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PIONEERING ANTI-TNF THERAPY: DO LESSONS LEARNED POINT PATH TO FUTURE PROGRESS?

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RHEUMATOID ARTHRITIS (RA)

- Chronic immune inflammatory disease
- Sex: F:M 3:1, ~1%
- Progressive joint damage & disability, reduced quality of life. Shortened lifespan
- Structural damage early & progressive
- 50% severely impaired by 10 yrs (not working)
- Pathology: leucocyte recruitment, inflammation, tissue destruction and repair

Pathology:
Pannus
Inflammation
Tissue destruction
PLAN OF TALK

1. TNF is a good therapeutic target
2. Optimal use of TNF blockade is with Methotrexate
3. Unexpected: a therapeutic revolution
4. Limitations of anti-TNF: need to get closer to a cure
5. Approaches to get closer to a cure
1983: A NEW HYPOTHESIS FOR AUTOIMMUNITY

Upregulation of HLA class II and antigen presentation.

Londei et al., 1984, Nature
Epithelial cells expressing aberrant MHC class II determinants can present antigen to cloned human T cells.

Pujol-Borrell et al., 1987, Nature
HLA class II induction in human islet cells by interferon-g plus TNF or lymphotoxin.

Hypothesis: Role of aberrant HLA-DR expression and antigen presentation in the induction of endocrine autoimmunity.

Human T-cell clones from autoimmune thyroid glands: specific recognition of autologous thyroid cells.

Autoantibodies and tissue damage

B

T

VIRUSES

CYTOKINES & INTERFERONS

TISSUE DAMAGE

Non tolerant autoantigen reactive T cells

Londei et al., 1985, Science

Marco Londei
ANALYSIS OF CYTOKINE REGULATION
REVEALED IMPORTANCE OF TUMOUR NECROSIS FACTOR

APPROACH     Operative sample synovium, active RA cells
             isolated, placed in ‘tissue culture’

OBSERVATION  Spontaneous production of many
             mediators of disease -
             cytokines, enzymes etc.

EXPERIMENT   Antibody to TNF inhibits production of other
             pro-inflammatory cytokines

**Brennan et al (1989) Lancet ii 244-247**

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**Rheumatoid Arthritis**

- **control**
- **anti TNFα**
- **anti LT**

**Days of culture**
- 1
- 3
- 6

**Osteoarthritis**

- **IL-1 (U/ml)**
- **Days of culture**
- 1
- 3
- 6
TNF DEPENDENT CYТОKINE CASCADE IN RHEUMATOID ARTHRITIS

Immune system → TNFα → IL-1 → IL-6, IL-8, GM-CSF etc

Anti-inflammatory
IL-10, IL-1ra, sTNF-R

Pro-inflammatory
RATIONALE FOR ANTI-TNFα THERAPY IN RHEUMATOID ARTHRITIS

1. Disregulated cytokine network in RA synovium is dependent on TNFα

2. TNFα/TNF-Receptor upregulated in synovium

3. Animal model of RA responds very well to anti TNFα administered after disease onset.
FORMAL PROOF:
RANDOMISED, PLACEBO-CONTROLLED TRIAL OF INFliximab IN RHEUMATOID ARTHRITIS

Design

<table>
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<th>Week</th>
<th>-4</th>
<th>0</th>
<th>4</th>
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<tr>
<td>cA2</td>
<td>Placebo 1 or 10 mg/kg cA2</td>
<td>3, 10 or 20 mg/kg or HSA</td>
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Results

well-tolerated

good clinical responses
dose-response

Swollen Joint Count

CRP

Paulus 20% responses at week 4

Ferry Breedveld

Jochen Kalden

Josef Smolen

FILLING AN UNMET NEED: EFFICACY OF ANTI-TNF WITH METHOTREXATE: ACR 50


Kennedy Institute gets royalties on USE patent

Used in >70% patients
SUCCESS OF ANTI-TNF THERAPY IN RHEUMATOID ARTHRITIS

1. CONTROL OF SYMPTOMS: pain, stiffness, fatigue
2. CONTROL OF SIGNS: swelling, tendernessness
3. CONTROL OF JOINT DESTRUCTION
4. INITIATION OF JOINT REPAIR: reduced Sharp Score
5. IMPROVEMENT IN HEALTH (HAQ)
6. > 5 x 10^6 treated patients
7. Long term benefit > 10 years
SAFETY ISSUES

TNF blockade interferes with host defence:
Risk becoming clearer with post-marketing registries
1. All cause mortality and cancer not increased (BSR register)
2. Serious infection risk 60/1000 Pt Years: skin - same as other DMARD (BSR register)
3. Reduced risk of cardiovascular events? 14/1000 PtY cf 35/1000 PtY (Jacobsson et al., 2005, J Rheum. 32: 1213)
5. No increased risk lymphoma (Askling et al., 2005, Am Rheum Dis. 64: 1414)
6. Demyelination

OVERALL: SAFER THAN PREVIOUS THERAPY
MECHANISM OF ACTION: TNFα DEPENDENT CYTOKINE CASCADE IS OPERATIVE IN VIVO

Also IL-1, GM-CSF, IL-8, VEGF etc

REDUCED LEUCOCYTE TRAFFICKING AFTER INFLIXIMAB THERAPY EXPLAINS EFFICACY IN MANY LOCAL DISEASES

UNEXPECTED: ACCELERATING A THERAPEUTIC REVOLUTION

1977  Kohler and Milstein: mouse Mab by fusion
      - problem immunogenicity

1980’ s  Molecular engineering
          Chimeric Ab
          - Infliximab, Rituximab
          approved 1999/2002

1990’ s  Humanization & Human Antibodies - Adalimumab
          Phage Display, Engineered Mice

SALES OF MONOCLONAL ANTIBODIES

2012  5 of top 10 drugs Mabs
      anti-TNF biggest drug class
      Mab revolution driven by
      - anti TNFs - $30bn in 2014
      - anti cancer - >$20bn  Herceptin, Avastin, Rituxan
CURRENT PROBLEMS OF ANTI-TNF THERAPY

1. Not all patients respond
2. Degree of response inadequate
3. Side effect profile
4. Cost of therapy ($30 K)
CURRENT ANTIBODIES INDUCE PARTIAL RESPONSE

NOT HEAD TO HEAD

ACR50
(Secondary Endpoint)

60:40:20

PBO + MTX
TNFi + MTX
Non-TNFi + MTX

Patients (%)

Etanercept\textsuperscript{2} Week 24
3

Infliximab\textsuperscript{3} Week 30
5

Adalimumab\textsuperscript{4} Week 24
27

Certolizumab\textsuperscript{5} Week 24
9.5

Golimumab\textsuperscript{6} Week 24
39.9

Anakinra\textsuperscript{7} Week 24
43

Rituximab\textsuperscript{8} Week 24
13

Abatacept\textsuperscript{9} Week 24
39.9

Tocilizumab\textsuperscript{10} Week 24
44

* \textsuperscript{1}

"NO PROGRESS THIS CENTURY"

Courtesy of Professor Peter C. Taylor
RESPONSE TO ANTI-TNF IN EARLY OR LATE STAGE RA

But no wheelchairs, walking frames, little joint surgery

Glass more than half empty!

1. Non Responsiveness variable
   • non responders can respond in future

2. Possible Mechanisms
   • Immunogenicity of therapeutic antibody
   • Other pathways involved in disease persistence
HOW TO GET CLOSER TO A CURE FOR A MULTIGENIC/MULTIFACTORIAL DISEASE?

DISEASE: Failure to compensate for multiple abnormal pathways

1. BIGGEST SUCCESSES
   - Combination therapy
   - HIV
   - Leukaemia

2. RISKS OF COMBINATION
   - INFECTION
   - Examples: anti TNF + anti IL-1 or CTLA4Ig

3. BUT POSSIBLE
   - Anti TNF + MTX

4. THE FUTURE
   - Combinations with anti-TNF+MTX as bedrock
   - ADD Inhibitors of different pathways and processes

CHALLENGES
- Regulatory Authorities
- Legal issues
- Costs of combination
- How to predict responders?
- How to monitor immune function to reduce infection risk
- Human Immune monitoring to reduce risk
CURRENT FOCUS:
WAYS OF GETTING CLOSER TO A CURE

antiTNF + MTX PLUS

A. REDUCE INFLAMMATION/IMMUNITY IN RATIONAL COMBINATION
   eg anti-TNF plus anti IL-17/23 (Williams)

B. RESTORE ABNORMAL HOMEOSTASIS
   eg Activate regulatory receptors – PD-1, CD200R (Davis & Williams)
      Upregulate Treg and FoxP3 (Brennan)

C. REDUCE ANTIGEN LOAD
   eg reduce PAD enzymes (Venables)

D. EMPIRICAL
   eg determine what signalling pathways are dominant
      Challenging: serial biopsies and CytoF (Taylor)

E. INHIBITING ANGIOGENESIS

F. INHIBITING STROMA : FIBROBLAST LIKE SYNOVIOCYTES (FLS):
   eg antiMMP14, antiCAD11
COULD TARGETING ANTI-TNF PLUS FLS LEAD TO SAFE AND EFFECTIVE THERAPY?

HOW COULD FLS BE TARGETED?

Wnt pathway
CAD-11 *(M. Brenner)*
Cytokines IL-33, IL-32 etc
Epigenetics *(S. Gay)*
MMP14

COMBINATION OF FLS INHIBITION PLUS IMMUNE INHIBITION?
GETTING CLOSER TO A CURE: REDUCING RESIDUAL INFLAMMATION VIA TARGETING IL-17 PATHWAY

ANTI-TNF THERAPY INCREASES IL-17 PRODUCTION IN MICE AND HUMANS

POTENTIAL SYNERGISTIC THERAPY
Anti-TNF plus p40 (IL-12 and IL-23) or Pp19, IL-23 specific

HUMANS: RISK OF INFECTION COULD BE MITIGATED BY REDUCING DOSE ANTI-TNF OR INTERMITTENT THERAPY
GETTING CLOSER TO A CURE:
B. RESTORING ABNORMAL HOMEOSTASIS

Activate endogenous regulatory receptors
e.g. CD200R activated by CD200Fc

Control
CD200-Fc 10μg
CD200-Fc 20μg
CD200-Fc 200μg
anti-TNF 300μg

IL-10 production in
LNC cultures (d10)

Clinical score
Days after onset of arthritis

Citrullinated proteins key autoantigens in RA

Citrullinated proteins (Cit autoantigens):
- Enolase (discovered Patrick Venables)
- Vimentin
- Fibrinogen
- Collagen II

Autoantibodies to Cit Protein Antigens = ACPA

ACPA influence disease:
- Antibody directly e.g. osteoclasts
- Immune complexes via TLR4

HYPOTHESIS: Reducing Cit Antigens will reduce autoimmunity

HOW: Inhibiting Peptidyl Arginase Deiminases (PAD)
P. Gingivalis PAD? Antibodies? Vaccines
KEY ISSUES FOR GETTING CLOSER TO A CURE FOR RA
1. Which patients to treat?
2. How to minimise risk of infection?

APPROACH: BETTER DIAGNOSTICS

The SOMAscan Assay:
1. Multiplex of modified aptamers
2. Monitors ~4000 proteins in 100μl

UTILITY
1. Can characterize patients before trials to profile likely ‘Responders’
2. Potential to monitor immune status during trial
CONCLUSION

1. Understanding pathogenesis of RA permits effective therapy

2. Getting closer to a cure is challenging but is possible

3. MULTIPLE THERAPEUTIC TARGETS NEEDED to get closer to a cure: antiTNF + MTX AND - restoring homeostasis T cells - removing antigen (PAD esp PPAD) - activating inhibitory receptors - Inhibiting Fibroblasts

DO WE HAVE THE AMBITION TO AIM TO CURE?
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