What’s New in Lupus

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Oct 2019 13th Annual Lupus Education Day
Lupus is a systemic inflammatory disease of autoimmune etiology.

Chronic disease characterized by unpredictable exacerbations and remissions.

It can affect virtually any organ, singly or in combinations that change from patient to patient.

Its severity ranges from mild in some cases to life-threatening in others.
Who develops lupus?

- African-Americans > Caucasians (3x)
  - Caucasian women (15-64 years of age): 1/700
  - African-American women (15-64): 1/245

- Age at diagnosis:
  - 16-55 years of age: 65% of cases
  - < 16: 20%
  - > 65: 15%

- Female/male ratio:
  - Age 14-65: 6-10 / 1
  - Age <14 or >65: 2-3 / 1
The etiology of SLE remains unknown. Yet, SLE is clearly multifactorial:

- Genetic factors
- Immunologic factors
- Hormonal factors
- Environmental factors

Genetic predisposition

Baseline immunological abnormalities

Abnormal (control of) immune responses

SLE
‘A genetic component’#

- **Strong genetic component suggested by:**
  - High concordance in identical twins (15-40%)
  - Higher incidence in families (2-10%) (10-fold increased risk in first degree relatives) (instead of 1:400 chance increased to 1:25)

- **Multiple loci (probably >100) may contribute to SLE:**
  - Multiple risk variants each conferring tiny increase risk
  - Many immune related genes

*Recent insights into the genetic basis of SLE. Moser et al. Genes Immun 2009*
Overlap in genetic risk between autoimmune diseases

- Surprising degree of overlap in genetic loci among autoimmune diseases

Farh et al. Nature 2015
A lot more than genetics.

The ‘exposome’.
Environmental factors

• The ‘microbiome’

• Findings: certain gut bacteria and immune response correlated with disease activity and nephritis

• Implications for clinical practice:
  – Development of bioassays with prognostic values for risk of development of nephritis
  – Paves the way for altering the microbiome

Azzouz et al. Annals of rheumatic disease 2019
Microbiome

Azzouz et al. Annals of rheumatic disease 2019
What’s new in treatment?

Treating inflammation or autoimmunity
• Anti-inflammatory agents
• Antimalarials
• Immunosuppressive/cytotoxic agents

Other
• Prevention: management of cardiovascular risk, immunization, etc.
• Anti-thrombotic therapy
• Dialysis and kidney transplantation
The ‘traditional treatment armamentarium’

**FDA Approved drugs**
- glucocorticoids
- hydroxychloroquine
- low dose ASA
  
  Benlysta

‘Off-label’ but standard of care
- azathioprine
- cyclophosphamide
- NSAIDs

**Immunosuppressives developed for other diseases**
- mycophenolate mofetil
- cyclosporin
- tacrolimus
  
  methotrexate
  leflunomide
  fludarabine
Treat to target

- Defined a lupus low disease activity state (LLDAS) - includes “no activity in major organ systems” and “prednisone use of less than 7.5mg a day”

- Patients who reach LLDAS do better:
  - 78% of the patients (n=1700) could reach LLDAS goals at least once
  - Patients who reached the LLDAS targets 50% of the time had fewer disease flares and were less likely to have further damage to their kidneys or other organs.

Lancet Rheum 2019
What’s new in treatment?

• WHY DO WE NEED NEW TREATMENTS?

• Current treatments do not always work

• Current treatments can have toxicity

• We have no cure for lupus
What’s new in treatment?

• HOW DO WE FIND THE RIGHT TREATMENTS:

The more that is known about clinical outcomes and immune abnormalities associated with lupus, the better equipped we are to fight the disease!

If we have a good target and drug, we need to test it in clinical trials
Identifying new treatment targets and biomarkers

Accelerating Medicines Partnership (AMP) Initiative

First-of-its-kind partnership and study,

**Goal:** To evaluate the molecular pathways and relevant, drug targets of autoimmune diseases to help develop new, therapies,

Learn more: [fnih.org/AMP-RA-Lupus](http://fnih.org/AMP-RA-Lupus)
Getting towards precision medicine

- Molecular and cellular stratification may improve outcomes in SLE and help identify new treatment targets
Many different kinds of cells in the lupus kidney.

Patients vary:
- types of infiltrating cells
- gene expression across corresponding clusters
Dominant cells may allow precision medicine.

Arazi et al. for the AMP; Nature Immunology 2019
Aims for Phase 2

Identify molecular + cellular features that define distinct subsets of nephritis

Histologic Classification

- Class I
- Class IV
- Class V

Molecular Classification

- Tx A
- Tx B
- Tx C

Adapted from JC Jennette
What’s new in treatment?

The importance of clinical trials

- We need to know what works
- We need better medications for lupus
- We need FDA approval
- We need to get insurance companies to pay for medications
Steps for drug approval &

- Pre-clinical studies – Non-Human
- Phase I studies – 1st time in humans <100 people *
  - *What are the side effects and what dose should be given?
- Phase II studies – 100+ people
  - Does the drug work and are there other side effects?
- Phase III studies – 1000+ people
  - *Does the drug work and is it safe long term?
Latest clinical trial results &

• B cells: #
  • #Phase 2 NOBILITY trial of a new B cell depleting therapy (anti-CD20 obinutuzumab) met endpoints
  • #Belimumab: SQ use approved, trial in black SLE patients (EMBRACE) did not meet primary endpoints- is there a silver lining?

• #Cytokines:
  • #Ustekinumab (approved for Ps, PsA, Crohn’s) Phase 2 trial: 1 yr improvement in disease activity drug 62%> placebo 33%. Phase 3 underway.
  • #Blocking interferon- Phase 3 TULIP 2 study meets endpoints (anifrolumab)

• Other: Phase 2 barcitinib #
Currently enrolling trials at UR

- Cell based therapies
  - Mesenchymal stem cell transfer

- Krill oil (omega-3-fatty acids) (through LUCIN: Lupus Clinical Investigators Network; other LUCIN studies include anti-CD38)

- Proteasome inhibitors (approved for myeloma) (Kezar)
Concluding points

• Therapy will attempt to target specific pathways in the body

• Despite failed trials, novel mechanism-based therapies are in development for SLE

• Personalized medicine

• Eventual treatments may involve combination therapies, i.e., “cocktails” of targeted and semi-targeted therapies
Thank You!
Learn More

- [www.lupusresearch.org/research/research_update.html](http://www.lupusresearch.org/research/research_update.html)
- [LupusTrials.org](http://www.lupusresearch.org/research/research_update.html)
- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the Office on Women’s Heath have developed a strategic plan for reducing health disparities. Lupus is included as an area of research focus. Recent first-ever National Public Health Agenda for Lupus in collaboration with the National Association of Chronic Disease Directors (NACDD). Further information on disparities in lupus and educational material at:
  - [http://thelupusinitiative.org](http://thelupusinitiative.org)
  - [www.couldihavelupus.gov](http://www.couldihavelupus.gov)
  - [https://fnih.org/what-we-do/current-research-programs/amp-ra-sle](https://fnih.org/what-we-do/current-research-programs/amp-ra-sle)