Cardiovascular and GI Side Effects of Rheumatologic Medications

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Learning Objectives

1. Recognize the burden of cardiovascular comorbidities in patients with inflammatory arthritis
2. Identify benefits of DMARD therapy on cardiovascular risk
3. Review and quantify the risks of NSAID use on the heart and gut
4. Develop strategies for dealing with nuisance GI complaints with methotrexate
5. Review the protocol for liver monitoring with MTX
6. Recognize the far reaching and significant toxicities of glucocorticoids
Disclosures

- None
Quantifying Cardiovascular Risk in RA

What do we know?

• Incidence of cardiovascular disease is increased in RA by about 50% compared to the general population
• Incidence of heart attack increased 68%
• Incidence of stroke increased 41%
• This excess risk only increases with age
Quantifying Cardiovascular Risk in RA

AT THE HEART OF DIABETES

U.S. DIABETES PATIENTS HAVE:

- 2-3x increased risk for heart disease
- 30% of coronary stents implanted in 2011
- 280,000 heart attacks annually
- 2-4x higher heart disease morbidity and mortality rates
- 60% chance of dying from heart disease

Traditional Cardiovascular Risk Factors Predict CVD in RA Patients
Cardiovascular Risk in RA not explained by Traditional Risk Factors Alone

• Undertreatment of traditional risk factors
  • RA patients post MI undertreated with usual secondary prevention pharmacotherapy compared to controls (Denmark).

• Disease specific factors
  • Rheumatoid cachexia
  • Autoantibody positivity
  • Rheumatoid nodules
  • CRP and chronic inflammation
  • Drug toxicity
Methotrexate and CV Benefits

Methotrexate use associated with a 70% reduction in CV mortality

<table>
<thead>
<tr>
<th>medication</th>
<th>Deaths/person-months</th>
<th>Hazard ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>46/27 122</td>
<td>0.2 (0.1–0.7)</td>
</tr>
<tr>
<td>Other DMARD</td>
<td>64/25 287</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>17/4253</td>
<td>0.9 (0.2–4.2)</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>27/9348</td>
<td>0.8 (0.3–2.5)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>61/23 577</td>
<td>0.7 (0.3–2.2)</td>
</tr>
<tr>
<td>Intramuscular gold</td>
<td>50/24 451</td>
<td>1.9 (0.7–5.2)</td>
</tr>
<tr>
<td>No DMARD</td>
<td>19/14 771</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Methotrexate and CV Benefits


- Methotrexate use decreases:
  - All cause mortality
  - CV mortality
  - CV morbidity (MI, CHF)

- Unknown (insufficient data) effects on:
  - HTN
  - Lipid Status
  - Insulin Resistance
  - Stroke
Methotrexate and CV Benefits

Practical Application

• Fewer patients with RA die from CV disease, if they take methotrexate
• Let’s use this as a marketing tool in the clinic!
• Cardiovascular Inflammation Reduction Trial
  • NIH funded
  • Low dose po MTX for secondary prevention of CVE in pts at risk (eg. DM, metabolic syndrome)
Biologic DMARDs and CV Benefits:


Incidence of CVE/1000 patient years in Swedish RA patients:

<table>
<thead>
<tr>
<th>Traditional DMARDS</th>
<th>TNF Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.4 (16.5–54.4)</td>
<td>14.0 (5.7–22.4)</td>
</tr>
</tbody>
</table>
Biologic DMARDs and CV Benefits:


- Systematic Review and Meta-analysis
  - TNF inhibitor use decreased risk of CVE by 30%
  - MTX use decreased risk of CVE by 28%
  - Trend toward a reduction in stroke with TNF inhibition
Caveat: Biologics and CHF

ATTACH Trial (2003)
  Remicade in moderate to severe heart failure
  Clinical worsening

RENEWAL Trial (2004)
  Enbrel in chronic heart failure
  No Benefit
Biologic DMARDs and CV Benefits

Practical application

- TNF inhibitors decrease CVE in patients with RA
- It is unclear if TNF inhibitors provide more benefit than MTX
- TNF inhibitors may decrease stroke risk in patients with RA
- TNF inhibitors are relatively contraindicated in severe (class 4) heart failure
Biologic DMARDs and CV Benefits –
The Lipid Paradox

If biologic drugs decrease CV risk, why do they increase cholesterol?
Biologic DMARDs and CV Benefits – The Lipid Paradox

- Chronic inflammation alters lipid metabolism counter-intuitively

<table>
<thead>
<tr>
<th></th>
<th>Healthy Heart</th>
<th>Active Inflammation</th>
<th>Treated Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>Low</td>
<td>Low</td>
<td>Increases</td>
</tr>
<tr>
<td>LDL</td>
<td>Low</td>
<td>Low</td>
<td>Increases</td>
</tr>
<tr>
<td>HDL</td>
<td>High</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Low</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>
The net effect of improving the inflammatory burden but increasing cholesterol levels with IL-6 antagonist treatment and JAK inhibitors on cardiovascular risk is undetermined.

Summary

- Recognize CV risk in RA
- Assess for and treat traditional risk factors
- Use methotrexate!
- Treat the disease!
- Recognize the lipid paradox. Monitor lipids after 3 months of therapy with tocilizumab or tofacitinib
NSAIDs and CV Risk – The Bad

Sometimes you can improve two lives with a single prescription.
Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

Robert S. Bresalier, M.D., Robert S. Sandler, M.D., Hui Quan, Ph.D., James A. Bolognese, M.Stat., Bettina Oxenius, M.D., Kevin Horgan, M.D., Christopher Lines, Ph.D., Robert Riddell, M.D., Dion Morton, M.D., Angel Lanas, M.D., Marvin A. Konstam, M.D., and John A. Baron, M.D., for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators*

Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention

Scott D. Solomon, M.D., John J.V. McMurray, M.D., Marc A. Pfeffer, M.D., Ph.D., Janet Wittes, Ph.D., Robert Fowler, M.S., Peter Finn, M.D., William F. Anderson, M.D., M.P.H., Ann Zauber, Ph.D., Ernest Hawk, M.D., M.P.H., and Monica Bertagnolli, M.D., for the Adenoma Prevention with Celecoxib (APC) Study Investigators*
Figure 7. Comparison of NSAIDs and Coxib Mechanisms of Action

Coxib and traditional NSAID Trialists’ (CNT) Collaboration


- Meta-analysis of individual participant data from RCTs of COXIBs and traditional NSAIDs
- >300 000 participants
- >600 trials
- Most of the data came from trials of high dose COXIB, ibuprofen, diclofenac and naproxen
Coxib and traditional NSAID Trialists’ (CNT) Collaboration


- Traditional NSAIDs no better than COXIBS
- Vascular risks of ibuprofen* and diclofenac (at high dose) are similar to coxibs
  - Major cardiovascular events increased by about 1/3 compared to placebo (largely due to an increase in MI)
  - Vascular death increased compared to placebo

- Naproxen (even at high dose) not associated with an increased risk of major vascular events
What are the absolute CV risks of NSAID use?

<table>
<thead>
<tr>
<th></th>
<th>High Baseline CV Risk (2% per year)</th>
<th>Low Baseline CV Risk (0.5% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COXIB</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Naproxen</td>
<td>−1</td>
<td>0</td>
</tr>
</tbody>
</table>
NSAIDs and CV Risk – The BAD

Practical Applications

- Limit NSAID use to a short course
- Educate your patient RE: PRN use
- Use the lowest effective dose
- Evaluate cardiovascular risk
  - CV Risk is present as early as the first week of use, but resolves promptly with discontinuation
- Choose naproxen* (at high dose) if you must use an NSAID in patients with known CAD
- Do not use in patients with CHF
- Follow BP

*ORAI Rheumatology Association
Corticosteroids and CV Risk – The UGLY


• CV Mortality Rate
  • 1.8 / 100 patient years all comers with RA
  • 2.5 / 100 patient years if glucocorticoid exposed
  • 1.3 / 100 patient years if glucocorticoid naive

• Risk of CV Death increased quantitatively with
  • Daily dose
  • Cumulative dose
  • Intensity of exposure (gms per year)
What is a “safe” dose?

**CV Death**

- 7.5 mg or less: No increased risk
- 8-15 mg/d: HR 3.17
- >15 mg: HR 4.08

**Cumulative dose**

- <40 grams: No increased risk
- >40 gms: HR 2.32
• How long does it take to reach 40 grams?
  • 3 mg/d - 36.5 years
  • 5 mg/d x 21.9 years
  • 10 mg/d x 10.9 years
Figure 7. Comparison of NSAIDs and Coxib Mechanisms of Action

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Risk Factors</th>
</tr>
</thead>
</table>
| **High Risk**   | • History of complicated PUD  
                  • >2 risk factors                                                                                                                           |
| **Moderate Risk** | • 1-2 risk factors  
                  • Age >65  
                  • High dose NSAID therapy  
                  • History of uncomplicated peptic ulcer  
                  • Concurrent use of ASA, steroids, anticoagulants                                                                                   |
| **Low Risk**    | • No risk factors                                                                                                                             |

NSAIDs and GI Risk – Predicting the BADNESS

American College of Gastroenterology 2009 Guidelines
COXIBs and traditional NSAIDs (Diclofenac, ibuprofen, naproxen) ALL increase risk of upper GI complications compared to placebo

Only 2% of upper GI bleeds are fatal

Coxib and traditional NSAID Trialists’ (CNT) Collaboration

What are the absolute GI risks of NSAID use?

### Absolute Annual Excess Risk of Upper GI Complications?

<table>
<thead>
<tr>
<th></th>
<th>High Baseline Risk for UGI Complications (0.5% per year)</th>
<th>Low Baseline Risk for UGI Complications (0.2% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COXIB</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Naproxen</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>
NSAIDs and GI Risk – The BAD


Ascending Risk of GI Complications:
1. Meloxicam    RR 1.24
2. Ibuprofen    RR 1.43
3. Piroxicam RR 1.66
4. Diclofenac  RR 1.73
5. Naproxen RR 1.83
6. Indomethacin RR 2.25
NSAIDs and GI Risk – The BAD


Dose Dependent GI Risk:

- High dose Indomethacin: RR 7.0
- Low dose Indomethacin: RR 3.0
- High dose Naproxen: RR 6.0
- Low dose Naproxen: RR 3.7
NSAIDs and GI Risk – The BAD

Practical Applications

• Avoid if possible
  • All NSAIDs (COX1 and COX2 inhibitors) increase the risk of upper GI complications
• COXIBs have less risk, but are not risk free
  • Any GI benefits of COXIBs are eliminated when using low dose ASA
  • COXIBs may not be any better than traditional NSAIDs in anticoagulated patients
• Limit duration of use
  • GI toxicity can be seen after only a week of use
• Use lowest effective dose
  • Dose dependent toxicity
### NSAIDs and GI Risk – Predicting the BADNESS

<table>
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<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of complicated PUD</td>
<td>• 1-2 risk factors</td>
<td>• No risk factors</td>
</tr>
<tr>
<td>• &gt;2 risk factors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Age >65**
- **High dose NSAID therapy**
- **History of uncomplicated peptic ulcer**
- **Concurrent use of ASA, steroids, anticoagulants**

*American College of Gastroenterology 2009 Guidelines*
MTX and GI Risk – The BAD

Nuisance Side Effects

• Nausea
• Mouth sores
• Diarrhea
MTX and GI Risk – Nausea


- 35 people out of 100 experience nausea when taking MTX alone

- 9 fewer people out of 100 experienced stomach problems when taking folic acid with MTX
  - 9% absolute improvement
MTX and GI Risk – Mucositis


• 22 people out of 100 experienced mouth sores when taking MTX alone

• 6 fewer people out of 100 experienced mouth sores when taking folic acid with MTX
  • 6% absolute improvement
MTX and GI Risk – Adherence


• 25 people out of 100 who took a placebo with their MTX stopped the drug

• 15 fewer people out of 100 who took folic acid with MTX stopped the drug
  • 15% absolute improvement
MTX and GI Risk – Coping with Nuisance Side Effects

Practical Application

- Try subcutaneous dosing
- Split the dose AM and PM
- Always supplement with folic acid
- Take at bedtime to sleep through toxicity
- Use an anti-nauseant if necessary
MTX and GI Risk: Hepatotoxicity
MTX and GI Risk: Hepatotoxicity

- Incidence of liver enzyme abnormalities with MTX
  - 22% MTX alone
  - 17% Leflunomide alone
  - 31% MTX with Leflunomide
  - 14% neither

- Psoriatic Arthritis and MTX use: 2.76 fold more likely to exhibit liver enzyme elevations than RA patients

21 people out of 100 had liver problems when taking MTX alone.

16 fewer people out of 100 experienced liver problems when taking folic acid with MTX.

16% absolute improvement.
MTX and GI Risk: Hepatotoxicity

Monitoring (ACR Guidelines)

- Hepatitis B and C testing before initiation of MTX
- Monthly monitoring of ALT and Albumin initially
- After 6 months – can move to q 12 weekly labs
- Liver biopsy if 6 of 12 tests are abnormal in any year
- Education re: alcohol use

- BMI and fatty liver disease
GI PERFORATION

- PreDMARD RA
  - Common cause of death (1/3 of these being lower GI perfs)
  - RR of dying from GI causes more than sixfold as compared to age and sex matched cohorts
- NSAIDS
  - RR of diverticular perforation 2.96
**Biologics and GI Risk: The UGLY**

**RATE OF GI PERFORATION**

<table>
<thead>
<tr>
<th></th>
<th>per 1000 pt years</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>0.1</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>3.9</td>
</tr>
<tr>
<td>DMARDs</td>
<td>1.3</td>
</tr>
<tr>
<td>TNF with Corticosteroids</td>
<td>1.12</td>
</tr>
<tr>
<td>TNF alone</td>
<td>0.47</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Adapted from Gout et al. Clin Rheum 2011;30:1471–1471
Practical Application

- Screen for diverticular disease in those patients anticipating biologic therapy
- Avoid NSAIDs
- Avoid steroids
- Remember the risk is small, but the mortality significant
Learning Objectives

1. Recognize the burden of cardiovascular comorbidities in patients with inflammatory arthritis
2. Identify benefits of DMARD therapy on cardiovascular risk
3. Review and quantify the risks of NSAID use on the heart and gut
4. Develop strategies for dealing with nuisance GI complaints with methotrexate
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6. Recognize the far reaching and significant toxicities of glucocorticoids