Advances in Lupus Clinical Research

Richard Furie, MD
Chief, Division of Rheumatology
Northwell Health
Professor of Medicine
Hofstra Northwell School of Medicine
Survival in SLE by Treatment Era

- Cytotoxic Agents
- Glucocorticoids
- Pre-Glucocorticoids

Y-axis: Probability of Survival
X-axis: Years After Diagnosis

Legend:

- Cytotoxic Agents
- Glucocorticoids
- Pre-Glucocorticoids
Current SLE Therapies

- NSAIDs
- Steroids (low dose to “pulse”)
- Antimalarials (hydroxychloroquine; quinacrine)
- Immunosuppressives
  - (MMF; AZA, MTX; calcineurin inh)
- Chemotherapy (cyclophosphamide)
- Biologics (belimumab; rituximab; abatacept)
- Miscellaneous (thalidomide)
- Adjunctive therapies (ACEI; bisphosphonates)
Do We Need New Lupus Treatments?

Absolutely!!!

• Safer therapies
• More effective therapies
• Replace steroids
• Replace immunosuppressives and chemotherapy
• Improve quality of life
• Prevent flares
• Cure!!!
How Will We Get These New Drugs?

Research
What are the Different Types of Research?

• Basic science research
  – “Test tube” research using biologic samples

• Translational research
  – Applied research that bridges basic science research and patient care

• Clinical research
  – Research involving patients
What are the Different Types of Clinical Research?

• Observational studies
  – “Non-invasive” collection of information
  – Questionnaires
  – Epidemiology
  – Registries

• Tissue acquisition studies
  – Provide materials for basic science research

• Clinical trials
  – Interventions with experimental therapies performed with the goal of improving clinical outcomes
What is a Clinical Trial?

• A study designed to yield information about an experimental therapy in development
• Generally sponsored by pharmaceutical or biotechnology companies
• Highly regulated with oversight by FDA and local authorities (IRB: Institutional Review Board) to assure patient protection and safety
• Necessary for new drug development
• Different phases (I-IV)
• Most always placebo controlled and double-blinded
• Successful completion generally means a drug approval
Drug Development Process

- Laboratory discovery
- Preclinical animal studies
  - Efficacy
  - Toxicity
- Human studies
  - Phase I
  - Phase II
  - Phase III
  - Phase IV
Drug Development Process

Goals

• Phase I (~50 patients)
  - Drug metabolism and safety
• Phase II (~100-300 patients)
  - Safety and efficacy
• Phase III (~500-800 patients)
  - Safety and efficacy
  - Two successes required for approval
• Phase IV (after drug approval)
  - Post-marketing surveillance
Why Participate?

1. To advance the search for better and safer therapies.
2. To receive state-of-the-art medical care.
3. To benefit one’s self, family members, or friends.
4. To receive medical care and treatment that might not be affordable.
What Are the Risks and Benefits?

• Risks:
  – Time commitment
  – Treatment might not work
  – There may be side effects
  – You might get placebo (not always a bad thing)

• Benefits:
  – Access to state-of-the-art therapy and care
  – The investigational drug might be beneficial
  – Possible modest financial rewards
What Can a Clinical Trial Participant Expect?

• Informed consent process
• Screening
• Randomization (placebo vs. investigational drug)
• Study visits (physical exam, blood tests, surveys, etc.)
• Careful medical attention
How is Safety Ensured?

• Approval by FDA
• Approval by IRB
• Frequent visits monitored by a physician and research coordinator
• Sites are monitored by the sponsor
• Safety data are reviewed by external review boards (DSMB: Data Safety Monitoring Board)
• Safety updates provided to sites
What is the Cost of Participating in a Clinical Trial?

• Generally covered by the study sponsor
• Travel expenses are often reimbursed
• Costs incurred as a result of a drug side effect are generally covered by the sponsor
What Happens After the Clinical Trial Ends?

• Data will be analyzed for safety and efficacy
• Investigational treatment may end or study medication is sometimes provided to all in what is called an open-label extension
• You will be eventually notified of the treatment you received during the study
• If the data are good, the drug advances to the next phase; if in phase III, probable drug approval!
An Example of Targeted Drug Development

• Targeting the interferon pathway: anifrolumab
Adaptive

B Cell

T Cell

Sun

mDC

CD28 - CD80/86

TCR - MHC

CD40L - CD40

ICOS - ICOS-L

BllyS/BAFF

APRIL

IL 10

pDendritic Cell

IL 12

IFNα

IFNγ

IFNα

IL 6

IL 10

DNA

mDC

TLR 9

FcR

PMN

C`

Plasma Cell

Ab

DNA

IC
Innate

Adaptive

DNA

TLR 9

FcR

pDendritic Cell

IL 6

IL 12

IL 10

IFNα

IFNγ

CXCL10
Interferons

• Type I
  – IFN-α, -β, -ω, -ε, -κ.
  – Bind to IFNAR

• Type II
  – IFN-γ
  – Binds to IFNGR

• Type III
Interferon alpha in SLE

• SLE patients:
  – Elevated IFN-α levels
  – SLE sera induce IFN gene signatures
  – 60%-75% have IFN gene signatures in PBMC
  – Clinical and serologic activity correlate with IFN gene expression

• Can IFN inhibitors reduce SLE clinical activity?
Targeting Type I IFNs: Strategies

- IFNα-Kinoïd: vaccine (inactive IFNα-KLH)⁰
- Ab to IFN alpha
  - 3 Ab (sifalimumab; rontalizumab; AGS-009)
  - 2 diseases (myositis¹, SLE²-⁵)
- Ab to type I IFN receptor (IFNAR)
  - 1 Ab (anifrolumab)
  - 2 diseases (scleroderma⁶; SLE⁷,⁸)
- Ab to IFN alpha and omega (sparing beta)⁹

How Do We Study a New Therapy?

– Who should participate?
– How do we study such clinical heterogeneity?
– How do we transform clinical impressions into data?
– How do we convince the FDA of a drug’s merit?
SLE: Clinical Heterogeneity
Disease Activity Measurements: Informal vs Formal

1. Clinical impression (gestalt): Mild, moderate, severe
2. Most commonly used disease activity instruments
   - SLEDAI
     - SLEDAI; SLEDAI-2K; hSLEDAI
     - SELENA-SLEDAI
   - BILAG
     - Classic BILAG; BILAG 2004
   - Composite indices
     - SRI
     - BICLA
**SLEDAI**

- Evaluates 24 lupus manifestations
- Parameters are scored if present
  - *Note: they must be attributed to active lupus*
- Manifestation items are weighted with scores ranging from 1 to 8
- Scores are totalled
  - Mild: 0-5
  - Moderate: 6-12
  - Severe: 13-20
- Score reduction requires *complete resolution* of a disease manifestation or laboratory test value abnormality
- 3- to 7-point reduction = clinically meaningful improvement

<table>
<thead>
<tr>
<th>Item</th>
<th>Weight</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1</td>
<td>Vasculitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulceration, gangrene, tender finger nodules, periungal infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than 2 joints with pain &amp; signs of inflammation (i.e. tenderness, swelling or effusion).</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Myositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Urinary Casts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heme-granular or red blood cell casts.</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Hematuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 red blood cells/high power field. Exclude stone, infection, or other causes.</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Proteinuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New onset or recent increase of more than 0.5 gm/24-hours.</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Pyuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 white blood cells/high power field. Exclude infection.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New or ongoing inflammatory lupus rash.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New or ongoing abnormal, patchy or diffuse loss of hair due to active lupus.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Mucosal Ulcers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New or ongoing oral or nasal ulcerations due to active lupus.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Pleurisy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Pericarditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Low Complement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decrease in CH50, C3, or C4 below the lower limit or normal for testing laboratory.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Increased DNA Binding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;25% binding by Farr assay or above normal range for testing laboratory.</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;38° C. Exclude infectious cause.</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;100,000 platelets/mm³</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3,000 white blood cells/mm³. Exclude drug causes.</td>
</tr>
</tbody>
</table>

TOTAL SCORE (Sum of weights next to descriptors marked present)
The SRI

- Generated post hoc from the belimumab phase 2 study\(^a\)
- Criteria for SRI response:
  - ≥ 4 point improvement in SELENA-SLEDAI score and
  - No BILAG worsening (new A or 2 B flares) and
  - No worsening in PGA (< 0.3-point increase)
- Primary end point for phase 3 belimumab studies (BLISS-52 and BLISS-76)\(^b,c\)

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Type I IFN Antagonists: SLE

- Rontalizumab phase II trial (n=238): failed\(^1\)
- Sifalimumab phase IIb trial (n = 431)\(^2\)
  - 4 treatment arms
  - 60% SRI response (1200 mg q4wk) vs 45% (placebo)
  - No significant toxicities
- Anifrolumab trials:
  - Japanese study: 50% greater IFN GS suppression with anifrolumab (97%) than with sifalimumab\(^3\)
  - Phase II: 300 patients, 3 arms\(^4\)

Anifrolumab Phase II: Study design

Screening

- SOC + Anifrolumab 300 mg IV Q4W (N = 99)
- SOC + Anifrolumab 1,000 mg IV Q4W (N = 104)
- SOC + Placebo IV Q4W (N = 102)

Follow-up

Day 1 85 113 169 281 309 365 422

Potential steroid tapering visits

OCS tapering target

Endpoints measured

Primary efficacy measure

- SLE Responder Index [SRI(4)] at Day 169 with a sustained reduction of oral corticosteroid to <10 mg/day prednisone and ≤Day 1 dose, between Days 85 and 169

Q4W, every 4 weeks; SOC, standard of care; SRI, SLE responder index

Furie R et al. ACR 2015

NCT01438489
Primary endpoint: SRI(4) including OCS taper

Day 169

Day 365

Responders (%)

All patients
N=305

All patients

Placebo
Anifrolumab 300 mg Q4W
Anifrolumab 1,000 mg Q4W

Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures

Delta=dosage vs. placebo
Primary endpoint: SRI(4) including OCS taper

Day 169

- All patients N=305
- IFN high N=229 (75%)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Responders (%)</th>
<th>Delta (%)</th>
<th>OR</th>
<th>90% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>36.0</td>
<td>34.3</td>
<td>2.38</td>
<td>(1.33, 4.26)</td>
<td>0.014</td>
</tr>
<tr>
<td>1,000 mg</td>
<td>28.8</td>
<td>17.6</td>
<td>1.94</td>
<td>(1.08, 3.49)</td>
<td>0.063</td>
</tr>
<tr>
<td>300 mg</td>
<td>28.2</td>
<td>26.0</td>
<td>3.55</td>
<td>(1.72, 7.32)</td>
<td>0.004</td>
</tr>
<tr>
<td>1,000 mg</td>
<td>15.0%</td>
<td>11.2%</td>
<td>2.65</td>
<td>(1.27, 5.53)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Day 365

- All patients
- IFN high N=229 (75%)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Responders (%)</th>
<th>Delta (%)</th>
<th>OR</th>
<th>90% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>51.5</td>
<td>35.5</td>
<td>3.08</td>
<td>(1.86, 5.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1,000 mg</td>
<td>38.5</td>
<td>25.5</td>
<td>1.84</td>
<td>(1.11, 3.04)</td>
<td>0.048</td>
</tr>
<tr>
<td>300 mg</td>
<td>52.0</td>
<td>42.3</td>
<td>4.30</td>
<td>(2.34, 7.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1,000 mg</td>
<td>38.5</td>
<td>38.5</td>
<td>4.25</td>
<td>(1.37, 4.64)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Delta = dosage vs. placebo

Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures.
Primary endpoint: SRI(4) including OCS taper

Day 169

Day 365

Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures.
Reduction in CLASI activity

≥50% improvement in patients with CLASI activity score ≥10 at baseline (N=77)

<table>
<thead>
<tr>
<th>Days</th>
<th>300 mg</th>
<th>Day 169</th>
<th>1,000 mg</th>
<th>Day 365</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta:</td>
<td>43.6%</td>
<td>39.4%</td>
<td>32.2%</td>
<td>27.5%</td>
</tr>
<tr>
<td>OR:</td>
<td>7.31</td>
<td>5.16</td>
<td>4.49</td>
<td>2.97</td>
</tr>
<tr>
<td>90% CI:</td>
<td>(2.56, 20.86)</td>
<td>(1.81, 14.73)</td>
<td>(1.67, 12.12)</td>
<td>(1.08, 8.19)</td>
</tr>
<tr>
<td>p:</td>
<td>0.002</td>
<td>0.010</td>
<td>0.013</td>
<td>0.077</td>
</tr>
</tbody>
</table>

* p≤0.05 compared with placebo

Day 1

Patient was receiving anifrolumab 300 mg Q4W

Day 281

Patient was receiving anifrolumab 1,000 mg Q4W

Delta=dosage vs. placebo
Reduction in joint scores

Active joint*

Swollen joint

Tender joint

Days

Change from baseline, mean (SE)

-10  -8  -6  -4  -2  0

0  29  57  85  113  141  169  197  225  253  281  309  337  365

Days

Change from baseline, mean (SE)

-10  -8  -6  -4  -2  0

0  29  57  85  113  141  169  197  225  253  281  309  337  365

*Defined as a joint with pain and signs of inflammation

SE, standard error

Placebo
Anifrolumab 300 mg Q4W
Anifrolumab 1,000 mg Q4W

Furie RA et al EULAR 2016
## Adverse events of special interest: safety population

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Placebo (N=101)</th>
<th>Anifrolumab 300 mg (N=99)</th>
<th>Anifrolumab 1,000 mg (N=105)</th>
<th>Anifrolumab Total (N=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes zoster</td>
<td>2 (2.0)</td>
<td>5 (5.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 (9.5)</td>
<td>15 (7.4)</td>
</tr>
<tr>
<td>Influenza</td>
<td>2 (2.0)</td>
<td>6 (6.1)</td>
<td>8 (7.6)</td>
<td>14 (6.9)</td>
</tr>
<tr>
<td>Varicella</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Latent tuberculosis</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis complex test positive</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Invasive ductal breast carcinoma</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Lung neoplasm (malignant)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>6 (5.9)</td>
<td>2 (2.0)</td>
<td>4 (3.8)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>One patient also had transverse myelitis with a qualitatively positive varicella-zoster virus PCR in the CSF
Conclusions

- Substantial benefit was achieved across multiple global and organ-specific disease activity measures
- The greater efficacy seen in patients with a high IFN gene signature supports the pathobiology of this treatment strategy
- Safety and tolerability were acceptable
- Phase III study underway with 300 mg as maximum dosage

Targeting the IFNAR is a promising therapeutic approach for patients with SLE who do not respond to currently available therapies
Study acknowledgments

- On behalf of the anifrolumab CD-IA-MEDI-546-1013 study team, the authors would like to thank the patients and investigators and their site personnel who contributed to the study.

- The study was funded by AstraZeneca/MedImmune.
Drugs in Development for SLE

Benlysta approved 2011
Number of Patients Required for SLE Clinical Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>1986</td>
<td>2,000</td>
</tr>
<tr>
<td>1996</td>
<td>4,000</td>
</tr>
<tr>
<td>2006</td>
<td>6,000</td>
</tr>
<tr>
<td>2016</td>
<td>12,000</td>
</tr>
</tbody>
</table>
Why Should You Participate?

• The lupus community needs to support the lupus community!

• “Let the other person do it” doesn’t work

• Narrow opportunity for success (companies might get frustrated and divert resources to other diseases)
Optimism About the Future

We will have:

• Many more medicines
  – No doubt they will become harder to pronounce

• Biomarkers

• Individualized therapy

• Better outcomes!!
The Physician-Patient Encounter in 2025

“Off hand, I’d say you’re suffering from an arrow through your head, but just to play it safe, I’m ordering a bunch of tests.”

As much as science and technology are integrated, treating lupus patients will remain an art.
Let’s Make this Era the Golden Era of SLE Drug Development

Rheumatoid Arthritis, Psoriatic Arthritis, Psoriasis, Crohn’s Disease, Ulcerative Colitis, Multiple Sclerosis collectively have had over 2 dozen drugs approved since the late 1990’s.

SLE has had just one!!

If interested in participation,
ask your lupus doctor