EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical trial designs in RA

Targeted consultation on development of new medicinal products for the treatment of rheumatoid arthritis

European Medicines Agency – 7th June 2016

Presented by Andreas Kouroumalis
Scientific Officer Rheumatology, Respiratory, Gastroenterology and Immunology Office
Scientific and Regulatory Management Department, EMA

Agenda

- Choice of control groups in RA clinical trials
    - Placebo vs active controls
    - Recommendations for different RA sub-populations
- Inclusion of treatment “non-responders” in trials
- Length of exposure to control groups

Therapeutic options today in RA

- Methotrexate: small RCTs, 24 weeks
- Leflunomide approved in 1999: comparisons with sulfasalazine, MTX and placebo, 6-12 months
- Etanercept and infliximab, first biological DMARDs, with RCTs following recommendations from the FDA and the EMA
- Anakinra, adalimumab, rituximab, abatacept, tocilizumab, cerolizumab, golimumab….

Typical clinical development programmes in RA

- General approach: 2 or more RCT of experimental agent versus placebo
- Initially applied for indication: inadequate responders to MTX or DMARDs
- Subsequent trials in TNF-IR (placebo-controlled on a background of MTX), and in MTX-naive patients
- Comparisons of experimental agent to placebo, favourable effects on physical function, inhibition of structural progression, and characterisation of safety

Challenges for the future

- Difficult to justify the same strategy today due to availability of multiple effective treatments
- Extended use of placebo: ethical concerns/difficulties with study recruitment
- Draft EMA Guideline:
  - Three-arm trials are the preferred option
  - Specific proposals for each sub-population in RA

Why 3-arms?

- Need for active control:
  - Comparative information
  - Excludes inferior efficacy or safety to established treatments
  - Contextualisation of the benefit-risk decision
- Need for placebo:
  - Assay sensitivity
  - Measures ‘absolute’ efficacy (+ safety)

DMARD naïve patients-study design

- **Monotherapy**: two-arm superiority to MTX or three-arm non-inferiority including a placebo arm (6-12 weeks)

- **Combination**: three-arm (experimental agent, MTX alone, and combination treatment), double dummy study

    - Recent approval of tocilizumab in early progressive rheumatoid arthritis: FUNCTION study

Patient selection in clinical trials based on prior treatment

- Clinical guidelines have developed with the availability of multiple classes of treatment options
- Inadequate responders to one type of therapy are eligible for other treatments
- Clinical trial designs also impacted
  - Add on therapy trials

MTX-inadequate responders-study design

- Active comparator preferred, placebo duration as short as possible
- Background treatment on MTX needs to continue
    - Tofacitinib ORAL Scan: double-blind, active comparator (adalimumab), placebo-controlled, patients with active RA on background MTX

Biological DMARD inadequate responders

- TNF inhibitors may prove ineffective in some patients
    - Primary lack of effect
    - Secondary loss response
    - Intolerance or safety concern can also lead to discontinuation
- Switch to other TNF inhibitors
- Switch to another biologic with different mechanism of action

Biological DMARD inadequate responders-study design

- Considered the most difficult to treat sub-population
- Further sub-groups defined based on type and number of failed treatments
- Design of the study as with other sub-populations
    - 2-arm superiority: experimental agent + former (non-biologic) treatment vs former treatment & placebo or 3-arm, non-inferiority
    - Deviations from the model more likely to be justified in this population

A recent paradigm from another therapeutic area: psoriasis

- Recent approvals for the treatment of moderate to severe plaque psoriasis include two anti-IL-17 antibodies: secukinumab and ixekizumab
- Pivotal studies submitted for approval of these 2 products include the 3-arm trial model recommended in RA
- Even though different disease model, alternative treatments available are similar to RA
- Illustrates that the concepts introduced in the RA guideline are feasible

Duration of trials

- Difficult to define minimum period but 3 months considered the minimum
  - Early RA: 3-6 months, but ethical concerns if pure placebo arm included
  - MTX and biological DMARD-IR: maintenance of effect for at least one year
  - Biological-DMARD IR: for multiple failure patients longer time might be required to demonstrate efficacy
  - In all cases, placebo treatment should not exceed 3 months

For discussion

- How important is it to contextualise efficacy and safety in RA through the use of active controls in trials?
- Is the 3-arm trial design feasible/necessary in all RA sub-populations?
- Are the guidelines recommendations regarding duration of controlled trials in the different RA sub-populations adequate?