Collaboration Within Rheumatology: Focus On Drug Interactions and Adverse Effects

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Disclosure

• The speaker, Carolyn Whiskin has received honoraria from the following companies:
  – AbbVie
  – Amgen
  – Janssen
  – Pfizer
## Disclosures

The speaker, Carter Thorne has received honoraria from the following companies:

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Commercial support disclosure

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Learning objectives

• Understand the clinical relevance of drug interactions and adverse effects within the common treatments in rheumatology
• Discuss when to refer a patient back to the rheumatologist
• Examine new models of care for patients with inflammatory arthritis
RA: Inflammation in early stages, joint destruction later

Graph: Used with permission of Journal of Rheumatology.
X-ray: © 2012 American College of Rheumatology. Used with permission

RA: Inflammation in early stages, joint destruction later.
Fig. 1. Evolution of RA drug treatment.
Results: Drug management and MTX use over time

**Drug Management**

- MTX: 62%
- SSZ: 16%
- Biologics: 22%

**Dose of MTX**

- Mean dose MTX (mg/week) (95% CI)

MTX = methotrexate; SSZ = sulfasalazine; CI = confidence interval

Kievit, W et al. Rheumatology 2013;52:1500-1508
Our goal

Control vs Remission

“It’s good to feel better…
BUT
It’s better to feel good”
RA Market Dynamics:
2015 Canadian Patient Waterfall (Pts. 18+ years)

- Prevalence: 269
- Diagnosed: 185 (69%)
- Treated by Rheum: 174 (94%)
- All DMARD Treated: 169 (97%)
- Biologics "Treated by Rheum": 56.6 (38%)
Patients who are diagnosed with new onset rheumatoid arthritis within the first year and see a Rheumatologist are more likely to receive DMARD therapy than those who don't see a rheumatologist*

Data from the CATCH Cohort (TOP 8 enrolling sites): >95% of patients on DMARD

A window of opportunity: RA patients should see a Rheumatologist

Quality Care in Seniors With New-Onset Rheumatoid Arthritis: A Canadian Perspective
Jessica Widdifield,1 Sasha Bernatsky,2 J. Michael Paterson,3 J. Carter Thorne,4 Alfred Cividino,5 Janet Pope,6 Nadia Gunraj,3 and Claire Bombardier1

2011. Arthritis Care & Research, 63(1), 53-57
Limited health human resources

Access to care is an important barrier to adopting guidelines into practice.

- 13 million residents in Ontario
- ~10,000 FMD’s
- ~160 Rheumatologists

2013: 100,000 RA patients
2000: 50,000 RA patients

New models of care for patients with inflammatory arthritis

Focus on early diagnosis and treatment of inflammatory arthritis (RA, PsA, AS) by:

• Reducing wait times to see a rheumatologist
• Utilizing each member of the health care team to their fullest scope of practice
• Analyzing models from across Canada
• Adaptability to various practice settings
• Motivating rheumatologists to adapt change within their practice
• Encouraging medical students to consider rheumatology
We **CAN** make a difference!

**Early diagnosis**
- Goal: see w/in 3 mos of Sx onset
- EAC

**Optimal Rx**
- MTX sc
- IAS/IMS

**Systematic review**

**Improved outcome**
- Conventional DMARD
- Biologics

**“Comprehensive MSK Exam”***
*Comprehensive MSK Exam: PRO + Exam + Lab + Imaging

T2T or GCP

**Jointly presented by**
Canadian Pharmacists Association
Association des Pharmaciens du Canada
Ontario Pharmacists Association
Association des Pharmaciens de l'Ontario
OPA / ORA Partnership

- OPA / ORA joint committee to promote enhanced communication between professions
- Referral encouraged prior to first rheumatologist visit
- Enhanced communication on rheumatologist generated prescriptions to outline the clinical relevance of known interactions that will be monitored
- Communication distributed by the respective association to their members regarding the collaboration
The goal of treatment is remission and, when not possible, minimal disease activity, while controlling symptoms, halting damage, preventing disability, and improving quality of life.

RA care providers should monitor disease activity as frequently as every one to three months in patients with active RA.

Traditional and biologic DMARD therapy should be adjusted every 3-6 months, as long as the goal has not been achieved (Treat to Target).

When might pharmacists suggest a review by the Rheumatologist

• When a patient on DMARD therapy is not improving after three to six months from its initiation
• When a previously controlled patient has a flare of their condition
• When a patient seeking OTC medication for joint pain is identified as having symptoms which indicate inflammatory arthritis:
  – Morning stiffness lasting more than 30 minutes
  – Symmetrical joint involvement
  – Small joint involvement of hands and feet as initial symptoms
  – Generalized fatigue
  – Family history of autoimmune disease
Case study:
Meet Irene

Irene is a 55 year old female who has been using OTC ibuprofen and a topical analgesic cream for the last month. Today, she comes to the pharmacy asking for help for her worsening joint pain of both hands. She is on PPI for GERD.

Her profile includes:

- Levothyroxine 0.1 mg daily
- Omeprazole 20mg po daily
- Vitamin D 2,000IU daily
- Ibuprofen 400mg t.i.d.

What questions will you ask?
Irene visits a Rheumatologist

Based on your recommendation, Irene visits her family physician and is referred to a rheumatologist. She has tested positive for two markers of rheumatoid arthritis; Rheumatoid Factor and anti-CCP. Her rheumatologist has prescribed:

– Methotrexate 20mg sc weekly
– Hydroxychloroquine 400mg daily
– Vitamin B12 (methylcobalamin) 1,000mcg sl daily
– Naproxen/esomeprazole 375mg/20mg po bid.
While processing the prescription, a few drug interactions are identified:

**NSAID’s and Methotrexate**

MTX is predominantly eliminated as an unmodified drug by the kidney (80 per cent) via the human organic anion transporter-3 (HOAT-3) in the renal proximal tubule

- Competition for tubular secretion via the HOAT-3 theoretically can increase MTX levels and adverse effects.
- Of 8671 studies, 17 publications reported a concurrent use of MTX and NSAID, but none reported ADRs on lung, liver, or renal function and no increase in MTX withdrawal or in other major toxicity.
**PPI’s and Methotrexate**

- PP’Is compete with MTX for elimination pathways, reducing MTX’s renal and biliary elimination causing an accumulation of MTX and increased risk of toxicity.

- A study of patients being treated with low dose (7.5-15 mg weekly) MTX for rheumatoid arthritis found no effect on MTX pharmacokinetics when lansoprazole 30 mg daily and naproxen 500 mg twice daily were co-administered.
Rheumatologist response

• Recall that there are 2 broad indications for MTX – MSK/Psor/CTD (≤25mg) & Oncology (1000mg)
• Interaction is not significant in doses used in rheumatic disease
• Please dispense as written
• Maintenance monitoring for methotrexate toxicity has been ordered, as per standard of care
Methotrexate monitoring

Baseline, monthly x 3 mos, then q 3 mos

• CBC with platelets
• ANC (Absolute Neutrophil Count)
• ALT,
• Albumin
• Creatinine and eGFR
• Chest X-Ray at baseline
Methotrexate is the “anchor” treatment

- Most effective traditional DMARD
- Approximately 30 per cent of people will achieve low disease activity on monotherapy
- Absorption is equivalent between oral and sc up to 15mg/week
- SC absorption 30 per cent higher than oral above 15mg/week, therefore if using oral- split dose over the day (no consistent evidence for this)
- Can take up to 3 months for maximum effectiveness
- “Optimal dosing strategies” include MTX 25mg sc qwk
Methotrexate: Adverse effects

- Nausea, vomiting, anorexia
- “Sick day” post methotrexate
- Oral ulcers
- Worsening of migraine headaches
- Hepatic Toxicity (?)
- Hematological toxicity: Leukopenia, thrombocytopenia, pancytopenia and megaloblastic anemia
- Pneumonitis (interstitial lung disease)
- Worsening nodulosis (5 per cent)
Putting it in perspective

How would you discuss the adverse effects of methotrexate with a patient?
Cochrane review analyzes methotrexate adverse effects

- Nine more people out of 100 discontinued methotrexate due to adverse events after three to 12 months compared to placebo (nine per cent absolute withdrawals)
- One more person out of 100 experienced serious side effects after three to 12 months with methotrexate alone compared to placebo (one per cent absolute harm)

Methotrexate for treating rheumatoid arthritis (Review) © 2014 The Cochrane Collaboration.
Importance of folic acid

• 16 people out of 100 who took folic acid or folinic acid with their MTX developed mouth sores or ulcers (22 people with no folic acid)

• 26 people out of 100 experienced stomach problems such as nausea when they took folic acid or folinic acid with their MTX (35 people without folic acid)

• Five people out of 100 experienced abnormal liver blood tests when they took folic acid or folinic acid with their MTX (21 people without folic acid)
Folic acid vs folinic acid

• Folate: general term for a group of water soluble b-vitamins; known as B9.
• Folic acid activity is dependant on its conversion to L-5methyltetrahydrofolate (L-5-MTHF) by the metabolizing enzyme methylenetetrahydrofolate (MTHFR)
• Due to a single nucleotide polymorphism (SNP) up to 40 per cent of people may have a disruption in the activity of MTHFR
• Folinic acid (5-formyltetrahydrofolate) is a derivative of tetrahydrofolic acid and is readily converted to a tetrahydrofolate, and does not require the action of dihydrofolate reductase for its conversion
Is there a common folic acid dosage?

How many dosage regimens have you seen from rheumatologists?

Is one better than another?

Role of B12 s/c??
Role of vitamin B12 po/sl/sc
Hydroxychloroquine

- Part of the family of anti-malarial treatments
  - Also Chloroquine
  - Least toxic of all DMARD’s
- Dose: 200-400 mg/day (less than 60 inches 200-300mg/day)
- Can safely be combined with other DMARD’s and pregnancy
- Complete mechanism of action is unknown, but does decrease the production of: IL-1, IL-6, interferons and prostaglandins
- Other benefits:
  - Decrease insulin degradation, decrease platelet adhesion and aggregation, increase LDL receptors to decrease circulating LDL
Hydroxychloroquine adverse effects

- Nausea and vomiting (start low and slow - take with food)
  - Generic has caused more nausea
- Headache and dizziness
- Rash, hyperpigmentation of the skin, bleaching of hair
- Sun sensitivity possible
- Retinal toxicity
  - 1-2 per cent of people on treatment > 5 years; more common in with chloroquine
- Myopathy, cardiomyopathy and peripheral neuropathy – uncommon
- Hemolysis (in patients with G6PD deficiency)
What do you tell a patient about hydroxychloroquine adverse effects?

- Cochrane review: There was no difference between the placebo and active groups in terms of those who had to withdraw from trials due to side effects.
Hydroxychloroquine: Monitoring

• Baseline ophthalmologic exam at six months post initiation

• New recommendations suggest annual exams start five years post treatment initiation
Hydroxychloroquine interactions

• Amiodarone*
  – The risk of peripheral neuropathy may be increased during concurrent use; at risk: patients with diabetes and over age 60.

• Digoxin
  – Hydroxychloroquine may increase the blood levels and effects of digoxin. Blood monitoring of digoxin suggested as may need a dose adjustment.

• Hypoglycemic Agents*
  – Hydroxychloroquine potentiates the hypoglycemic effect of these agents; blood glucose monitoring required.
Irene questions antibiotic use

Irene has used antibiotics in the past for urinary tract infections. She asks you if there are any antibiotics that she will not be able to take while on the new medications?
Methotrexate interactions: Are either clinically significant?

Penicillin*

- Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with methotrexate. Use of methotrexate with penicillins should be carefully monitored.

Sulfa antibiotics

- Methotrexate level increased by plasma protein drug competition.
- Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.
Irene’s condition worsens

Irene found great benefit from her methotrexate and hydroxychloroquine after the first three months on the treatment. One year after this regimen was introduced, she came to the pharmacy complaining that her joint pain had worsened and was now affecting her sleep. She noticed pain in her knees and shoulders in addition to her hands and feet.

What additional questions might you ask?
Reasons for not using DMARDs

• Fear of side-effects (26 per cent)
• Prefer avoiding meds (24 per cent)
• Don’t think they need it (23 per cent)
• Bad past experience: S/E (22 per cent) or LOE (11 per cent)
• Not aware it prevents joint damage (19 per cent)
• Cost (13 per cent)
• Don’t believe it will help (per cent)
The World Health Organization has declared that more people worldwide would benefit from efforts to improve medication adherence than from the development of new medical treatments.
Adherence interventions must be broadly based, rather than targeted to specific population subgroups; and counseling with a trusted clinician needs to be complemented by out-reach interventions and removal of structural and organizational barriers. To achieve the adherence goals set by CMS, front-line clinicians, interdisciplinary teams,
• Irene returns to the pharmacy with a prescription for: leflunomide 10 mg daily.
• She has been instructed to add this to her current regimen of methotrexate and hydroxychloroquine.
• When processing the prescription and interaction is again flagged by your computer software.
What is the clinical relevance?

- **Leflunomide and methotrexate**
  - Several papers reported an increase in both liver toxicity and blood dyscrasia (i.e., pancytopenia) with MTX and leflunomide; the UK manufacturer suggests that the co-administration of MTX and leflunomide is not advisable.
  - Lee et al. reported an increased risk of liver fibrosis in patients with RA treated with leflunomide plus methotrexate.
  - SMILE study evaluated 2975 patients with RA, documented the safety with the association between MTX and leflunomide.
Leflunomide

• Inhibits pyrimidine synthesis
• Comparable to low dose MTX for effectiveness
• Slows radiographic progression in RA
• Used when MTX contraindicated or not tolerated or in combination with MTX
• Dose; 10-20mg per day
• May take up to two years to reach undetectable plasma concentration (elimination procedure men and women: cholestyramine 8gm tid for 11 days; plasma level must be less than 0.02ug/ml on two occasions two weeks apart*)

*plasma levels not easily accessible, and not funded
Leflunomide adverse effects

- Nausea, vomiting, diarrhea (17 per cent); may lead to weight loss
- Skin rash; eight per cent
- Alopecia (reversible); eight per cent
- Neutropenia > Thrombocytopenia
- Hepatic Enzyme Elevation
- Hypertension
- Teratogenicity (category X)
- Pneumonitis (less common than with MTX)
What would you say to a patient regarding the adverse effects of leflunomide?
Leflunomide drug interactions

• Warfarin*
  – Warfarin may increase the level or effect of leflunomide oral by affecting hepatic enzyme CYP2C9/10 metabolism. Leflunomide may increase the level of warfarin via CYP2C (increased INR rarely reported)

• Rifampin
  – Leflunomide levels increased by 40 per cent after one dose with patients on rifampin
Leflunomide monitoring

- Hepatitis B and C serology at baseline (note: now Std of Care at Dx)
- CBC
- ALT
- Creatinine
- Precautions: Contraindicated in pregnancy, hepatic impairment or hepatitis serology
Irene’s pain worsens

• Irene’s leflunomide dosage was increased to 20mg daily and after three months her pain was worsening. She had more tender and swollen joints and her sleep was not improved.

• Her rheumatologist decides to add biologic therapy.
What is so different about biologics?

Molecular comparison

- Aspirin
- Biologic (hormone)
- Biologic (antibody)
Another interaction....

• This is a common combination!
• Does the combination of a traditional and a biologic DMARD increase infection risk?

So, what is the true infection risk?
Infection rates in RA patients

- Possible link between infection risk and alterations of the immune system in RA
- RA patients hospitalized between 1963 and 1998, pneumococcal infection, RR >2
- Increased risk for serious infections with GCs,
  - <5 mg/day, RR of 1.4
  - for 5-10 mg/day, RR of 1.9
  - 10-20 mg/day, RR of 3.0
- Anti-TNF treated patients: RR 1.2-1.4

RABBIT risk score a helpful tool for infection risk.

RA Cohorts including OBRI and an ICES analysis indicate that only Steroid use increased the risk of infection. There appears to be no increased risk of infection related to MTX use.
### Table 7. Summary of CRA recommendations for vaccination in patients with rheumatoid arthritis (RA) (Recommendations 7–9).

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<th>Inactivated/Killed Vaccines</th>
<th>Live Attenuated Vaccines</th>
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<tr>
<td></td>
<td>Influenza (annual)</td>
<td>Pneumococcal (booster after 3-5 yrs)</td>
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<tr>
<td>Methotrexate*</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Leflunomide</td>
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<td>✓</td>
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<tr>
<td>Sulfasalazine</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>All biologics</td>
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✓ Recommended; ideally administer prior to initiating therapy. † Recommended in high-risk groups including residents, travelers or close contact with individuals from hepatitis B endemic areas, illicit drug users, persons engaging in risky sexual behaviors/history of sexually transmitted infection, men who have sex with men, chronic liver disease, occupational exposures, frequent blood transfusions. †† Recommended in RA patients > 60 years old. * Methotrexate ≤ 25 mg per week.
Adverse effects associated with biologics

- Injection site reactions
- Infusion reactions
- Headache/dizziness
- Rash
- Abdominal pain/indigestion
- Opportunistic infections
- CHF in at risk patients
- Autoimmune syndromes: psoriasis, lupus-like reaction
- PML (rituximab)

Screen before treatment
- Tb skin test (except rituximab)
- Hepatitis B and C
“Drugs don’t work in patients who don’t take them.”

C Everett Koop MD
(US Surgeon General 1982-89)
Reasons for not using DMARDs

• Fear of side-effects (26 per cent)
• Prefer avoiding meds (24 per cent)
• Don’t think they need it (23 per cent)
• Bad past experience: S/E (22 per cent) or LOE (11 per cent)
• Not aware it prevents joint damage (19 per cent)
• Cost (13 per cent)
• Don’t believe it will help (9 per cent)
Dispel the fear

Patient fears

- Vulnerability to infection
- Cancer risk
- “Must be dangerous because it is infused or injected”

Rationale

- Active inflammatory disease increases vulnerability more than biologic. Prednisone has greater vulnerability
- Increase in lymphoma not significantly higher than risk conferred by RA
- Large molecular size- many oral medications have more adverse effects (i.e.. prednisone)
Help create a balance

Risk of treatment
- Possible infusion or injection reaction
- Increased vulnerability to infection

Benefits
- Prevent joint destruction
- Decreased pain (sleep, social, work, fatigue, mood)
- Decreased cardiovascular risk
Next steps

• Promote dialogue with rheumatologists to understand the clinical relevance of interactions and their approach to withholding treatment during active infection.

• Screen patients seeking help for joint pain

• Be aware of patients not improving on treatment and refer back to their rheumatologist
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