POPULATION PHARMACOKINETIC MODEL OF ETANERCEPT IN RHEUMATIC DISEASE: PROGNOSTIC FACTORS AND DOSE RECOMMENDATIONS
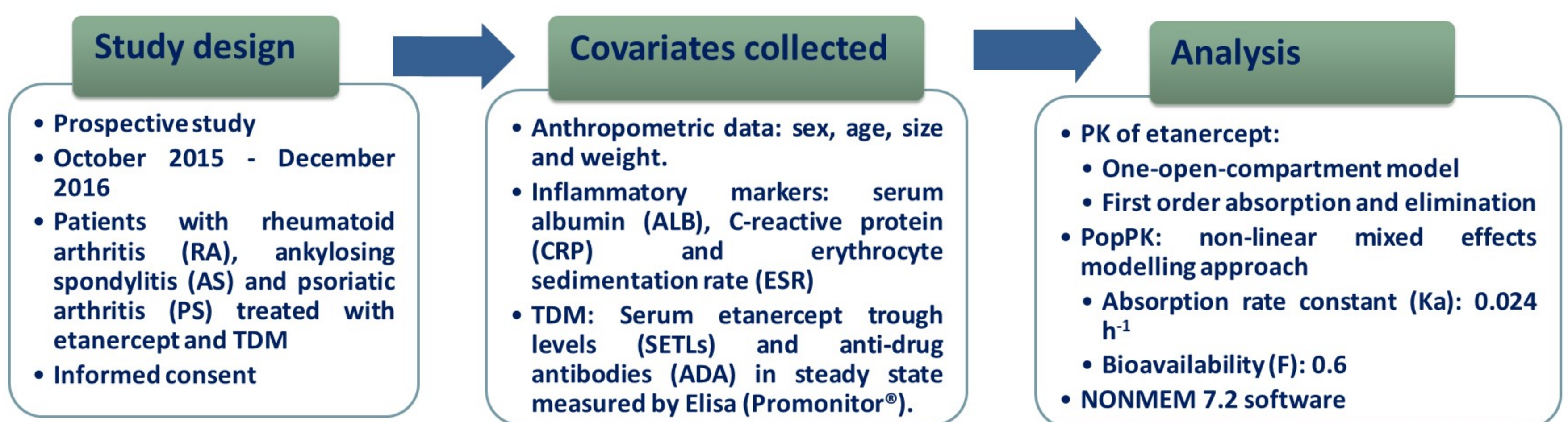
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Etanercept is an approved monoclonal antibody for the treatment of rheumatic disease (RD). Individual clinical response to etanercept can be influenced by their pharmacokinetics (PK) and immunogenicity, so therapeutic drug monitoring (TDM) can guide these biologic treatments.

Objeive

Develop a population pharmacokinetic (popPK) model of etanercept in patients with RD and explore the clinical relevance of covariates which affect significantly the PK of this drug.

Materials and Methods

Study design
- Prospective study
- October 2015 - December 2016
- Patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PS) treated with etanercept and TDM
- Informed consent

Covariates collected
- Anthropometric data: sex, age, size and weight.
- Inflammatory markers: serum albumin (ALB), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
- TDM: Serum etanercept trough levels (SETLs) and anti-drug antibodies (ADA) in steady state measured by Elisa (Promonitor®).

Analysis
- PK of etanercept:
  - One-open-compartment model
  - First order absorption and elimination
- PopPK: non-linear mixed effects modelling approach
  - Absorption rate constant (Ka): 0.024 h^{-1}
 - Bioavailability (F): 0.6
- NONMEM 7.2 software

Results

- Patients: 32 (63.3% females)
- Median age: 53 years old (18-75)
- Diagnostics: RA (N=15), AS (N=9) and PS (N=8)
- 42 SETLs quantified: mean value 1.29 mcg/mL (±1.10 mcg/mL)
- No ADA found in any patient
- PopPK parameters obtained:
  - Volume of distribution (V) = 5.46L (IIV=44.7%)
  - Clearance (CL) = 0.046L/h (IIV = 5.9%)
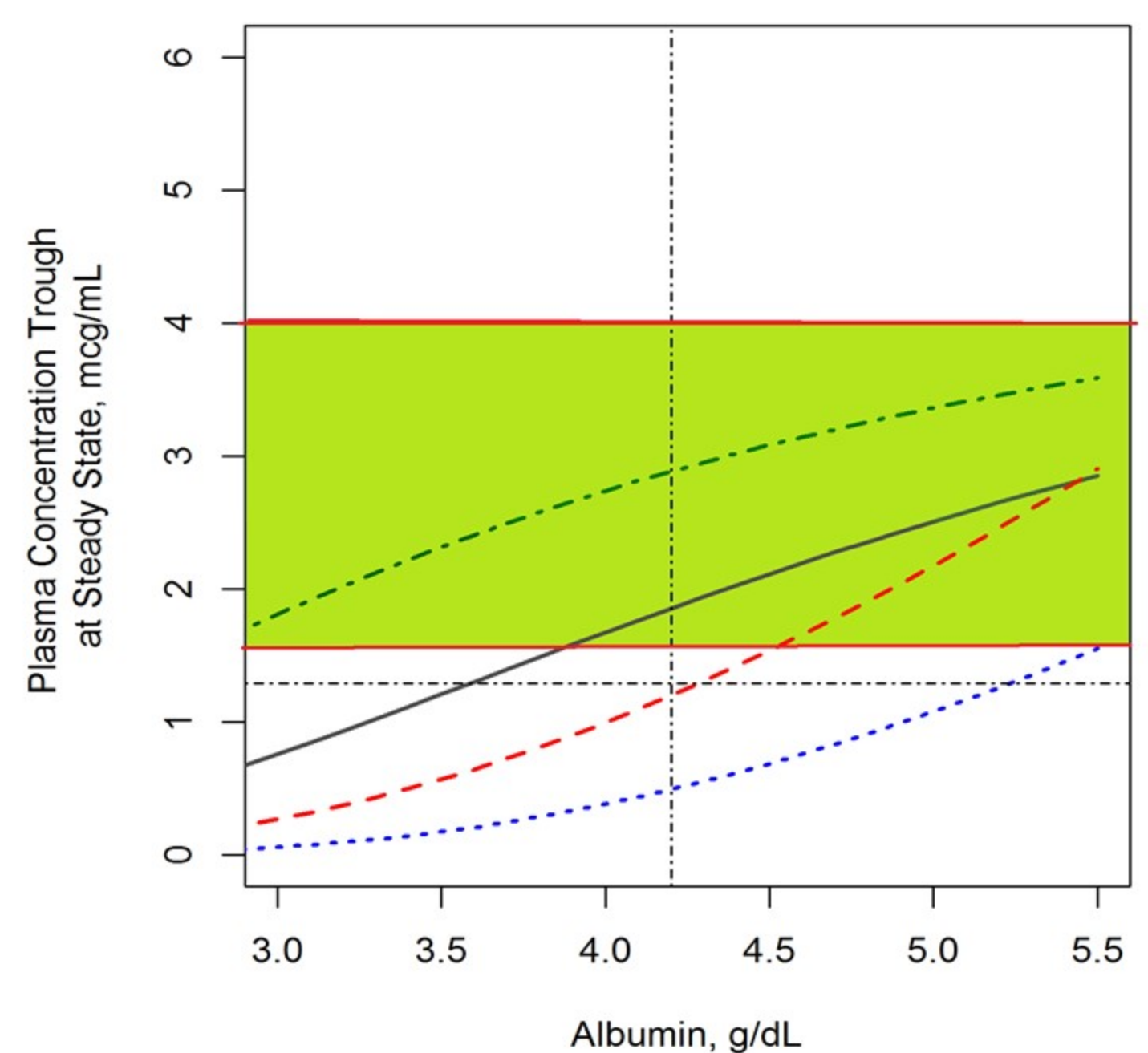
FINAL EQUATION: $CL=0.05 \times (ALB/4.24)^{-1.99} \times (PCR/0.50)^{0.13}$
[ALB (g/dL); PCR (mg/dL)]

PHARMACOKINETIC ADJUSTED DOSES RECOMENDED
-Therapeutics range: 1.5-4 mcg/mL –

PCR (mg/dL)/ Albumine (g/dL)	≤ 0.2 mg/dL	0.2 – 2 mg/dL	≥ 2mg/ dL
< 4	50 mg/4 d	50 mg/ 4 d	50 mg/ 4 d
4.0 -4.7	50 mg/7 d	50 mg/7 d	50 mg/ 4 d
4.7 – 5.5	50 mg/10 d	50 mg/7 d	50 mg/ 4 d
> 5.5	50 mg/14 d o 25 mg/ 7 d	50 mg/10 d	50 mg/ 4 d
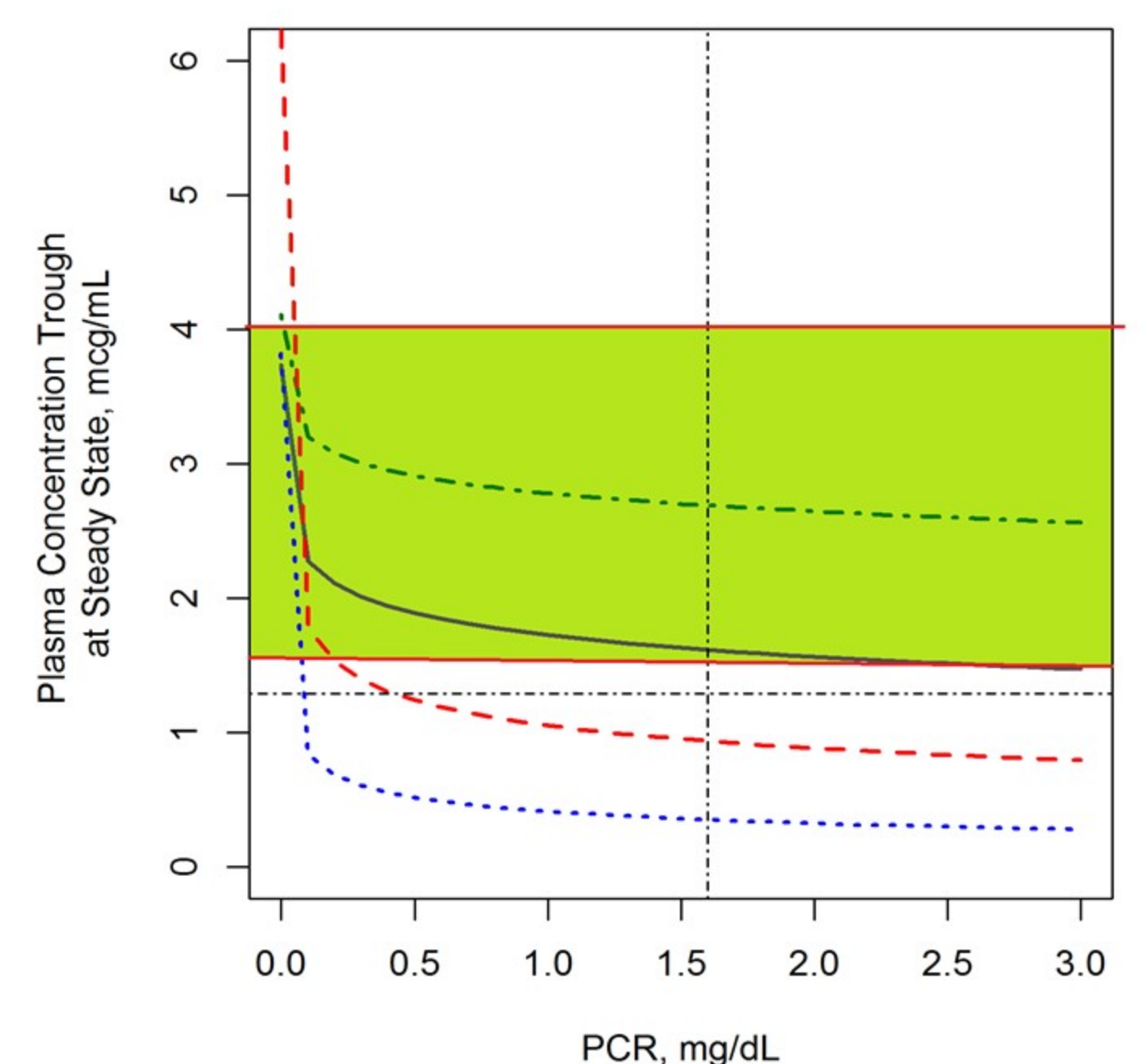
Conclusion

- A popPK model of etanercept in RD has been successfully developed.
- ALB and PCR have been identified as significant prognostic factors of the CL of etanercep and can be useful for its dose adjustment.