Lecture: Rheumatology - Update on DMARDs in Common Rheumatologic Diseases for the Family Physician

Scott Jay Harris, DO, FACFR
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Please check where applicable and sign below. Provide additional pages as necessary.

Name of CME Activity: ACOFP 52nd Annual Convention and Scientific Seminars

Dates and Location of CME Activity: March 12-15, 2015, The Cosmopolitan Las Vegas, Nevada

Lecture: Rheumatology
- Hyperuricemia & Gout as an Independent Risk Factor of Atherogenesis (Forman)
- Update on DMARDs In Common Rheumatologic Diseases for the Family Physician (Harris)

Thursday, March 12, 2015 8:00-10:00 am

Name of Faculty/Moderator: Scott Harris, DO

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A. Neither I nor any member of my immediate family has a financial relationship or interest with any proprietary entity producing health care goods or services.

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*If you checked "Speakers' Bureaus" in item B, please continue:

- Did you participate in company-provided speaker training related to your proposed topic? Yes: No: x
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Signature: [Signature]

Scott Harris, DO

Date: [Date]

Please fax this form to ACOFP at 866-328-1835 or email to joank@acofp.org as soon as possible

Deadline: Monday, January 12, 2015
UPDATE ON DMARDS, BIOLOGICALS, CYTOKINE INHIBITORS/B CELL DEPLETIONS/CO-STIMULATION BLOCKAGE: HOW PRIMARY CARE CAN BE INVOLVED IN MANAGEMENT ISSUES

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Touro University Nevada College of Osteopathic Medicine
ACOFP 52nd Annual Convention and Scientific Seminar
March 12, 2015

OBJECTIVES

• Review the latest in DMARD/Biological and varied approaches to treatment in RA and SLE
• Understand the contraindications and pitfalls
• Review the standard monitoring for adverse effects, vaccination prophylaxis and infection prevention
• Review how these therapies (and some old ones) can affect the co-morbidities of patients and necessity of interaction between Primary Care and Specialist
• While this lecture is primarily aimed at new treatments it is important to review the old ones and their particular issues as well as most are now combined with new
• Disclosures: none to report but there may be times Non-FDA approved indications of drugs may be discussed as much of Rheumatic Disease management is with such cases.
REFERENCES

• Saunders D, Burdette S; Infections Associated with Anti Tumor Necrosis (TNF) Medications; Antimicrobe; http://antimicrobe.org/e58.asp
• Jain V, et al; Reactivation histoplasmosis after treatment with anti-tumor necrosis factor α in a patient from a nonendemic area; Respiratory Medicine; Vol 100 (7); July 2006; pp1291-1293
• Stone, J, et. Al; Tumor necrosis factor alpha inhibitors: risk of malignancy; UpToDate; last updated Jun 26, 2014
• Singh, et al; 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biological Agents in the Treatment of Rheumatoid Arthritis; Arthritis Care & Research Vol 64, no.5, May 2012, pp 625-639
• Bermas, B. et al; Rheumatoid arthritis and pregnancy; UpToDate; last updated Feb 15, 2015
• Pam Harrison, New Rheumatoid Arthritis Guidelines in the Works for 2015; Medscape Multispecialty Nov 27, 2014
• Dao k, Cush J; A vaccination primer for Rheumatologists; DAQ Vol4 (1) Jan 2012 (an online drug safety publication fro ACR)
• Tofacitinib: Drug Information Lexicomp®
• Stone, J. et al; Overview of biologic agents in the rheumatic diseases; UpToDate; last updated Aug 29, 2012
• Stone, J. et al; Tumor necrosis facto-alpha inhibitors: Risk of bacterial, viral, and fungal infections; UpToDate; last updated May 30, 2014

A BRAVE NEW WORLD

• The world of treatment that once existed in RA and SLE has evolved and grown.
  • More aggressive
  • The old “pyramid approach is now upside down”
    More combinations utilized, newer “smarter” drugs available
    Greater frequency use of low dose corticosteroids that may really be DMARD
  With greater benefit there comes greater risks
    Infections
    Malignancies
    Effect upon co-morbidities and alterations of treatment
WHAT’S AT HAND

- Analgesics
- Steroids
- NSAIDS
- DMARDs (antimetabolites, antibiotic based, anti-malarials, etc.)
- Anti-TNF Agents
- Anti-Cytokine Therapies
- B Cell Depletion
- Co-Stimulation Blockade
- Signal Transduction Pathways
- Anti BLyS in SLE

ANTI-TUMOR NECROSIS FACTOR ALPHA TREATMENT (ANTI TNF)

- What’s out there
  - Infliximab - Remicade®
  - Adalimumab - Humira®
  - Etanercept - Enbrel®
  - Certolizumab pegol - Cimzia®
  - Golimumab - Simponi®

- Routes
  - IV, SQ

- Frequency
  - Titration to every 8 weeks
  - Biweekly to Weekly
  - Twice Monthly
  - Monthly
ANTI-TNF

- Via depletion of free or bound TNF
- May actually cause Cellular Mediated Cytotoxicity via Monoclonals (mab)
- Cannot be used in combination with other biologicals
- Are not for everyone
- The route is made upon a case by case choice
  - IV requires hours
  - SQ injections may be limited by deformities, choice, a surrogate to give the injection
  - Pre-existing conditions
    - MS, CHF, Tb, Cancers

OTHER NON TNF BIOLOGICAL TREATMENTS

- Abatacept - Orencia®, prevention of CD28 binding to CD80/CD86
  - IV or SQ and requires titration IV till once monthly, or once weekly SQ
- Rituximab -Rituxan®, a B Cell depletion via anti CD20 antibody
  - May cause Cellular mediated cytotoxicity or cell lysis, growth arrest, apoptosis of B cells
  - IV 2 doses separated by 2 weeks every 6 months
- Tocilizumab - Actemra®, an anti IL-6 receptor antibody (humanized) binds both membrane and soluble cytokine
  - Titration once monthly IV dosing or titration once every two weeks to weekly SQ
- Anakinra – Kineret an anti IL-1 receptor antagonist not used much anymore
- Tofacitinib - Xeljanz®, an inhibitor of JAK 3 signal pathway (DNA transcription)
  - First oral “biological” type agent but non cytokine
  - Daily oral up to twice daily
THE FIRST BIOLOGICAL FOR SLE

- Belimumab – Benlysta an anti B Lymphocyte Stimulator antibody
  - IV once monthly
  - The first drug in 50 years approved for SLE
    - Indicated for antibody positive and failure of prior immunosuppression
    - Infections including JC Virus
    - Malignancy not well known yet
    - Depression has been reported

INFECTIONS WITH BIOLOGICALS

- Will mostly discuss what has been observed with ant TNF and most often can be extrapolated to other
  - JC Virus with Rituximab and Belimumab
- Duration of use associated with risk: decreases over time by two years
- Combination therapy more likely to cause infection
  - Infliximab and Methotrexate
- Perioperative infections have a 2-4 fold increased risk
  - ACR recommends holding biologics 1 week before and 1 week after surgery

Saunders D, Burdette S; Infections Associated with Anti Tumor Necrosis (TNF) Medications; Antimicrobe; http://antimicrobe.org/e58.asp
WHICH INFECTIONS

- TNF plays a role in granuloma formation and infection prevention
  - Greater incidence of bacterial, viral, fungal
  - Tuberculosis reactivations and atypical mycobacterium
  - Atypical infection risk unknown
- Histoplasmosis
  - 3 times more likely in endemic regions
  - Consider in any severe febrile presentation
  - 1 case of reactivation in a patient from non-endemic region
- Cocciidiodomycosis
  - Few reported cases and all from endemic regions: all were pneumonic
- Aspergillus remains an issue and has always been especially with pulmonary nodular disease that cavitates.
- Pneumocystis is extremely rare

STONE, J. et al; Tumor necrosis factor–alpha inhibitors: Risk of bacterial, viral, fungal infections; UpToDate last updated May 30, 2014
Saunders D, Burdette S; Infections Associated with Anti Tumor Necrosis (TNF) Medications; Antimicrobe; http://antimcrobe.org/e58.asp
Jain V, et al; Reactivation histoplasmosis after treatment with anti-tumor necrosis factor α in a patient from a nonendemic area; Respiratory Medicine; Vol 100 (7); July 2006; pp1291-1293

VIRUSES

- Zoster
  - Especially if in association with steroids and other dmards
- Hep B reactivation and Hep C
  - Increased ALT correlates with TNF levels in Hep C
    - No flares with Etanercept or Infliximab but ACR only recommends Etanercept
    - Hep B reactivation seems to occur within first 3 months of use
      - Avoid use but when absolutely necessary needs concomitant antiretroviral therapy
- PML
  - Single case with infliximab with mtx and prednisone.
  - Very rare with other biologicals and is being monitored

Saunders D, Burdette S; Infections Associated with Anti Tumor Necrosis (TNF) Medications; Antimicrobe; http://antimcrobe.org/e58.asp
IMMUNE RECONSTITUTION SYNDROME

- Has been reported after withdrawal of anti TNF in cases of Tb and Histoplasmosis
  - Consider in any patient with histoplasmosis that deteriorates after initial treatment

Saunders D, Burdette S: Infections Associated with Anti Tumor Necrosis (TNF) Medications; Antimicrobe; http://antimicrobe.org/e58.asp

MALIGNANCY

- DMARDs and Biologics intended target play roles in immune regulation of malignancies, especially TNF.
- Tofacitinib has been associated with Lymphomas and EBV associated renal transplant lymphoproliferative malignancies.
- Solid, skin, and hematogenous forms have all been seen with biologics.
  - More common in patients treated with high dose
  - Etanercept and Cyclophosphamide not recommended (Study in combo use in treatment of ANCA Positive Granulomatosis and Polyangiitis)
  - But no evidence of increased risk with long term use to date
- Problems in truly determining risk
  - Natural risk in underlying disease, other drugs, other trial evidence
    - NO patients with prior history were allowed in trials.

Stone, J, et. Al; Tumor necrosis factor alpha inhibitors risk of malignancy; UpToDate; last updated Jun 26, 2014
HYPERLIPIDEMIA

• All inflammatory disorders are associated with a greater incidence of CVD
• Usual Risk Factors
• Specific due to:
  • Steroids, NSAIDS, Disease
  • Tofacitinib associated with rise in lipids
    • Usually within 1st 6 weeks of treatment
      • Check lipids 4-6 weeks post treatment initiation and adjust meds accordingly
  • Tocilizumab affects CYP P450 at 34A which will decrease levels of many statins
• Greater risk of CVD in SLE and is often overlooked due to age of patients
  • i.e. Young female less than 50 years with presentation of Chest Pains

PREGNANCY

• 50-80% of RA patients go into “remission” while pregnant
  • 1st trimester and can last many months post partum
    • May be affected by breast feeding: Prolactin may be associated
  • Most flares occur within 3 months post partum
• Most DMARDs and Biologics should be stopped
  • Most are Category C or Higher including Belimumab
  • Sulfasalizine and Hydroxychloriquine may be used
    • Stop sulfasalazine in men at least 3 months prior to conception: limited oligospermia
  • Leuflonamide must be reversed with Cholestyramine until levels are <0.2 mg/dl
    • 8gms TID for 11 days
  • Generally stop all DMRADs for at least 3 months before pregnancy
• Anti TNF are category B but generally not recommended and case by case basis and stop by week 32.

Bermas, B et al; Rheumatoid arthritis and pregnancy; UpToDate; last updated Feb 15, 2015
MANAGEMENT IN PREGNANCY AND POSTPARTUM

- Steroids (low dose), NSAIDs, analgesics
  - Beware NSAIDS affect implantation and closure of Ductus Arteriosuus
    - Stop by third trimester (best to avoid in my opinion)
- Choice of DMARD/Anti TNF on case by case basis
  - Other biologics not recommended
- Most of us recommend starting therapy soon after pregnancy especially in moderate to severe disease
  - Flares seem to be related to breast feeding
- Breast feeding
  - No ASA, NSAIDs ok, low dose steroids ok
    - More than 20mg wait four hours to feed
    - Belimumab not recommended

Bermas, B et al; Rheumatoid arthritis and pregnancy; UpToDate; last updated Feb 15, 2015

FOOD FOR THOUGHT

- Use of Anti- TNF with:
  - Hepatitis B&C
    - Etanercept may be considered in patients with Hep C
    - Though not for untreated Chronic Hep B or with Child-Pugh Class B or greater (any biologic)
      - No recommendations made about Hep B with a positive B core ab
  - Malignancies
    - Any treated solid tumor more than 5 years (including non-melanoma skin disease)
      - Any biological can be considered
    - Any treated solid tumor, melanoma, or lymphoproliferative disease may consider Rituximab
      but not an anti TNF
  - CHF (class 3-4)
    - No use of anti TNF

Singh, et al; 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease Modifying Antirheumatic Drugs and Biological Agents in the Treatment of Rheumatoid Arthritis; Arthritis Care & Research Vol 64, no.5, May 2012, pp 625-639
FOOD FOR THOUGHT

• Tuberculosis
  • All should be screened for latent Tb with skin testing Interferon Gamma release assay (when necessary such as with prior BCG vaccination)
    • Positive results necessitate Chest Xray
    • Positive needs treatment
    • High risk or unsure consider sputum
  • Once one month of treatment of latent disease may begin anti TNF
    • Consider referral to specialist for the care of latent disease
  • Annual testing for all RA patients risk factors for disease (travel, work, exposures)

Singh, et al; 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease Modifying Antirheumatic Drugs and Biological Agents in the Treatment of Rheumatoid Arthritis; Arthritis Care & Research, Vol. 64, no.5, May 2012, pp 625-639

VACCINATIONS

• Much has changed over the years
  • Pneumococcal, influenza, Hepatitis B, and Human Papilloma Virus vaccinations can be given with any DMARD with or without biologicals (including non-TNF treatments)
    • Follow standard recommendations
  • Herpes Zoster vaccination
    • Recommended with all DMARDs but not with anti-TNF or non anti TNF Biologicals consider vaccination before use of all biologicals
  • All other Live Attenuated viral vaccinations are not recommended in “severe” immunosuppression including use of prednisone more than 20mg for two weeks
  • Per package insert Belimumab should not have live viral vaccination within 30 days of infusion

Singh, et al; 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease Modifying Antirheumatic Drugs and Biological Agents in the Treatment of Rheumatoid Arthritis; Arthritis Care & Research, Vol. 64, no.5, May 2012, pp 625-639
Dao k, Cush J; A vaccination primer for Rheumatologists; DAQ Vol4 (1) Jan 2012 (an online drug safety publication by ACR)
• Vaccination when possible before treatment, noting that other than HZV, all other live attenuated viral vaccination contraindicated
• Close eye on patients with CHF on TNF
  • Especially those on NSAIDs and steroids
  • Risk factor reduction for CVD
  • Close monitor of lipids with use of tofacitinib and tocilizumab
• Whenever possible screen for the risk of fungal infections especially by geographic location or prior history
• Development of serious infection needs to be communicated to Rheumatology for adjustment in management

• Development of neurological symptoms should prompt evaluation for MS while on ant TNF therapy and be notified to Rheumatology and consideration of holding treatment till further notice
• Watch for risk factors of Hepatitis B&C and communication
• Pregnancy: not recommended generally while on treatment and should be stopped (except sulfasalazine or hydroxychloriquine) and notified immediately. Case by case basis for treatment.
• Report depressive symptoms in SLE on Belimumab
POSSIBLE NEW RECOMMENDATIONS IN 2015

• Active Hep B or C receiving treatment can receive dmard, TNF, Non TNF biological treatment
• NYHA CHF 3-4 should consider dmard with/without non TNF biological or tofacitinib
• New recommendations on those with lymphoproliferative disorders
• Serious infections new consensus has been reached but remain up in the air till approved

Pam Harrison, New Rheumatoid Arthritis Guidelines in the Works for 2015; Medscape Multispecialty Nov 27, 2014