DISCLOSURES

• Consultant fees from SOBI pharmaceuticals
• Arthritis & Rheumatism Vol. 54: January 2006, pp 38–46
• Ann Rheum Dis 2016;75:2060-2067
• Ann Rheum Dis 2016;75:1824-1830
• Arthritis & Rheumatology. Vol. 69; 2017, pp 926
• Lancet 2016; 387: 1921
• International Journal of Rheumatology Volume 2013, Article ID 912562
• Abstract 911. American College of Rheumatology Conference Proceedings.
• Ann Rheum Dis 2016;0:1–14.
• Arthritis Care & Research Vol. 64, No. 10, October 2012, pp 1431–1446
RHEUMATOLOGY UPDATE

Sources:

• My own experience and what I like
• Highlights from American College of Rheumatology 2017 meeting
• Journal clubs with pizza
• Recommendations from UAB faculty
ROADMAP

• Pre-disease
• New treatment for an old disease
• A new disease
• A controversy
CASE PRESENTATION 1: PRE-DISEASE

• A 40 year-old man presents for a well-check visit
• Tells you that his older sister has been recently diagnosed with rheumatoid arthritis
• There also is a history of RA in his father and grandparents
• He does not have any symptoms or physical findings
• He is afraid about RA and asks for advice about what to do
You suggest:

A. He needs to lose weight
B. He needs to have comprehensive genetic testing
C. He should strongly consider stopping smoking
D. He should go into an antioxidant diet
E. He should start taking methotrexate
WHAT IS EARLY DISEASE?

Phases of RA development
Genetic Susceptibility to RA

- Heritability ~ 50% for seropositive RA
- Familial aggregation (risk of RA in 1st degree relatives increased 3 fold)
- Concordance rates of 15-30% between monozygotic twins
- Concordance rates of 5% in dizygotic twins
- >100 genetic susceptibility loci associated with RA

Associations of Smoking and Age With Inflammatory Joint Signs Among Unaffected First-Degree Relatives of Rheumatoid Arthritis Patients: Results From Studies of the Etiology of Rheumatoid Arthritis
RELATIVE RISK RA IN CCP+ SUBJECTS EXPOSED TO SMOKING AND HLA–DR (SE) GENES
MODERN IMAGING TECHNIQUES

Musculoskeletal ultrasound

Magnetic resonance imaging

Wakefield RJ and O'Connor P. Hochberg at al (eds) Rheumatology 5th ed, 2011

DEVELOPMENT OF CLINICAL SYNOVITIS IN ASYMPTOMATIC CCP+ PATIENTS

• PD: Musculoskeletal ultrasound power Doppler score

DEVELOPMENT OF CLINICAL ARTHRITIS IN PATIENTS WITH ARTHRALGIAS ACCORDING TO MRI-DETECTED INFLAMMATION

OPPORTUNITIES FOR INTERVENTION: METHOTREXATE TREATMENT IN HIGH RISK UNDIFFERENTIATED ARTHRITIS PATIENTS

Plus 2 ongoing trials with abatacept and rituximab.....

CONCLUSIONS

• Immune dysregulation and inflammation occur pre-clinically in RA (and possibly other autoimmune diseases)
• Initial insult may occur in locations other than the joint (lung, mucosae)
• Cohorts of individuals at risk, CCP antibodies, advanced imaging are providing valuable information
• Early intervention and modification of natural history is a realistic goal
CASE PRESENTATION 2: NEW TREATMENT FOR AN OLD DISEASE

• 74 year old white woman develops headache, blurry vision, diplopia, and fever
• Past medical history remarkable for type 2 diabetes and osteoporosis
• Sedimentation rate is 82
• She is started on 1 mg/kg of prednisone
BIOPSY SPECIMEN OF THE LEFT SUPERFICIAL TEMPORAL ARTERY AND THE DURA.

Which cytokine is known to drive the inflammatory process in this condition:

A. TNFα  
B. IL-1  
C. IL-6  ✔️
D. TGF-β  
E. VEGF
CLINICAL SPECTRUM OF GIANT CELL ARTERITIS

Cranial arteritis
- Headache, optic ischemia, jaw claudication

Cachexia/wasting syndrome
- Fever, night sweats, weight loss, depression

Large vessel vasculitis/aortitis
- Limb claudication, pulse discrepancy, aortic insufficiency and aneurysms

Polymyalgia Rheumatica
- Pain & stiffness in shoulder and pelvic girdles

GCA/PMR Syndrome
COMMON CLINICAL FEATURES
GIANT CELL ARTERITIS

- Headache
- Increased sensitivity of the scalp
- Pulsating, enlarged, or nodular temporal artery
- Jaw claudication
- Less common: Trismus, facial pain, tongue claudication or infarction, carotidynea, visual or auditory hallucinations
GCA: TREATMENT PARADIGM AND CHALLENGES

• Glucocorticoids in high doses
  ➢ Hyperglycemia, mood alterations, sleep disruption

• Glucocorticoid taper

• Frequent relapses
  ➢ No effective glucocorticoid sparing agents

• Chronic long term glucocorticoids
  ➢ Osteoporosis, infections, depression
GCA AND INTERLEUKIN 6

Roche N. *Arthritis Rheumatol.* 1993; 36: 1286
TOCILIZUMAB IN GCA

- IL6 receptor antagonist

- Open label, phase II

A: Relapse free survival

B: Time to taper off prednisolone

Lancet 2016; 387:1921
TOCILIZUMAB IN GIANT CELL ARTERITIS TRIAL
### EFFICACY AND SAFETY OF TOCILIZUMAB IN PATIENTS WITH GIANT CELL ARTERITIS: PRIMARY AND SECONDARY OUTCOMES FROM A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

<table>
<thead>
<tr>
<th></th>
<th>Short course prednisone (n=50)</th>
<th>Long course prednisone (n=51)</th>
<th>Weekly Tocilizumab (N=100)</th>
<th>Every other week Tocilizumab (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained remission at 52 weeks, n (%)</td>
<td>7 (14)</td>
<td>9 (17.6)</td>
<td>56 (100)</td>
<td>26 (53.1)</td>
</tr>
<tr>
<td>Cumulative prednisone dose, mg</td>
<td>3296</td>
<td>3817</td>
<td>1862</td>
<td>1862</td>
</tr>
<tr>
<td>Withdrawals due to adverse events, n (%)</td>
<td>2 (4.0)</td>
<td>0</td>
<td>7 (7.0)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>Serious adverse events, n (%)</td>
<td>11 (22.0)</td>
<td>13 (25.5)</td>
<td>15 (15.0)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>Infection serious adverse events, n (%)</td>
<td>2 (4.0)</td>
<td>6 (11.8)</td>
<td>7 (7.0)</td>
<td>2 (4.1)</td>
</tr>
</tbody>
</table>

Stone JH. 2016 ACR Conference. Abstract 911
GIACTA TRIAL: TOCILIZUMAB VERSUS PREDNISONE

- Weekly tocilizumab versus short-term prednisone:
  - Sustained remission difference 42.0 % (18-66) \( p < 0.0001 \)

- Weekly tocilizumab versus long-term prednisone:
  - Sustained remission difference 38.4 % (17.9-58.8) \( p < 0.0001 \)
CONCLUSIONS

• Interleukin 6 plays a role in the pathophysiology of giant cell arteritis

• Interleukin 6 inhibition is a promising approach for inducing remission, symptom control, and minimizing glucocorticoid exposure
FDA News Release

FDA approves first drug to specifically treat giant cell arteritis

For Immediate Release

May 22, 2017
CASE PRESENTATION 3: A NEW DISEASE

• 56 year old man

• Presents after a year of weight loss, enlargement of submandibular salivary glands, lower extremity swelling, increased creatinine

• Biopsy of submandibular gland is non-diagnostic: “benign” “fibrosis”
Which laboratory abnormality is more likely:

A. Elevated levels of SSA (Ro) antibody

B. Positive titers for anti-nuclear antibodies

C. Elevated levels of IgG4

D. Monoclonal lymphocyte population in flow cytometry

E. Peripheral eosinophilia and elevated IgE levels

Response Counter
IgG4-RELATED DISEASE: YOU MAY HAVE SEEN IT BEFORE

MICULIZ’S DISEASE
Arch Soc Esp Oftalmol. 2014;89:332

RIEDEL’S THYROIDITIS
Endocrinol Metab (Seoul). 2013; 28: 138

RETROPERITONEAL FIBROSIS AND AUTOIMMUNE PANCREATITIS

PRIMARY SCLEROSING CHOLANGITIS
World J Gastroenterol. 2014; 20: 3245

FIBROSING MEDIASTINITIS
Clinical Imaging 39 (2015): 993
IgG4-RELATED DISEASE

• Fibro-inflammatory condition of unknown etiology
• Multiorgan: likely integrates multiple single organ diseases
• Unexplained swelling, infiltration, or enlargement of one (40% of cases) or more organs
• Indolent presentation: weight loss (21%), asthenia (26%), fever uncommon (8%)
IgG4RD: ORGAN SPECIFIC SYMPTOMS

<table>
<thead>
<tr>
<th>Organ syndrome</th>
<th>Differential diagnosis or prior single-organ diagnosis</th>
</tr>
</thead>
</table>
| Salivary gland enlargement (42%), lymphadenopathy (42%), Lacrimal gland swelling (26%) | • Mikulicz syndrome  
• Sjogren’s syndrome  
• Orbital pseudotumors, lymphoma, Tolosa-Hunt, sarcoidosis |
| Jaundice (23%), pruritus, abdominal discomfort, hepatomegaly (6%) | • Autoimmune pancreatitis  
• Sclerosing cholangitis |
| Renal dysfunction, lower extremity swelling, low back pain | • Retroperitoneal fibrosis  
• Membranous glomerulopathy |
| Aortitis | • GCA  
• Takayasu’s  
• Syphilis |
| Headache, ophtalmoplegia, pachymeningitis | • CNS vasculitis  
• Granulomatosis with polyangiitis |
| Neck pain and enlargement | • Riedel’s thyroiditis |
| Dyspnea, pulmonary nodules, ground glass opacities, bronchial thickening | • Interstitial lung disease  
• Fibrosing mediastinitis |
IgG4-RD: PATHOGENIC MECHANISMS

• Genetic factors: increased susceptibility among Asians
• Unknown trigger: molecular mimicry and bacterial infections
• Autoimmunity: induced by IgG4 and other antibodies
• Inflammation: induced by cell infiltration, eosinophilia, and increased IgE production
• IgG4 antibodies play an unclear role: pathogenic? Destructive? Protective?

IgG4RD: COMMON LABORATORY FEATURES

- IgG4 neither sensitive nor specific
- Wide laboratory variability
- IgG4 prozone
- Flow cytometry: Increased circulating plasmablasts (CD19 low CD38+ CD20- CD27+)

<table>
<thead>
<tr>
<th>Laboratory abnormalities</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgG4 &gt; 135 mg/dL</td>
<td>84</td>
</tr>
<tr>
<td>Serum IgG levels &gt; 1800 mg/dL</td>
<td>61</td>
</tr>
<tr>
<td>Serum IgE &gt; 360 IU mL</td>
<td>58</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>34</td>
</tr>
<tr>
<td>Elevated C-reactive protein</td>
<td>18</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td></td>
</tr>
<tr>
<td>- Anti-nuclear</td>
<td>32</td>
</tr>
<tr>
<td>- Rheumatoid factor</td>
<td>20</td>
</tr>
<tr>
<td>- SSA</td>
<td>6</td>
</tr>
<tr>
<td>Low complements</td>
<td>36</td>
</tr>
</tbody>
</table>

Adapted from Mayo Clin Proc. 2015;90(7):927-939
IgG4-RD: HISTOPATHOLOGICAL FEATURES

Storiform fibrosis

Obliterative phebitis

Positive immunostain for IgG4 plasma cells:

- IgG4+ cells per high-power field >10
- IgG4+/total IgG+ cell ratio >40%

IgG4-RD: TREATMENT APPROACH

• Initial good responses to glucocorticoids (prednisone equivalent at 0.5-0.6 mg/kg/day)
• Methotrexate, azathioprine, mycophenolate unproved steroid sparing agents
• Good experience with rituximab, likely by depleting plasmablast precursors
CONCLUSIONS

• IgG4RD is a fibro-inflammatory disease of unknown origin which causes tumefaction in ≥ 1 organ
• Laboratory features are supportive but not diagnostic
• Diagnosis is best established by histopathological features
• Glucocorticoids and rituximab are the best proven treatment approaches
CASE PRESENTATION 4: A CONTROVERSY

• A 52 year old man was diagnosed with gout 4 months ago, after recurrent episodes of podagra
• No tophi, normal kidney function
• First serum urate is 10.2 mg/dL
• Started on 100 daily mg of allopurinol, increased to 300 mg
• Last flare was 3 months ago
• On current visit serum urate is 7.0 mg/dL
What should be done with his allopurinol?

A. Serum urate is still too high, it should be increased

B. No attacks have happened recently, it should be continued at the same dose

C. Allopurinol dose is already maximized, allopurinol should be changed to febuxostat

D. Allopurinol dose is already maximized, probenecid should be added
BASIC CONCEPTS IN GOUT

• Painful inflammatory arthritis caused by the deposition of monosodium urate in tissues
• Treatment is aimed at decreasing flares and other symptoms (tophi, quality of life)
• Urate lowering therapies (e.g; allopurinol) are the mainstay of treatment
• Quality of care in gout is uniformly poor
TREAT TO TARGET VS. TREAT TO SYMPTOMS

• American College of Rheumatology and European treatment guidelines recommend:
  
  ➢ A serum urate treatment goal of 6mg/dL or less in patients without tophi
  ➢ 5 mg/dL or less in patients with tophi or joint damage

• This is called a treat to target (T2T) approach
• Soluble monosodium urate precipitates as monosodium urate crystals (MSU) past its saturation point

• Such saturation point at 37 °C is 6.8 mg/dL
Over time, untreated, chronic hyperuricemia increases body urate stores, advancing the severity of the disease. Flares last longer, flares occur more often, intercritical segments decrease, persistent pain and stiffness.

SMALL AMOUNT OF CLINICAL EVIDENCE FOR T2T- Lowering Serum Urate Decreases Acute Flares

- 86% (71/81) of patients who had serum urate < 6.0 mg/dL did not experience an acute flare during the study period.

LOWERING SERUM URATE DECREASES TOPHI SIZE

The lower the serum urate, the faster the velocity of tophi reduction

63 patients followed for a mean of 5 years

ACCP RELEASES GOUT MANAGEMENT GUIDELINES

• ACCP recommends “treatment to avoid symptoms (T2aS)”

• Limited evidence for T2T versus risk of medication escalation or repeated monitoring of serum urate

• View of serum urate as a surrogate for a clinical endpoint (like LDL, blood pressure, blood sugar)
MY CONCLUSIONS

• T2T is supported by decades of clinical experience and (true) limited evidence

• Serum urate is more than a surrogate for gout, is a causative factor for the disease

• ACP guidelines could impair gout care in the US

• But: ACP has exposed an important need for gathering evidence supporting T2T strategies
SUMMARY: 2017 RHEUMATOLOGY UPDATE

• Pre disease: Significant progress in rheumatoid arthritis pre-clinical and early disease
• New treatment for an old disease: IL-6 inhibition effective for GCA
• New disease: recognition and characterization of IgG4RD
• A controversy: goals for gout treatment