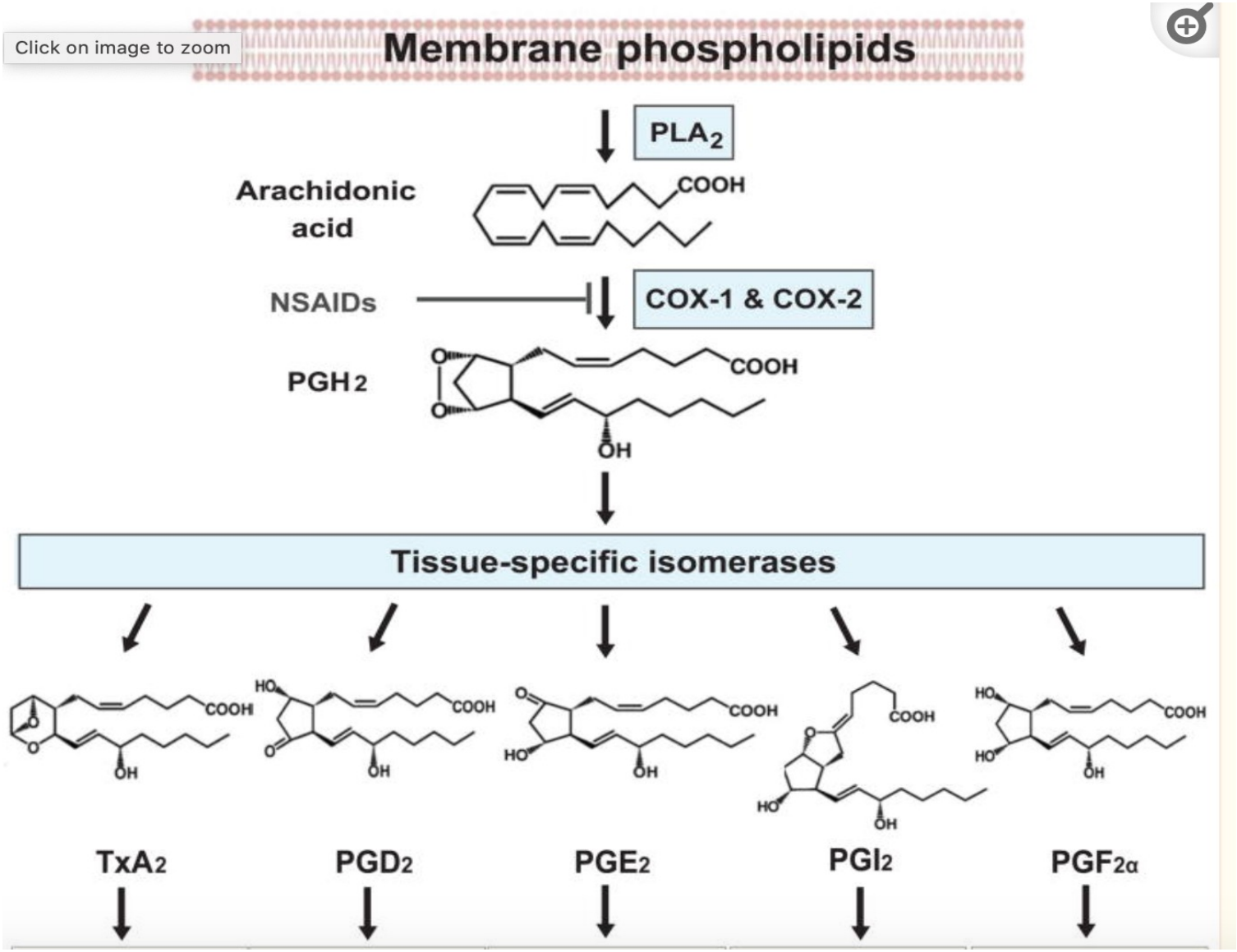
- They are widely used in RA and are effective for treating inflammation and pain
- They do not reduce levels of acute phase reactants or prevent radiographic progression (ie, they are not DMARDs)
- All work by blocking production of prostaglandins via the cyclo-oxygenase enzyme (COX)
- Prostaglandins play a key role in the inflammatory response BUT are also protective in certain tissues

NSAIDs: The Basics

NSAIDs - Key Points

- COX-1: expressed under basal conditions
  - Platelets (thromboxane A2 is a PG that signals platelet aggregation)
  - GI mucosa (PGs have a protective effect)
  - Kidney (renal tubules; PGs help maintain perfusion)

- COX-2: expressed during inflammation/stress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Membrane phospholipids
PLA2
Arachidonic acid
COOH
NSAIDs
COX-1 & COX-2
PGH2
COOH
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Tissue-specific isomerases
COOH
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TxA2
PGD2
PGE2
PGI2
PGF2α

NSAIDs: The Basics

NSAIDs - Key Points

NSAIDs are grouped according to:

- **chemical structure**
- **half life**

”short acting” (< 6 hrs): IBU, diclofenac, ketoprofen, indomethacin

“long acting” (> 6 hrs): naproxen, celecoxib, meloxicam, nabumetone, piroxicam

- **COX-1 vs COX-2 selectivity**

NSAIDs: The Basics

NSAIDs - Key Points

Most NSAIDs inhibit both COX-1 and COX-2, with variable relative potency for these targets

NSAIDs tend to accumulate in synovial fluid; anti-inflammatory effect may last longer than the ½ life suggests

Overall, efficacy of different NSAIDs is about equal although individual responses may vary

Toxicities are largely related to COX-1 effects but also to bioavailabilty, individual patient risk factors

NSAIDs
The Basics

Major Structural Class	Subclass	Examples
Carboxylic Acids	Acetylated	ASA
	Acetic Acids	indomethacin, sulindac, diclofenac
	Propionic Acids	ibuprofen, naproxen
	Pyrollizine Derivatives	ketorolac
Enolic Acids	Oxicams	meloxicam
COX-2 Inhibitors		celecoxib

NSAIDs
The Basics

Short acting (< 6 hrs)

IBU
diclofenac
ketoprofen
indomethacin

Long acting (> 6 hrs)

naproxen
celecoxib
meloxicam
nabumetone
piroxicam

NSAIDs
The Basics

INHIBITION	Examples
COX-1 Specific	ASA (irreversibly binds/inhibits COX-1)
COX Nonselective	ibuprofen, naproxen, indomethacin
COX-2 Selective	meloxicam, diclofenac
COX-2 Highly Selective	celecoxib

NSAIDs
The Basics

NSAIDs: Complications

GI: dyspepsia, esophagitis, ulcers, erosions, strictures, colitis

Renal: Na retention, edema, HTN, ARF, RTA, AIN, accelerated CKD

CV: CHF exacerbation, MI, stroke

Hepatic: transaminase elevations

CNS: headache, confusion, seizures, aseptic meningitis

Allergic: ASA-exacerbated asthma; rash

Bone: delayed healing

NSAIDs
The Basics

NSAIDs: Mitigation Strategies

< 65 years, uncomplicated (no GI, renal or CV risk; no ASA or anticoag)

- traditional NSAID; short acting and lowest dose possible

> 65 years, intermediate risk

- Traditional NSAID + PPI or misoprostol or **high dose** H2 blocker
- If on ASA→ Celecoxib + PPI

NSAIDs
The Basics

NSAIDs: Mitigation Strategies

> 65 years, or otherwise high risk
- intermittent, low-dose, short half-life
- avoid chronic NSAIDs if possible
  if required:
    CV risk > GI risk: use naproxen + PPI
    GI risk > CV risk: use Celecoxib + PPI
- acetaminophen < 3 gm/day
- Consider topical NSAIDs (diclofenac gel)

NSAIDs
The Basics

NSAIDs in RA

- Avoid concomitant use with glucocorticoids
- MTX & NSAIDs: theoretically NSAIDs may increase MTX plasma concentrations. However, a 2012 Cochrane review concluded that NSAID + MTX was safe
- Monitor CMP/CBC annually in chronic use

NSAIDs
The Basics

NSAIDs in Pregnancy

- **Safe up to 20 weeks**
- **Possible increased risk of oligohydramnios at 20-30 weeks**
- **Avoid > 30 weeks (premature closure of the PDA)**

Glucocorticoids: The Basics

Glucose metabolism + adrenal cortex + steroid structure =

Glucocorticoids

”Corticosteroids” = glucocorticoids + mineralocorticoids

GCs bind to intracellular GC receptor and inhibit a broad range of immune responses; inhibit synthesis of almost all pro-inflammatory cytokines

Addison used adrenal extracts in the 19th C to treat “Addison’s disease”

1940’s push to isolate active compounds from adrenals

1948: first therapeutic use of glucocorticoids (compound E) in human disease

Glucocorticoids: The Basics

GCs - Key Points

- both ACR and EULAR's guidelines advocate for using the lowest dose (10 mg or 7.5 mg) for the shortest time possible

- recommended to use with initiation of DMARD therapy with plan for taper off by 3 months (US) or 6 months (EU) and for flares

= clear data that GCs reduce disease activity in the short term

- medium and long term benefit? Some studies show decreased radiographic progression at 2 years in GC + MTX vs PBO + MTX

Glucocorticoids: The Basics

DURATION	GLUCOCORTICOID	POTENCY	MINERALOCORTICOID
Short Acting	Hydrocortisone	1	1
Intermediate Acting	Prednisone	4	0.25
	Prednisolone	4	0.25
	Methylprednisolone	5	+/-
Long Acting	Dexamethasone	40	+/-

Glucocorticoids: The Basics

GCs - RA

- Initial: 10 - 15mg QD, then taper to 5 mg while introducing DMARD therapy
- For flares:
  - Multiple options but if treating for 3-10 days, no need to taper
  - Unusual to require > 15 mg for flare
  - Consider IM methylpred at 80-120 mg; self-taper over 2 weeks
- Chronic low-dose (5mg or less) used, rarely, as chronic therapy

Glucocorticoids: The Basics

Toxicities are generally related to dose and duration

Very low dose GC (3 mg/d) = no increased risk of toxicities at 7 years

- *Endocrine:* osteoporosis
- *Infectious:* any infection
- *GI*: gastritis/erosion/ulcers
- *Endo*: Risk of adrenal insufficiency at 3-5wks
- *Endo*: Risk of insulin resistance incr. at >10 pred/day
- *CV*: Fluid retention/hypertension; cardiovascular events
- *Integument:* skin fragility

Glucocorticoids: The Basics

Glucocorticoids: Mitigation Strategies

Lowest dose, shortest duration

Ca/Vit D supplementation

Screening/treatment for osteoporosis (bone loss is most pronounced in the first few months of treatment; GCs associated with higher fracture risk and at higher BMD)

GI protection

PJP prophylaxis for prednisone > 20 mg x 4 weeks

increased risk with baseline lymphopenia, pulse steroids, cyclophosphamide use

GCs and NSAIDs
The Basics

SUMMARY

- NSAIDs treat pain and inflammation - but are NOT effective DMARDs in RA
- GCs at low dose may have some DMARD effects but are generally not used in this fashion, given other effective therapies
- NSAID and GC treatment-related AEs common but often manageable with proper screening/mitigation

Opioids and RA

Any benefit in treating RA pain?

- Trials are of short duration
- Benefit is neutral/modest in these trials
- Most evidence does not support the use of opioids in chronic non-cancer pain

Opioids and RA

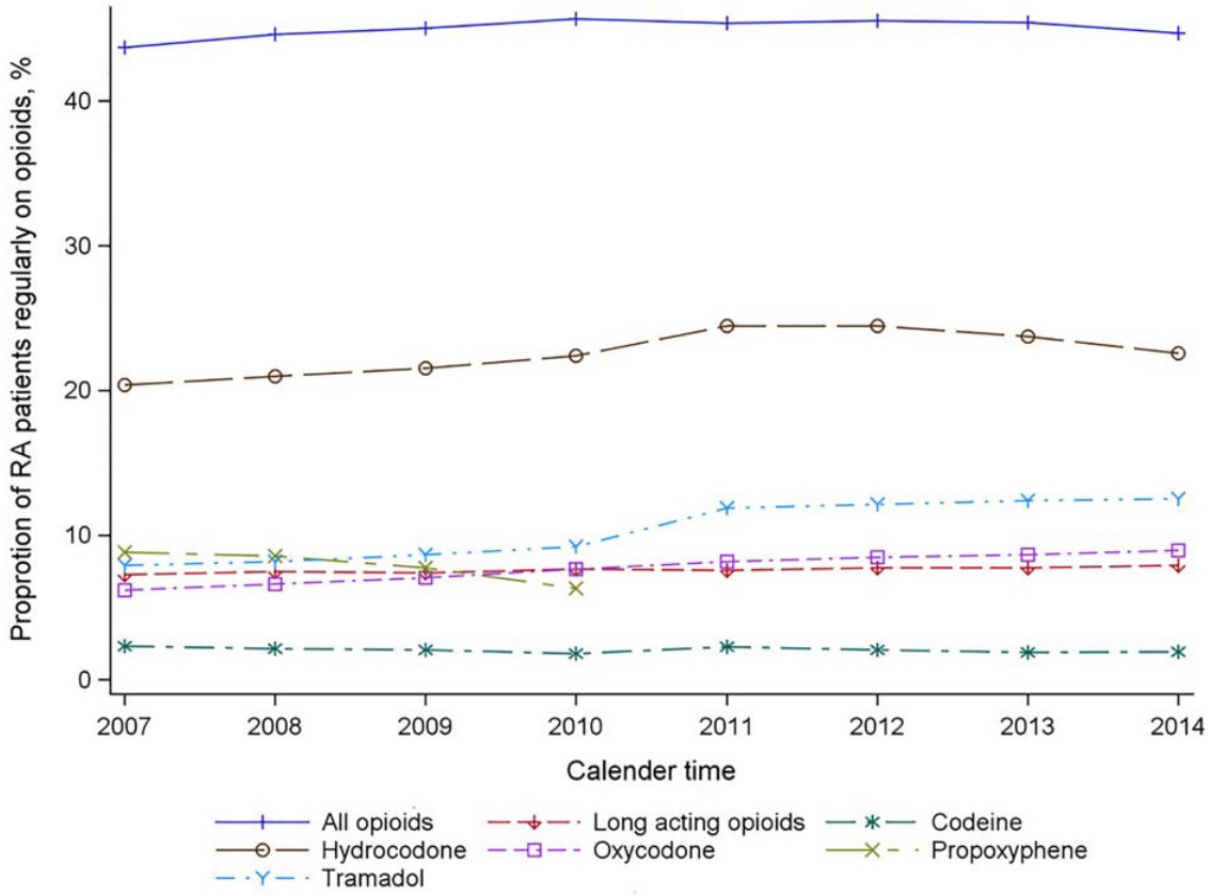

Figure 1. Trends in regular opioid receipt (defined as ≥3 filled prescriptions or at least 90 days of cumulative use in each 12-month calendar interval) in patients with rheumatoid arthritis (RA).

Curtis et al. Arthritis and Rheumatology. Vol 69, No 9, Sept 2017; 1733-1740

Opioids and RA

Regular opioid use was associated with

- female sex
- fibromyalgia
- depression/anxiety
- back pain
- use of durable medical equipment

In a separate study, 25% of regular opioid use among RA patients was associated with obesity

Curtis et al. Arthritis and Rheumatology. Vol 69, No 9, Sept 2017; 1733-1740

What about Diet?

Altered microbiome postulated as possible etiology in pathogenesis of RA

Foods purported to promote/exacerbate inflammation:

- refined sugar/sugary drinks
- preservatives
- saturated and trans fats
- red/processed meats
- highly processed foods

What about Diet?

Most trials of diet in RA are small (15-30 patients)

Short term benefits found in:

- Subtotal fasting → vegan diet
- Vegan diet
- Mediterranean diet
- ITIS diet (Mediterranean plus)

Obesity and RA

- Higher disease activity scores
- Higher pain scores
- Reduced remission rates
- Decreased response to c/b DMARDs

Weight loss effects

In 53 patients who underwent bariatric surgery, 68% achieved remission at 6 months

References

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