How will we prevent rheumatoid arthritis?

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Outline

1) Brief overview of natural history of RA and how current understanding of disease development supports prevention

2) Discuss who to target for prevention

3) Discuss potential preventive strategy
Keys for prevention

1) Accurate prediction
2) Effective screening
3) Effective preventive measures

Foundation of:
Detailed understanding from high-quality studies of the natural history and mechanisms of disease development
Let’s start with the “foundation”...
Phase 1: Genetic and environmental risks

Phase 2: Asymptomatic autoimmunity and inflammation

Phase 3: Symptoms of autoimmunity and inflammation – NO detectable IA (undifferentiated)

Phase 4: Signs and symptoms of IA defined by classification criteria (1987; 2010)

Phase 5: RA defined by classification criteria (1987; 2010)

“Preclinical” RA

Intervention to interrupt autoimmunity/inflammation

Sokolove et al PLOS One 2013

Deane et al Arthritis Rheum 2010
What factors initiate and propagate RA?

Genetic factors
Environmental exposures
Lifestyle and nutritional factors
Stochastic changes

Examples:
  HLA
  Tobacco smoke
Predicting future onset of RA

Likelihood = will I get RA?
Timing = when will I get RA?

Important for clinical trials and personalized medicine
Methods to predict RA

‘Questionnaires’
- family history, environmental exposures, symptoms

Biomarkers
- genetics
- autoantibodies
- inflammatory
Biomarkers

ACPA + RF highly predictive for future RA
>90% (most studies 100%) PPV

ACPA + RF, and genetic factors (HLA, PTPN22)
~100% PPV

Rantapaa-Dahlqvist et al Arthritis Rheum 2003
Nielen et al Arthritis Rheum 2004
Majka et al Ann Rheum Dis 2008
Berglin et al 2008
Gene-Epi

Nurses’ Health Study (Beth Karlson)
Combination of high-risk SNPs and environmental factors predicts RA
AUC >0.7

Karlson et al Arthritis Care Research 2013
Timing of getting RA

On average, ACPAs and RF elevated 3-5 years prior to clinically apparent disease.

But some cases up to ~15 years prior to clinically apparent disease.

How do we improve on this?
Testing multiple biomarkers can predict likelihood and timing of RA

**Sokolove et al. PLOS One 2012**
- high number of positive ACPAs and cytokines predicted ‘imminent’ RA (<2 years vs. ≥2 years; ~80% specific)

**Deane et al. A&R 2010**
- CCP and/or 2 or more RFs 96% specific for RA
- increasing numbers of positive cytokines/chemokines predict timing in age-dependent manner
Estimated years to diagnosis of rheumatoid arthritis

Cytokine/chemokine count

Age 20-29
Age 30-39
Age 40-49
Age 50-59

Deane et al A&R 2010
Predidictive model including 9 items: biomarkers, environment and symptoms.
Even simpler…

CCP2 3x normal plus any RF (IgG, M and A)

PPV 70% for RA within 3 years
Screening: How to identify subjects for prevention?

Easiest to target high-risk groups – e.g. family members of patients with RA
But is that optimal for public health since only ~10% RA familial?
Why not screen everyone for high risk biomarkers?
You’ve identified people at high risk for future RA – what do you do to stop it?

Based on sound understanding of the mechanisms of disease development
What causes RA?
(and would prevent it if you addressed it!)

* Immune dysregulation
  * Smoking
  * Being a woman (who gets pregnant)
  * Too little fish oil
  * Too much dust
  * Too little alcohol
  * Periodontal disease?
  * Certain organisms?

Karlson and Deane, Rheum Dis Clin N Am 2012
What pharmacologic agents might stop RA?

- Antibiotics
- NSAIDs
- Corticosteroids
- Hydroxychloroquine
- Methotrexate/leflunomide
- Anti-TNF agents
  - Anakinra
  - Rituximab
  - Abatacept
  - Tocilizumab
  - Tofacitinib
Challenges to preventing RA

Limited knowledge of natural history and mechanisms of RA development
Screening methods
Interventions

Preclinical RA

Clinically Apparent RA

Resources
Do we know enough to try and prevent RA now?

1) Autoantibodies highly predictive of likelihood and timing of future RA, probably PPV >50%
2) We have an idea about environmental actors that may initiate and/or propagate disease
3) We have established pharmacologic agents that work in clinically apparent RA
4) We know that treating RA soon after onset of clinically apparent disease results in improved long term outcomes – therefore moving therapy to a ‘preclinical’ phase may be more effective
Do we know enough to try and prevent RA?

5) Anti-malarials can help prevent progression to classified RA in patients with palindromic rheumatism (Garcia-Lopez et al 2000)

6) MTX or abatacept may halt progression from undifferentiated IA to RA (Emery et al 2012; van Dongen et al 2007)

7) $5 million will get you a good clinical prevention trial (more to come!)
Let’s do a trial!

Prevent RA
Learn about the natural history within a clinical trial
Trial design: Inclusion Criteria

CCP (high) + RF, no IA
- PPV >50% for RA within 3 years?

Subjects screened through:
- Relatives of patients with RA
- Clinics – rheumatologists seeing more patients with aches/pains and positive autoantibodies but no clear IA
- General population
Trial design: Outcome

Prevent RA

Altering biomarkers to show that autoimmunity has been improved would be nice too

But we’d be happier with clinical outcome
Trial design: Treatment

Controversial!

Key issue: balance of risk, benefit, tolerability and acceptance by at-risk subjects

Lifestyle, nutritional factor modification – smoking cessation?

Antibiotics
NSAIDs
Corticosteroids
Hydroxychloroquine
Methotrexate/leflunomide
Anti-TNF agents
Anakinra
Rituximab
Abatacept
Tocilizumab
Tofacitinib
Why HCQ?

1) Efficacy in established RA (and FDA approved for RA)
2) ‘Prevention’ in palindromic RA
3) Mechanisms of efficacy
   - decreased cellular activation
   - decreased antigen presentation
4) Price not bad (~$750 per year of therapy per MediSpan®)
5) Tolerable and relatively safe

In sum, agent that should be allowed to ‘fail’ prior to trying other agents
Trial design: Duration

10+ years if you do a lifestyle intervention

Minimum of 5 years if you use a pharmacologic therapy

1-2 years for recruitment (screen 14,000)
1 year of drug therapy followed by 2 years of follow-up to assess durability of response
(Need 3 years to get ≥50% of people developing RA)
Trial design: Power

Expected:
50% of subjects to get RA within 3 years
Reduce that to 25% through intervention

In randomized (1:1) placebo-controlled trial, need 140 subjects (70 in each group) for 89% power
The Dutch are doing it, why don’t we???

The PRAIRI Study

The Netherlands, 2009

Enroll 90 individuals with elevations of RF and ACPA in absence of physical examination evidence of inflammatory arthritis and one or more of the following measures including elevated C-reactive protein, or evidence of subclinical synovitis by imaging

Treated with a single dose of rituximab (1000 mg) or placebo with the primary outcome being a decrease in the number of subjects who develop classifiable RA at 4 years (expect 75% decrease in RA)

The results of this trial should be become available in the next several years and will be highly informative to the field of preclinical RA, and RA prevention.

www.trialregister.nl/trialreg/admin/rctview.asp?TC=2442
Summary

Knowledge about the preclinical period of RA supports that we are able to identify at-risk individuals and prevent disease.

We already know enough about RA to consider rational prevention trial.

$5 million, 5 years

POTENTIAL BENEFITS:

- May prevent RA
- Greatly inform future prevention studies
Studies of the Etiology of Rheumatoid Arthritis (SERA)

V. Michael Holers
Jill M. Norris
Michael Weisman
James R. O’Dell
Ted Mikuls
Hani El-Gabalawy
Elizabeth Karlson
Christopher Striebich
Vivian Bykerk
Mark Genovese
William Robinson
Additional Slides
How much does it cost to test CCP and RF?

CCP $44

RF $28

Lab draw and test reporting ~$100
Other Screening

Colonoscopy: “Everybody” in USA at age 50, and typically more often
Cost ~$1200

Fasting lipids: “Everybody” in USA at age 35 (men) or 45 (women), and typically every few years
Cost ~$40 for the test, more for the visit

U.S. Preventive Services Task Force
Lifetime risk of colon cancer

Overall, the lifetime risk of developing colorectal cancer is about 1 in 20 (5%).

Source: American Cancer Society website
What is the lifetime risk for RA?

Limited data, and controversial so hard to say...

“The lifetime risk of RA developing in US adults was 3.6% for women and 1.7% for men, and the lifetime risk of rheumatoid factor-positive RA was 2.4% for women and 1.1% for men”

Crowson et al Arthritis Rheum 2011
Issues

Should we really know more about the natural history of RA prior to prevention?

Is a high-risk biomarker profile actually too late to easily prevent disease?

Durability of preventive intervention

Cost-effectiveness

Seropositive vs. seronegative RA
Predicting RA – Caveats

ACPA + RF

High PPVs in case-control studies (>90%)

Lower PPVs using population prevalence of RA of ~1% (16%)

Rantapaa-Dahlqvist et al 2003
Questions

How many people are you willing to treat with a statin to prevent 1 death?

NNT = 1429 patients treated for 1 year to prevent 1 CVD death in patients without known cardiac disease

Ray et al Archives Int Med 2010 (meta-analysis)
Clinically Apparent RA

Preclinical RA

$5 M

Resources