Overview of NSAIDs and DMARDs in rheumatic diseases

Chingching Foocharoen
Faculty of Medicine
Khon Kaen University
NSAIDs

- NSAIDs classification
- NSAIDs in special conditions
- Comparative analgesic efficacy
- Comparative toxicity
  - Cardiovascular safety
  - COX-2 inhibitor VS nonselective COX-2 and gastrointestinal events
- Recommendation for reducing toxicity
- Drug interactions
DMARDs

- Clinical application
- Comparative efficacy
- Treatment strategy in RA (EULAR recommendation)
- Safety concerns of treatment
- DMARDs and pregnancy
NSAIDs
NSAIDs classification

- Duration of action
  - Short / intermediate / long acting
- COX specific
  - Nonselective COX inh
  - Selective COX-1 inh
  - Selective COX-2 inh
  - Highly selective COX-2 inh
- Chemical structures
**NSAIDs in special conditions**

- **Elderly patient:** short acting NSAIDs
- **Acute inflammation:** short acting NSAIDs
- **Liver disease**
  - avoid sulindac, indomethacin, mefenamic acid, diclofenac
- **Renal disease**
  - avoid if GFR<30 ml/min
- **SLE**
  - avoid ibuprofen
- **Preoperative / postoperative condition**
- **History of GI problem**
- **History of CVS problem**
Comparative analgesic efficacy
### Efficacy of NSAIDs for OA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of Patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>800</td>
<td>0.006</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>53</td>
<td>0.002</td>
</tr>
<tr>
<td>Etodolac/naproxen</td>
<td>254</td>
<td>0.006</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>219</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Naproxen/nabumetone</td>
<td>279</td>
<td>0.733</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>386</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valdecoxb/naproxen</td>
<td>613</td>
<td>0.002</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>271</td>
<td>0.034</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>347</td>
<td>0.080</td>
</tr>
<tr>
<td>Celecoxib/diclofenac</td>
<td>600</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Etodolac/nabumetone</td>
<td>270</td>
<td>0.002</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>1,702</td>
<td>0.003</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>39</td>
<td>0.119</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>328</td>
<td>0.351</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>104</td>
<td>0.053</td>
</tr>
<tr>
<td>Etodolac</td>
<td>715</td>
<td>0.015</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>801</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>10,845</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Efficacy of NSAIDs

- **RA**
  - RCT: no different between COX-2 selective and conventional NSAIDs

- **Ankylosing spondylitis**
  - RCT: celecoxib = conventional NSAIDs
Comparative toxicity
## Incidence rate of major events

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence rate per 1000 patient-yr</th>
<th>Increased risk</th>
<th>Hospitalizations per 100,000 users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>2-4</td>
<td>2-fold</td>
<td>300</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1-4</td>
<td>2-fold</td>
<td>300</td>
</tr>
<tr>
<td>UGIB</td>
<td>0.6-1.7</td>
<td>4-fold</td>
<td>300</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0.02-0.08</td>
<td>2-4 fold</td>
<td>4-8</td>
</tr>
<tr>
<td>Acute liver injury</td>
<td>0.02-0.04</td>
<td>2-fold</td>
<td>5</td>
</tr>
</tbody>
</table>

Hochberg MC. Rheumatology 2011
Cardiovascular safety

<table>
<thead>
<tr>
<th>Myocardial infarction</th>
<th>Rate ratio (95% credibility interval)</th>
<th>Rate ratio (95% credibility interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>0.82 (0.37 to 1.67)</td>
<td>1.61 (0.50 to 5.77)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.82 (0.29 to 2.20)</td>
<td>1.35 (0.71 to 2.72)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.75 (0.23 to 2.39)</td>
<td>2.12 (1.26 to 3.56)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>2.00 (0.71 to 6.21)</td>
<td>2.00 (0.71 to 6.21)</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>2.00 (0.71 to 6.21)</td>
<td>2.00 (0.71 to 6.21)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2.00 (0.71 to 6.21)</td>
<td>2.00 (0.71 to 6.21)</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>2.00 (0.71 to 6.21)</td>
<td>2.00 (0.71 to 6.21)</td>
</tr>
</tbody>
</table>

Favours NSAID

Favours placebo

Trelle S. BMJ 2011; 342: c7086
Cardiovascular death

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate ratio (95% credibility interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>0.98 (0.41 to 2.37)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2.39 (0.69 to 8.64)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.98 (1.48 to 12.70)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>2.07 (0.98 to 4.55)</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>4.07 (1.23 to 15.70)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.58 (0.88 to 2.84)</td>
</tr>
<tr>
<td>Lumaracoxib</td>
<td>1.89 (0.64 to 7.09)</td>
</tr>
</tbody>
</table>

Trelle S. BMJ 2011; 342: c7086
Reducing CVS risk

American College of Cardiology
- lowest effective dose NSAIDs using

American College of Rheumatology
- avoid all NSAIDs in CVS risk patients
  - HT
  - Hypercholesterolemia
  - Angina
  - Recent bypass surgery
  - History of MI
- Naproxen if require
COX-2 inhibitor VS nonselective COX-2 and gastrointestinal events

Graph showing the relative risk (RR) and 95% CI for various COX-2 inhibitors compared to nonselective COX-2 inhibitors. The graph indicates a higher relative risk for COX-2 inhibitors, with specific p-values and sample sizes provided for each comparison.
### Upper gastrointestinal adverse events

#### COX-2 inhibitor VS nonselective COX-2 and gastrointestinal events

#### Upper gastrointestinal (UGI) adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Coxib Events</th>
<th>Coxib Total</th>
<th>NSAID + PPI Events</th>
<th>NSAID + PPI Total</th>
<th>Weight</th>
<th>Risk ratio M-H, random, 95% CI</th>
<th>Risk ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. [25]</td>
<td>3</td>
<td>64</td>
<td>6</td>
<td>66</td>
<td>10.4%</td>
<td>0.52 (0.13, 1.97)</td>
<td></td>
</tr>
<tr>
<td>Chan et al. [24]</td>
<td>7</td>
<td>144</td>
<td>9</td>
<td>143</td>
<td>14.4%</td>
<td>0.77 (0.30, 2.02)</td>
<td></td>
</tr>
<tr>
<td>Chan et al. [23]</td>
<td>20</td>
<td>116</td>
<td>26</td>
<td>106</td>
<td>20.2%</td>
<td>0.70 (0.42, 1.18)</td>
<td></td>
</tr>
<tr>
<td>Chan et al. [22]</td>
<td>33</td>
<td>2239</td>
<td>115</td>
<td>2246</td>
<td>21.8%</td>
<td>0.29 (0.20, 0.42)</td>
<td></td>
</tr>
<tr>
<td>Goldstein et al. [26]</td>
<td>42</td>
<td>426</td>
<td>38</td>
<td>428</td>
<td>21.4%</td>
<td>1.11 (0.73, 1.69)</td>
<td></td>
</tr>
<tr>
<td>Lai et al. [27]</td>
<td>4</td>
<td>120</td>
<td>7</td>
<td>122</td>
<td>11.7%</td>
<td>0.58 (0.17, 1.93)</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 310 3111 100.0% 0.61 (0.34, 1.09)

Total events 109 201

Heterogeneity: $I^2 = 0.36, \chi^2 = 23.41, df = 5 (P = 0.0003); I^2 = 79\%$

Test for overall effect: $Z = 1.67 (P = 0.09)$

---

Reducing gastrointestinal risk

- PPI, misoprostal, H2-blocker
  - Aging >65 yr
  - Previous GI event
  - NSAIDs combination with ASA / steroid / anticoagulant
  - Co-morbid disease

- PPI cannot prevent LGIB & ulcer

- Fixed dose combination NSAIDs + PPI
  - Diclofenac 50-75 mg + misoprostol 200 mcg
  - Naproxen 500 mg + esomeprazole 20 mg
  - Ibuprofen 800 mg + famotidine 26.6 mg

## Drugs interaction

<table>
<thead>
<tr>
<th>Drug</th>
<th>NSAID</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulant</td>
<td>All</td>
<td>Increase anticoagulant effect</td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>All</td>
<td>Increase risk of hypoglycemia</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>All</td>
<td>Displace phenytoin from plasma protein</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>ASA</td>
<td>Inhibit valproate metabolism</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>All</td>
<td>Reduced clearance of MTX</td>
</tr>
<tr>
<td>Digoxin</td>
<td>All</td>
<td>Reduced clearance of digoxin</td>
</tr>
<tr>
<td><strong>Antihypertensive (beta-blocker, diuretic, ACEI)</strong></td>
<td>All</td>
<td>Reduced hypotensive effect</td>
</tr>
<tr>
<td>Low dose ASA</td>
<td>Ibuprofen</td>
<td>Reduced cardioprotective effect</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>All</td>
<td>Reduced aminoglycoside clearance</td>
</tr>
</tbody>
</table>

Hochberg MC. Rheumatology 2011
DMARDs
DMARDs

- Clinical application
- Comparative efficacy
- Treatment strategy in RA (EULAR recommendation)
- Safety concerns of treatment
- DMARDs and pregnancy
Clinical application

- Inflammatory arthritis
- Autoimmune diseases
Comparative efficacy

Weak DMARDs
- Chloroquine
- Hydroxychloroquine
- Sulfasalazine
- Gold compound
- Leflunomide
- Cyclosporin A

Strong DMARDs
- Azathioprine
- Methotrexate

Treatment strategy in RA

- **Goal:** low disease activity-remission
- **1st line DMARD** = MTX
- **Before starting**
  - Infection screening: HIV, HBV, HCV, CXR
  - Routine check up: CBC, LFT

Algorithm based on EULAR recommendation

Clinical diagnosis of RA

- MTX
  - If no contraindication
- LFN, SSZ or gold
  - If contraindication to MTX

- + GCs

Not achieve target within 3-6 months

- Unfavorable prognosis
  - add biological agent (anti-TNF)
- No unfavorable prognosis
  - Start LFN, SSZ, gold as combination Rx

- Not achieve target within 3-6 months

REFER

Switch to 2nd anti-TNF or other biological Rx
Safety concerns
Chloroquine / Hydroxychloroquine

**Side effect**
- Eyes: 
  - Corneal deposit
  - Accommodation defect
  - Retinopathy (maculopathy)
  - Classic Bull’s eye lesion
- Myopathy
- Nausea vomiting
- Hyperpigmentation
- Hemolysis

**Recommendation**
- Eye examination:
  - every 6 mo for CQ
  - every 12 mo for HCQ
Dose adjustment for CQ / HCQ

CQ (250)
- 4 mg/kg/d
- 1 tab oral hs
- ½ tab oral hs
- ½ tab oral EOD

HCQ (200)
- 6 mg/kg/d
- 1 tab oral bid
- 1 tab oral hs
- ½ tab oral hs
- ½ tab oral EOD
Sulphasalazine

**Therapeutic dose:**
- 2-3 gm/d  start 0.5 gm/d initially
- SSZ(500)  1x1  for 1 week
  then  1x2  for 1 week
  then  1x3  for 1 week
  then  2x2  for 1-3 mo

max dose  2x3
Sulphasalazine side effect & monitoring

- Nausea vomiting and anorexia
- Metallic taste
- BM suppression
- Proteinuria
- Yellow secretion

**Monitor:** CBC, liver function test every 2 wk initially, then q 4-12 wk
Methotrexate

- **Started dose**: 7.5 mg/wk (3 tab/wk)
- **Max dose**
  - 15 mg/wk oral form
  - 25 mg/wk injection form

**Side effects**
- Mucositis
- Megaloblastic anemia
- BM suppression
- Hepatic fibrosis

**Monitoring**
- CBC, MCV
- Serum albumin
- LFT
Combination Therapy

- SSZ + HCQ
- MTX + SSZ
- MTX + HCQ
- MTX + SSZ + HCQ
- MTX + leflunomide
- MTX + CSA
- MTX + anti-TNF alpha
- Gold salt
DMARDs in special conditions

- Liver disease
  - SSZ, gold salt, cyclosporin A
- Viral hepatitis
  - Cyclosporin A
- Renal problem
  - Unsafe: SSZ, cyclosporin A
- HIV
  - SSZ, cyclosporin A
DMARDs and pregnancy

Methotrexate
Leflunomide
Sulfasalazine
Gold salt
Cyclosporin A

CQ / HCQ
Azathioprine
Thank you