Comparing of 10mg vs 20mg ARAVA in treatment of rheumatoid arthritis
- A Population PK / PD Analysis -

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Introduction

Leflunomide is an isoxazole with immunosuppressive and anti-proliferative activity being developed for the treatment of rheumatoid arthritis. After oral administration, leflunomide is metabolised almost completely during first pass. More than 99% of the systemically available, primary, and pharmacologically active metabolite HMR1726 (metabolite of ARAVA, responsible for therapeutic effect) is bound to plasma proteins.

ACR20 response rate The key criterion for measuring the effect in the present analysis is the ACR20 (American College of Rheumatology score indicating 20% improvement) criterion [2] [3]. According to the American College of Rheumatology [1], the ACR20 response is defined as:

1. 20% improvement in tender and swollen joint counts and
2. 20% improvement in 3 of the 5 remaining ACR core set measures:
   (a) patient pain assessment
   (b) patient and physician global assessments
   (c) patient self-assessed disability (HAQ)
   (d) acute-phase reactant (ESR or CRP)

Objectives

The pharmacokinetics and pharmacodynamic data of a 10 mg and a 20 mg dose group are investigated and compared in the light of the

1. relationship between concentration of active metabolite & probability of therapeutic success
2. the onset of efficacy,

Materials and Methods

402 patients with RA (rheumatoid arthritis) were dosed po over 24 weeks as follows:

10mg daily: 100mg loading dose

20mg daily: 3 x 100mg loading dose

A one-compartment model with first order input was used as the population pharmacokinetic model. Data were analysed using NONMEM Version 5 & Splus6.

Results

Pharmacokinetic Model

mean [95% confidence interval]

$\mathbf{CL/F}$ = 0.0192 [0,0175 - 0.0209] L/h

$\mathbf{V/F}$ = 14.6 [13.9 - 15.3] L

Because of lack of data describing the input function, the invasion rate constant k_a was fixed to $1h^{-1}$ and the bio-availability F_a was fixed to one.

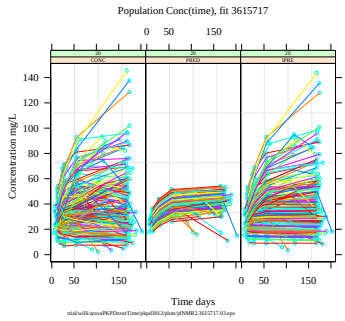

Figure 1: Observed concentration time course.

PK/PD Model: Concentration dependency of the probability of a positive ACR20

Known a priori from previous investigations: the probability of observing of a positive ACR20 is dependent on the exposure to the active metabolite HMR1726 of the pro-drug ARAVA.
The clinical outcome ($R = ACR20$) was given as a dichotomous random variable with R=1 for success and R=0 for failure. We used a logistic population model with inter-individual random effects and the effect-compartment concentration as predictor variable.
Even when the patient is under drug treatment, clinical success is caused either as placebo effect $P_0(R = 1)$ or as a treatment effect $P_1(R = 1)$ in the remaining patients without a placebo effect, $P_0(R = 0) = 1 - P_0(R = 1)$. Not all patients missing the placebo effect show a drug effect, i.e. these patients are partly drug responder, $P_1(R = 1)$, and non-responder, $P_1(R = 0)$.
In a placebo controlled clinical study, we observe the probability of a clinical success in the placebo treatment group, $P_0(R = 1)$. In the drug treated group, a clinical success is either a placebo effect $P_0(R = 1)$ or it is not a placebo effect $P_0(R = 0)$ but a response to the drug treatment $P_1(R = 1)$.
The overall probability of observing a clinical success P(R=1) is given as:

$$P(R = 1) = P_0(R = 1) + P_0(R = 0) * P_1(R = 1) \quad (1)$$

With increasing drug concentrations, the drug effect is approaching a maximum, $P_{1,max}(R = 1)$. At lower concentrations the probability of observing a clinical success $P_1(R = 1)$ decreases concentration dependently. We used logistic transformation of the classical Hill model [5] given as,

$$l = S_{Hill}\ (ln(C) - ln(EC_{50})) \quad (2)$$

to calculate the fraction of the maximum drug effect. The probability for achieving a certain fraction of $P_{1,max}(R = 1)$ in the i-th patient was calculated as a reverse logit transformation:

$$F = \frac{e^l}{1 + e^l} \quad (3)$$

If a particular patient is not a placebo responder $P_0(R = 0)$, then the probability of observing a clinical success given the drug concentration is given as:

$$P_1(R = 1|C) = P_{1,max}(R = 1)\ F \quad (4)$$

were $P_{1,max}(R = 1)$ corresponds to the responder rate.

Placebo treatment

As there is no placebo treatment in this study we took this information from previous studies [4].

1. Probability of success versus ACR20
   $IC_{50} = 11mg/L$ potency
   $P_{placebo} = 0.1$ fixed
   $P_{ARAVA} = 0.78$
   $S_{Hill} = 2$ Hill coefficient
2. Time delay by the effect compartment
   $\tau_{eo,ARAVA} = 9weeks$
   $\tau_{eo,Placebo} = 10weeks$ fixed

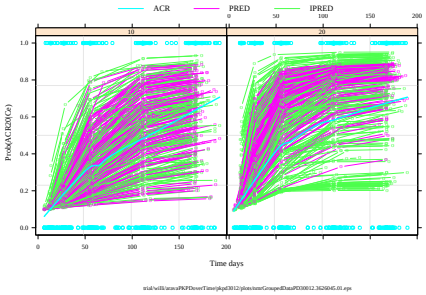

Figure 2: Probability of success ACR20 versus time (observed ACR versus time summarised by lowess, PRED & IPRED)

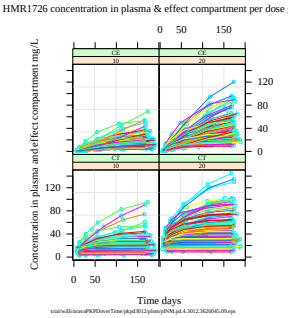

Figure 3: Concentration versus time courses shown by dose groups 10mg and 20mg in the left and right panels, respectively. Lower panels: central (plasma) compartment, Upper panels: effect compartment.

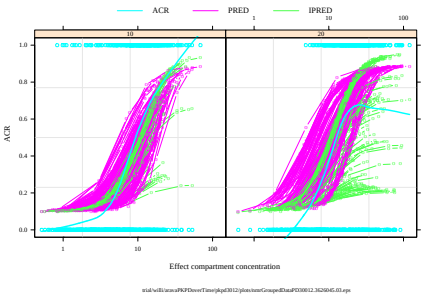

Figure 4: Probability of success versus concentration in effect compartment. (observed ACR versus concentration in effect compartment summarised by lowess, PRED & IPRED)

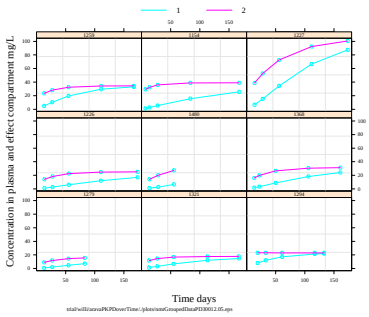

Figure 5: Concentration in 1. effect- and in 2. plasma compartment versus time

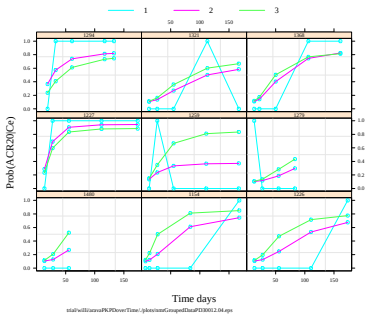

Figure 6: Probability of success versus time, 1=ACR 2=PRED & 3=IPRED.

Summary & conclusions

1. Using a loading dose of 100mg for the first 3 days followed by a 20 mg maintenance dose showed a trend of an earlier onset of efficacy than starting treatment with a single 100mg loading dose followed by 10 mg maintenance dose.
2. After RA is diagnosed, an aggressive treatment using a 20 mg daily maintenance dose should be more effective in avoiding irreversible joint destruction than using a 10 mg dose.

References

[1] The American Rheumatism Association. Revised criteria for the classification of rheumatoid arthritis, arthritis rheumatism. 31, 1988.

[2] W Horn and C Oed. Comparative trial of the efficacy and safety of leflunomide 10 mg versus 20 mg daily doses in patients with active rheumatoid arthritis. Technical Report F2002CLN00017, Aventis Pharma, Frankfurt/Main, September 2003.

[3] W Weber and L Harnisch. Use of population PK/PD modelling to estimate the optimal dose regimen for treating active rheumatoid arthritis with leflunomide. In *Measurement and Kinetics of in vivo drug effects*, Leiden/Amsterdam, 1998.

[4] W Weber and L Harnisch. ARAVA Comparison of population PKPD between Caucasian and Japanese population. Document F2002CLN0028. Technical report, Aventis Pharma, Frankfurt/Main, Germany, April 2002.

[5] I Yano, SL Beal, and LB Sheiner. The need for mixed-effects modeling with population dichotomous data. *J. Pharmacokinet Pharmacodyn*, 28(4):389–412, 2001.