Anatomy of a Clinical Trial: In a drug that works in 3 diseases, what went wrong (and right) in 3 clinical trials

Michael H. Weisman, MD
Cedars-Sinai Chair in Rheumatology
Director, Division of Rheumatology
Professor of Medicine
Cedars-Sinai Medical Center
Distinguished Professor of Medicine
UCLA David Geffen School of Medicine
Before we start; a few principles about picking a disease for which you would like to perform a clinical trial
The characteristics of an ideal disease to study in a clinical trial

• Clear well defined clinical phenotype
• Biomarkers that predict outcome (surrogate)
• Disease recognizable in early stages and reversible
• Drug toxicity clearly distinct from disease flare
• Well defined, validated outcome measures that are clinically relevant
My Own Experience

- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Osteoarthritis
- Dermatomyositis/Polymyositis
- Auto Immune Inner Ear Disease (AIED)
- Ankylosing Spondylitis
- Psoriatic Arthritis
- Reactive Arthritis
- ANCA associated vasculitis (AAV)
- Polymyalgia Rheumatica/GCA
- Scleroderma
Is Lupus the ideal disease to study in a clinical trial?

- The phenotype is highly variable and no two patients are alike
- We have no biomarkers that predict outcome
- Yes, the disease is potentially reversible in its early stages, but this is not proven
- Drug toxicity can easily mimic disease activity
- There are no validated and relevant outcome measures
ACR (1997) Revised Criteria for Classification of SLE

• Skin Criteria
  – Butterfly rash
  – Discoid rash
  – Sun sensitivity
  – Oral ulcerations

• Systemic Criteria
  – Arthritis
  – Serositis
  – Kidney disorder
  – Neurologic disorder

• Laboratory Criteria
  – Blood abnormalities
  – Immunologic disorder (antiphospholipid antibodies, lupus anticoagulant, anti-DNA, false-positive syphilis test, or a positive anti-Sm)
  – Positive ANA blood test

4 of 11 needed for a diagnosis

Common Signs and Symptoms of Lupus

- Painful or swollen joints and muscle pain
- Unexplained fever
- Red rashes, most commonly on the face
- Chest pain upon deep breathing
- Unusual loss of hair
- Raynaud’s phenomenon
- Sensitivity to the sun
- Edema in legs or around eyes
- Mouth ulcers
- Swollen glands
- Extreme fatigue

Active SLE Organ Involvement: Musculoskeletal

- Musculoskeletal symptoms
  - Arthralgia
  - Arthritis
  - Myositis
  - Inflammatory tendonitis
  - Myalgia

- Musculoskeletal system organ damage
  - Tendon degeneration
  - Fixed deformities
  - Osteoporosis

Lupus is a problem

Solution: develop a “composite” measure that takes many of these domains into account
Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus

The Randomized, Double-Blind, Phase II/III Systemic Lupus Erythematosus Evaluation of Rituximab Trial

Joan T. Merrill,1 C. Michael Neuwelt,2 Daniel J. Wallace,3 Joseph C. Shanahan,4 Kevin M. Latinis,5 James C. Oates,6 Tammy O. Utset,7 Caroline Gordon,8 David A. Isenberg,9 Hsin-Ju Hsieh,10 David Zhang,10 and Paul G. Brunetta10

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The Explorer Study

- Rationale: B cells have a critical role in SLE pathogenesis.
- Study: Double blind placebo controlled study in moderately to severely active non-renal SLE patients over 52 weeks.
- Design: Primary end point for success was ability of either arm of the trial to achieve a major, partial, or no clinical response based on appearance of BILAG index organ system scores.
- Results: At week 52 there were no differences between active and placebo groups.
- Interpretation: This was a negative study – did it fail because of the drug, the study design, or both?
Screening

Week -1

Rituximab+Prednisone Taper Arm

Prednisone Taper

Placebo+Prednisone Taper Arm

Weeks 1 and 2 (Days 1 and 15)

Week 10

Weeks 24 and 26 (Days 168 and 182)

Week 52

Follow-Up Period

Open-Label Retreatment Study

↑ = Study drug infusion

◆ = Prednisone (started at screening and taken daily during the study)
Figure 3. A, Mean British Isles Lupus Assessment Group (BILAG) index global scores over time.
Figure 4. A, B cell depletion over time. Values are the means. B, Changes in the level of anti–double-stranded DNA (anti-dsDNA) over time. C and D, Changes in complement C3 and C4 levels over time in patients with low baseline levels of C3 and C4.
Development and Assessment of a Computerized Index of Clinical Disease Activity in Systemic Lupus Erythematosus

D. P. M. SYMMONS, J. S. COPPOCK, P. A. BACON, B. BRESNIHAN, D. A. ISENBERG, P. MADISON, N. McHUGH, M. L. SNAITH, and A. S. ZOMA

Members of the British Isles Lupus Assessment Group (BILAG)
What is the BILAG?
The British Isles Lupus Assessment Group

• A group of SLE specialists in 1988 achieved consensus that 8 organ systems should be evaluated to determine SLE disease activity.

• If a rheumatologist instituted new aggressive corticosteroid or immunosuppressive therapy – those elements were to be considered BILAG “A” scores. Implementing symptomatic therapy and close surveillance was considered a “B” score.

• The “gold standard” was the MD’s intention to treat – when a rheumatologist institutes aggressive therapies.

• Thus the BILAG is a “disease state” and not a “change score”

• Unmet need in lupus: a change score, derived from a trial, that can separate a drug effect from placebo.
What really happened?

- Sustained B cell depletion occurred along with a reduction in anti-DNA antibodies, etc. There was clearly a biological and pharmacodynamic effect of the intervention.
- All patient responses occurred in the first month when high doses of corticosteroids were administered, and these responses remained unchanged for the rest of the trial.
- The BILAG instrument was derived from observations of patients in practice. It is untested as a change score, and from its origins it is unlikely to be sensitive to change enough to make it useful in a clinical trial.
- Thus, both groups were treated adequately (high dose steroids on background immunosuppression) such that little difference could possibly be shown.
Let’s try this again, a different disease but use the same drug

ANCA-Associated Vasculitis, otherwise known as Wegener’s Granulomatosis (now GPA) and Microscopic Polyangiitis (now MPA)
Is AAV the ideal disease to study in a clinical trial?

• The phenotype is heterogeneous and no two patients are alike, even worse than lupus
• The biomarker ANCA fails to predict outcome
• Yes, like lupus the disease is potentially reversible in its early stages, but this is not proven
• Drug toxicity can easily mimic disease activity
• Yes, there is a validated and relevant outcome measure derived from clinical trial experience
Wegener’s Granulomatosis
Organ System Involvement in 158 Patients

Percent of Patients
Pulmonary Involvement

Occurs in ~ 85% of Patients
Wegener’s Granulomatosis
Upper Airway Involvement
Occurs in ~95% of Patients
Wegener’s Granulomatosis

Ocular Involvement – Occurs in 56%

Can affect any ocular structure and be visually threatening

Scleritis / episcleritis

Retro-orbital disease
Wegener’s Granulomatosis
Cutaneous Involvement
Occurs in 46% of Patients
Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis


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The RAVE study: Rationale

- Cytoxan and glucocorticoids are standard of therapy for ANCA associated vasculitis. Not all patients achieve remission; those who do still have flares that require additional management.
- Activated B-cells do correlate with disease activity, and cytoxan B-cell effects are associated with treatment efficacy. Rituxan depletes B cells and open label uncontrolled studies showed promise.
- Many pundits have said that a blinded trial vs. cytoxan would either be unethical or unable to be rigorously achieved.
RAVE Study Design

- Randomized, double-blind, non-inferiority trial comparing Rituxan to standard cytotoxic therapy. Success was induction of complete remission by 6 months including complete discontinuation of prednisone.
- Patients received either daily cytoxan 2 mg/kg or Rituxan 375 mg per sq. meter BSA weekly for 4 weeks.
- All patients received one to three pulses of Solumedrol followed by prednisone at 1 mg/kg/day with tapering doses so that by 5 months all patients who had achieved a clinical remission without disease flares had discontinued corticosteroids.
- **Statistical approach:** A non-inferiority margin of -20 percentage points was set for the difference in remission rates.
- Rationale: Need to not withhold standard of care for AAV.
RAVE Results

• 197 patients were enrolled in 3½ years. No patient was lost to follow-up.

• Major result: 64% of the rituxan group and 53% of the cytoxan group reached the primary endpoint, meeting criteria for non-inferiority.

• There was a treatment difference of nearly 11 percentage points favoring rituxan, clearly reaching the criterion for non-inferiority (P=<.001) but the difference was not statistically significant (95% confidence interval -3.2 to 24.3 percentage points, P=.09.)

• Among patients with relapsing disease at baseline, rituxan was more efficacious than cytoxan -- 67% compared to 42% of the control group (p=.01).

• No differences were noted between the groups in numbers of total adverse events or serious adverse events.
Non-inferiority was met and exceeded
Positive pharmaco-Dynamic response

Figure 3. Peripheral-Blood B-Cell Counts.
Panel A shows the peripheral-blood B-cell counts in the rituximab and control groups according to antineutrophil cytoplasmic antibody (ANCA) type. The counts in most patients who received rituximab decreased to less than 10 CD19+ cells per cubic millimeter after two infusions and remained at that level until 6 months. B-cell counts decreased more slowly in the control group than in the rituximab group and remained detectable, at low levels. MPO-ANCA denotes ANCA directed against myeloperoxidase, and PR3-ANCA ANCA directed against proteinase 3. Panel B shows box plots of log₂-transformed values for CD19+ B cells at six time points, according to treatment group. The horizontal line within each box indicates the median value; the bottom and top lines of the box depict the 25th and 75th quartiles, respectively; and the whiskers show the upper and lower values at 1.5 times the interquartile range. The open circles represent values outside this range and are considered outliers. Values equaling 0 were converted to the lowest nonzero value of 0.06 before log₂ transformation.
The RAVE story – what does it mean?

• The trial design assay system worked; patients were not over-treated with corticosteroids.
• This trial design was different from prior studies (and usual care situations) wherein patients are permitted to continue to receive corticosteroids for 1 year or longer.
• Rituxan was superior to cytoxan for relapsing disease – however this may be an artifact of the trial design.
• Bottom line: this was an innovative study with an assay system (no steroids at 5 months) that permitted a benefit to be shown for an additional intervention. This is NOT standard of care.
• Further, it proved that a blinded trial against cytoxan can be done – separate drug toxicity from disease activity.
Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis: A Randomized, Placebo-phase Trial

Is PM/DM the ideal disease to study?

- Hugely variable clinical phenotypes
- No biomarkers to predict outcome
- No evidence that we can reverse the disease in its early stages (they studied “treatment refractory” subjects in the trial)
- Yes, we can sort out drug toxicity from flare
- Consensus derived outcome measures – no real testing in a clinical trial situation
The ‘delay start’ design
Figure 3. Peripheral Blood B cell Numbers Prior to and Following Rituximab Treatment of IIM Subjects in the RIM Study
Peripheral blood samples were obtained at baseline (week 0) and at time points (weeks 4, 8, 12, 20, 32 and 44) following the baseline visit. Whole blood white blood cell counts and a differential were obtained at each time point and used in conjunction with flow cytometry to estimate the number of B cells/μL of blood at each time point (Methods). Median B cell numbers are displayed as a horizontal line with the distribution of B cells represented by boxes (25-75% of each sample set) and whiskers (10-90% of each sample set). Subjects treated at weeks 0 and 1 with rituximab (n=85) are represented by white boxes and subjects treated with rituximab at weeks 8 and 9 are represented by shaded boxes (n=98). The number of subjects represented in this figure (n=183) does not match up with those analyzed (n=195; Results) for either technical reasons or performance of flow cytometry locally at European sites.
DOI-free Survival for the Entire Cohort and Individual Myositis Subsets

A. Entire Cohort

B. Juvenile DM

C. Adult PM

D. Adult DM
The RIM study – what happened?

- Great rationale – multiple small studies indicated a favorable drug effect
- Well crafted outcome measures
- Unique design – called the delay start design
- Everyone got better; they did so much later than expected – **83% of all subjects reached the DOI by the end.**
- Overestimate of the rapidity of the Rituxan response and underestimate of the placebo response in their DOI
- Reason? Likely due to ethical duration of placebo administration felt to be only 8 weeks.
Clinical trials 101: Take home messages from three studies using the same drug:

- All trials are a compromise between the ideal, the practical, and ethical considerations
- Key: Use of a validated outcome measure derived from prior trials
- Make sure that your assay system works and concomitant treatment does not obscure results
- A clinical trial patient population is always different from the real world (how were these patients selected?)
- Finally, these 3 trials were designed by two entirely different groups (drug company, research consortium) – did that factor in the results?