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Short Communication Open Access

Adalimumab Biosimilar Adalimumab-adbm and Reference Product Population Pharmacokinetics in Healthy Persons and Patients with Rheumatoid Arthritis to Determine Pharmacokinetic Similarities

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Introduction

The goal of this study was to use Pharmacokinetic-Pharmacodynamics (PK-PD) modelling to describe adalimumab Pharmacokinetics (PK) and the concentration effect relationship of adalimumab in patients with Rheumatoid Arthritis (RA). A multicentric observational study was used to acquire adalimumab PK and PK-PD data. A one-compartment model was used to characterize the pharmacokinetics of adalimumab (40 mg) given subcutaneously every other week. An indirect response model with inhibition of CRP input was used to describe the relationship between adalimumab concentration and C-Reactive Protein (CRP) concentration, whereas a direct inhibition model was used to describe the relationship between adalimumab concentration and Disease Activity Score in 28 joints (DAS-28). Simulated dosage regimens contained a loading dose of adalimumab [1].

Description

Thirty patients who had been treated for RA were studied. The following pharmacokinetic and PK-PD parameters (individual coefficient of variation) were calculated: CRP input (kin)=22.0 mg l^{-1} day^{-1} (65%); apparent Volume of distribution (Vd/F)=10.8 l (92%); apparent Clearance (CL/F)=0.32 l day^{-1} (17%); first order absorption rate (ka)=0.28 day^{-1}; adalimumab concentration leading to a 50% decrease in kin (C_{50})=3.6 mg l^{-1} (88%); baseline DAS28 (DAS0)=(71%). According to simulations, a 160 mg loading dose should shorten the time it takes for CRP and DAS28 to reach effectiveness following the first injection [2].

This is the first study to describe adalimumab pharmacokinetics and the concentration effect relationship in RA. A 160 mg loading dose may lead to an increased benefit from treatment in RA patients. To compare the pharmacokinetics, safety, tolerability and immunogenicity of FKB-327, a biosimilar of adalimumab, with European Union (EU) approved Humira and US licensed Humira after single subcutaneous doses in healthy subjects. In a randomized, double blind, parallel group study, 180 healthy subjects received by subcutaneous injection 40 mg of EU Humira or US Humira or FKB-327, in a 1:1:1 ratio, stratified by bodyweight. Pharmacokinetics, local tolerability, immunogenicity, adverse events, vital signs, electrocardiography and laboratory safety tests were assessed prior to and up to 1536 h after treatment [3].

FKB-327's pharmacokinetics was comparable to those of Humira in the EU and the US. For all three pairwise comparisons by analysis of covariance with baseline characteristics age, body weight and (for Cmax only) sex as covariates, the 90 percent confidence interval for the ratios of AUC0–t, AUC0–inf and Cmax geometric means was in the acceptance range for bioequivalence of 0.80-1.25. The three therapies were all tolerated equally well and there were no changes in their safety profiles or immunogenicity. Antidrug antibodies were found in around 70% of those who received each therapy; larger titres were linked to faster adalimumab clearance [4].

The study found that FKB-327 had pharmacokinetic properties that are similar to Humira in the EU and the US. Healthy participants tolerated FKB-327 well, with side effects similar to those seen with Humira. FKB-327 will meet the criteria for bio-similarity to Humira if clinical similarities, including efficacy, can be demonstrated in patients. In this investigation, healthy Chinese male individuals were used to compare the bioequivalence of a proposed biosimilar HOT-3010 to its reference product (adalimumab). Tolerance, immunogenicity, and pharmacokinetics were also studied in the study (PK).

The bioequivalence of HOT-3010 (40 mg) with adalimumab (Humira®, AbbVie) as a reference medicine was investigated in a randomized, double-blind, two-arm, parallel research. The study participants were followed for a total of 71 days [5].

The HOT-3010 (N=66) and adalimumab (N=68) groups had similar PK characteristics. When comparing the two groups, the 90% confidence intervals for the ratios for C_{max}, AUC0-t, and AUC0 were found to be in the range of 80-125%. The number of participants positive for Anti-Drug Antibodies (ADA) in the HOT-3010 and adalimumab groups was 29 (43.94%) and 32 (47.06%), respectively, whereas the number of subjects positive for NAb was 27 (40.91%) and 27 (39.71%). In both groups, treatment related Treatment Emergent Adverse Events (TEAEs) were reported in 32 participants each. HOT-3010's PK characteristics and immunogenicity were comparable to that of the reference product, adalimumab. Both therapy groups had similar safety profiles, with mild-moderate side effects [6].

Adalimumab-adbm is a biosimilar to adalimumab that is a monoclonal antibody (Humira, AbbVie Inc.). The study's main goals were to assess Pharmacokinetic (PK) similarity between adalimumab-adbm and Humira in patients with active Rheumatoid Arthritis (RA), quantify the effects of potential covariates on adalimumab PK, and

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assess the impact of switching treatment from Humira to adalimumab-adbm on PK using a Population Pharmacokinetic (PPK) approach.

Conclusion

Using intensive PK data from the phase 1 investigation in healthy subjects, a PPK model was first built (NCT02045979). In patients with active RA, PPK models were created separately for the phase 3 base study (NCT02137226) and its extension study (NCT02640612). PPK models for adalimumab were established based on the treatment of healthy volunteers and RA patients with adalimumab-adbm and Humira. Adalimumab clearance was found to be influenced by weight and anti-drug antibodies. The PK of adalimumab-adbm and Humira were quite similar. Humira's effect on clearance was predicted to be 1.02 times that of adalimumab-adbm (*i.e.* Humira has 0.02 greater clearances). In the phase 3 extension research, the effect of treatment arms (switching) on clearance was assessed to be 1.00 and 0.997, respectively, for the Humira:Humira:BI and Humira:BI:BI arms, compared to the BI:BI:BI arm (BI refers to adalimumab-adbm).

The PPK method was used to demonstrate PK similarities between adalimumab-adbm and Humira in patients with active RA. When moving from Humira to adalimumab-adbm at week 24 or 48, the PK of adalimumab was also similar.

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