Individual Patient Characteristics Are There Differences in Responsiveness: Or How to Characterize Patients for Pivotal Trials

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Consulting

- Affinergy
- Astrazeneca
- Abraxxis
- Alpha Rx
- NuvoResearch
- Roche
- Pfizer
- Novartis
- PLx Pharma
- Hisamatsu
- Dr Reddys
- Avanir
- Cerimon
- Leerink Swann
- Alimera
- Nomura
- Luxor
- Paraexel
- Nitec
- Bayer
- Rigel
- Chelsea
- Regeneron
- Cypress
- Savient
- Nicox
- Fidelity
- Extera
- Wyeth
- Asahi
- Winterex
- Metabolix
- Solace
- Puretechventures
- White Mountain Pharma
- Abbott
- Omeros
- Jazz
- Takeda
- Teva
- Zydus
- Proprius
- Savient
- Alder
- Cephalon
- Purdue
- EMDSerono
- Altea
- Talagen
- Tigenix
- Antigenics
- Forest
- Genzyme
- CaloSyn
- King
- Horizon
- Pozen
- ILPharma
- Analgesic Solutions
- Creabilis
- Kowa
- Array
- Astra Zeneca

Types of Patients Studied

- The label for a drug often reflects the types of patients with a certain disease state who are studied
- Some labeling for RA drugs in the recent past have included definition of use for patients with moderate or severe disease
  - Is this based on responsiveness of drug or predicated more on risk?

Baseline Descriptors Often Seen

- Baseline activity of disease,
  - Serological positivity: RF positive, anti CCP positive
  - CRP, ESR
  - HAQ DI
  - Tender and swollen joint counts
  - Patient and physician Global assessments
  - Pain measure
  - Xray at baseline
  - SF 36 and/or other HrQoL

Heterogeneity of RA Disease Course

- A systematic review and a post hoc analysis demonstrated that 39-73% of patients with early RA develop hand and wrist erosion of one or more joints within 5 years

Scott DL et al Clin Exp Rheumatol 21: S20-S27, 2003; Smolen JS at al Arthritis Rheum 52: 1020-1030 2005

Early and Late Disease Heterogeneity

- In post hoc analyses of RCTs with DMARDs both small molecules and biologicals, the amount of disability (HAQ) and amount of radiographic damage are not closely correlated until RA has been ongoing for at least 12-18 years.
- Measured changes with radiographs do not totally correlate with clinical responses as measured by ACR 20,50,70 or DAS

Tugwell et al Arthritis Rheum 43: 506-514, 2000; ; Smolen JS at al Arthritis Rheum 52: 1020-1030 2005

Should New Criteria be Applied to Better Define the Patient Population Studied

- Early vs. late disease
- Indequate responders to SOC/Baseline therapy
  - What is the definition of an inadequate responder?
- Disease activity at baseline
  - Mild vs moderate vs severe disease activity
    - Defined by DAS, CDAI, SDAI?
    - By amount of x ray damage accrued?
    - Number of tender and swollen joints?
    - HAQ DI
    - SF 36 as compared to age matched US norms?
    - Patient or physician global or both?

Does How Long a Patient Has RA Matter in Terms of Responsiveness?

- Does length of time suffering RA matter in predicting responsiveness? Or extent of disease?
  - Early RA vs Late RA, drugs with more risk typically are not used “early” vs used later after “failure” of other therapies
- Do patients with worse disease, worsen more rapidly? And how other than extrapolation (xray) could that be defined, and what measures define that: xray change, functional worsening, more or less joints involved? And over what time period?

Inadequate Responders

- For newly developed therapies without extensive evidence of efficacy or safety, initial trials are designed to recruit patients who are inadequate responders to methotrexate or to biologics depending on the characteristics of the drug
- Is there a generally accepted definition of what is an inadequate responder?

How is Severity of Disease Defined?

- Is mild disease only those patients with clear cut diagnosis but no x ray findings?
- Is moderate disease those patients with diagnosis, abnormal HAQ, and one or two erosions at baseline?
- Is severe disease those patients with diagnosis, abnormal HAQ, and many erosions at baseline?
- Is it defined by established outcome measures which are validated and express multiple measured dimensions of disease state?

SEVERAL EXAMPLES OF MEASURES OF DISEASE ACTIVITY

Disease Activity Score 28

Tender-joint count of 28 joints, square-root transformed
Swollen-joint count of 28 joints, square-root transformed
Acute-phase reactant (ESR or CRP), log transformed
Patient global assessment of disease activity by visual analogue scale (0–100 mm)

Calculation

The DAS28 score is calculated according to the following formula:

$$DAS28(ESR) = 0.56 \times SQRT(TJC28) + 0.28SQRT(SJC28) + 0.70 \times \ln(ESR) + 0.014 \times GH$$

$$DAS28(CRP) = 0.56 \times SQRT(TJC28) + 0.28SQRT(SJC28) + 0.36 \times \ln(CRP+1) + 0.014 \times GH + 0.96$$

Total score, range 0.49–9.07

Zatarain and Strand Nat Clin Prac Rheum 2006

DAS 28

Scoring

Disease remission ≤2.6

Low disease activity ≤3.2

Moderate disease activity >3.2 and ≤5.1

High disease activity >5.1

Zatarain and Strand Nat Clin Prac Rheum 2006

Clinical Simplified Disease Activity (CDAI)

- **CDAI criteria**
  - Tender-joint count of 28 joints
  - Swollen-joint count of 28 joints
  - Patient global assessment of disease activity by visual analogue scale (0–100 mm)
  - Evaluator global assessment of disease activity by visual analogue scale (0–100 mm)

- **Calculation**
  - The Clinical Disease Activity Index is the numerical sum of the equally weighted components, range 0–76

Zatarain and Strand Nat Clin Prac Rheum 2006

CDAI

- **Scoring**
  - Remission ≤2.8
  - Low disease activity ≤10
  - Moderate disease activity ≤22
  - High disease activity >22

Zatarain and Strand Nat Clin Prac Rheum 2006

The Simple Disease Activity Index (SDAI)

- **The Simple Disease Activity Index criteria**
  - Tender-joint count of 28 joints
  - Swollen-joint count of 28 joints
  - Acute-phase reactant (C-reactive protein)
  - Patient global assessment of disease activity by visual analogue scale (0–100 mm)
  - Evaluator global assessment of disease activity by visual analogue scale (0–100 mm)

- **Calculation**
  - The Simple Disease Activity Index is the numerical sum of the equally weighted components of the Disease Activity Score 28, range 0.1–86

Zatarain and Strand Nat Clin Prac Rheum 2006

SDAI

- **Scoring**
  - Remission ≤5
  - Low disease activity <20
  - Moderate disease activity 20–40
  - High disease activity >40
  - Major improvement change of –22
  - Minor improvement change of –10 to –21

Zatarain and Strand Nat Clin Prac Rheum 2006

Comparison of Clinical Outcome Measures

DAS28	SDAI	CDAI
SJC (0-28)	SJC (0-28)	SJC (0-28)
TJC (0-28)	TJC (0-28)	TJC (0-28)
PtGA (0-10)	PtGA (0-10cm)	PtGA (0-10 cm)
ESR (mm/hr)	MDGA (0-10 cm)	MDGA (0-10 cm)
or CRP (mg/dl)	CRP (mg/dl)	

AN EXAMPLE OF A STUDY RECRUITING PATIENTS WITH LOW DISEASE ACTIVITY BY CDAI

CERTAIN Trial 52 Week

- DB RCT; enrolled patients with low-to-moderate disease activity for 24 weeks
- Patients in CDAI Remission stopped randomized Rx but remained on DMARDs
- CDAI Remission at weeks 20 and 24: 18.8% for CZP and 6.1% for PBO ($P<0.05$)

Research Agenda

- Determine what is important about the extent of disease as determined by a measure of disease activity
- Determine if early versus late disease is an issue in determining responsiveness to therapy
- Develop if possible an applicable algorithm, dealing with extent of disease as measured by clinical state as well as radiographic state