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Clinical Pharmacokinetics of Tumor Necrosis Factor Antagonists

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ABSTRACT. Clinical pharmacokinetics of the 3 existing marketed tumor necrosis factor (TNF) antagonists, adalimumab (Abbott Laboratories), etanercept (Amgen, Inc.), and infliximab (Centocor, Inc.) are reviewed. The relevance and potential clinical implications of any differences in their pharmacokinetic properties are outlined. The major therapeutic goal when administering TNF antagonists is to eliminate the surplus of TNF from the circulation and from sites of inflammation. Within the causal chain of events after a drug is administered the exposure (or pharmacokinetics) precedes the effect (or pharmacodynamics). The differences in the observed concentration-time profiles and the exposure characteristics derived from them are induced either by differences of the inherent properties of the molecules (such as binding to various receptors, absorption and clearance mechanisms and rates, etc.), or by the differences in the dosage and administration regimens of the drugs (such as dose magnitude, administration frequency, route of administration, etc.). Review of the dose exposure-response cascade of the TNF antagonists shows that: (1) their pharmacokinetic properties should be interpreted in the context of the "therapeutic window" paradigm; and (2) exposure of tissues and fluids is a primary determinant of the drug action/adverse action. Therefore, efforts should be made to evaluate the pharmacokinetics of the TNF antagonists in such tissues/fluids of interest as the inflammation sites (e.g., synovium, gut mucosa, skin lesions) and sites of potential adverse effects (e.g., lungs). (J Rheumatol 2005;32 Suppl 74:13-18)

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INTRODUCTION

Strong academic, industrial, and regulatory interest has emerged with respect to exploring and characterizing the exposure-response relationships of existing and developing drugs. As specified in a recent US Food and Drug Administration (FDA) Guideline for Industry[1], "...a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known." It is widely accepted to denote by the broad term "exposure" the dose and the various acute or integrated measures of the resulting concentrations in blood (plasma, serum) and/or tissues/fluids. Similarly, the term "response" refers to any direct measure of the pharmacologic effect (beneficial or otherwise) of the drug.

The first part of the exposure-response cascade is the relationship between the administered dose and the observed concentration-time profiles in the organism of interest, often referred to as pharmacokinetics (PK). The second part is the relationship between the concentration levels and the observed pharmacodynamic (PD) responses, often called the PK-PD relationship.

Within the causal chain of events after a drug is administered, the exposure (or PK) precedes the effect (or PD). Therefore, whenever any differentiation in the beneficial and/or adverse effects between drugs with similar mechanisms of action is observed, their clinical pharmacokinetics is among the first to consider.

Currently, 3 marketed TNF antagonists – adalimumab (Abbott Laboratories), etanercept (Amgen, Inc.), and infliximab (Centocor, Inc.) – are indicated in a variety of diseases characterized by abnormally elevated TNF levels. The clinical data available indicate that marked exposure-response relationships exist for all of them. At the same time, certain subtle differences in their efficacy and safety profiles have been reported.

This article reviews clinical pharmacokinetics of the 3 marketed TNF antagonists, with discussion of the relevance and potential clinical/safety implications of any differences in their PK properties.

EXPOSURE-RESPONSE CASCADE OF TNF ANTAGONISTS

The indications targeted by TNF antagonists are characterized by elevated TNF levels both systemically and at sites of inflammation. For rheumatoid arthritis (RA), higher than normal TNF levels have been detected in both serum and synovial fluid[2,3]. In Crohn's disease TNF concentration is abnormally high in serum as well as in the gut mucosa[4-6]. In psoriasis elevated TNF levels have been measured in serum and in the epidermis of the psoriatic

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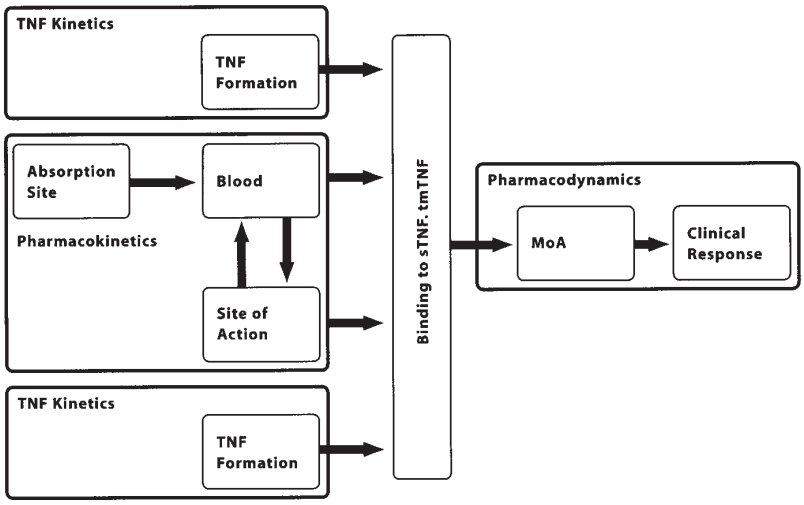

Figure 1. Cascade of processes after administration of TNF antagonist. sTNF: soluble tumor necrosis factor; MoA: pharmacologic mechanisms of action; tmTNF: transmembrane TNF.

plaques[7,8]. The major therapeutic goal when administering TNF antagonists for treatment of these conditions is to eliminate the surplus of TNF both from the blood circulation and from sites of inflammation.

Administering a dose of TNF antagonist starts a cascade of complex processes and events, shown in Figure 1. If the drug is administered extravascularly (etanercept and adalimumab are administered via the subcutaneous route), an absorption process from the administration site to the circulation begins. From the blood compartment, the drug penetrates various tissues and fluids. This group of processes represents the drug pharmacokinetics.

As counterpart to the TNF antagonist pharmacokinetics, there are the processes of TNF generation and expression by immune (and other) cells, and of soluble TNF (sTNF) secretion both systemically and in the tissues/fluids. These processes (denoted as TNF Kinetics in Figure 1) provide the ligand for the TNF antagonists and are in fine-tuned equilibrium.

Once a TNF antagonist inhibitor is administered, it starts binding to the sTNF and to TNF expressed on the surfaces of various (immune system) cell membranes (mTNF). It is important to note that binding part or all the TNF at various compartments may create TNF concentration gradients, destroying the existing equilibrium and leading to TNF redistribution. This means that TNF kinetics is likely to change before and after a TNF antagonist administration, which in turn should affect the TNF antagonist's own pharmacokinetics.

How much TNF is bound depends on the molar concentrations, binding affinity, and the binding stoichiometry of the drug. As the molecular weights of the TNF antagonists considered here (infliximab, etanercept, and adalimumab) are very similar (150 kDa), identical mass concentrations produce identical molar concentrations. The latter may serve as a basis for comparison of PK between the 3 drugs.

The binding to soluble and cell membrane TNF triggers the various pharmacologic mechanisms of action (MoA) at subcellular, cellular, and higher levels. Subsequently, due to the integrated action of these MoA processes, clinically significant changes in the condition of the patients emerge, as indicated by the clinical response block in Figure 1.

Figure 1 reiterates at least 2 important circumstances related to the exposure-response cascade of TNF antagonists: First, within the causal chain of this cascade, drug pharmacokinetic events precede MoA and clinical response events. In other words, where differentiation between drugs is concerned, pharmacokinetics is causally the first process to look at. Second, concentration levels at the site of action (or adverse action) are at least as important as serum concentrations with respect to MoA. That the former are rarely measured due to poor accessibility and for ethical reasons is not relevant to the principle. It should be noted that considering the serum concentration as a surrogate for the PK at the site of action may be misleading.

THERAPEUTIC WINDOW OF TNF ANTAGONISTS

As stated, the major therapeutic goal of TNF antagonists is to eliminate the surplus of TNF both from the blood circulation and from the inflammation sites. However, it is known that TNF is an important mediator of host defense and homeostasis and has been shown to increase resistance to infectious agents and tumor growth. Through its ability to induce apoptosis in virally infected cells, TNF represents an important defense against infection. Increased susceptibility to infection in TNF-deficient individuals has been observed in animal studies[9,10].

Thus, abnormally low TNF levels in the body lead to increased risk of opportunistic infections. This implies that the therapeutic goal for TNF antagonists should include a requirement that the targeted TNF surplus (both systemically and locally) should not reduce levels below physiological values that could compromise the individual's immunocompetency. Thus during anti-TNF therapy the aim is to administer sufficient doses of TNF antagonist to ensure elevated TNF levels are brought down to physiologically normal values, but not amounts that can potentially take out most of the TNF circulating in the bloodstream and tissues and render the organism susceptible to infection. This is a typical situation of a "therapeutic window" existing for TNF antagonists, by analogy to other drug classes, e.g., antibiotics.

If administered doses are translated to concentrations, the lower limit of the therapeutic window, the minimum effective concentration, is the minimum TNF antagonist concentration that brings elevated TNF levels down to normal values; the upper limit of the therapeutic window, the maximum safe concentration, is the maximum concentration that does not lead to the occurrence of unacceptable adverse effects. Both thresholds of the therapeutic window refer to concentrations in blood and tissue/fluids where potential beneficial or adverse effects can occur. Obvious candidates for tissues (compartments) where beneficial effects are sought are the synovium (in RA), gut (Crohn's disease), and skin lesions (psoriasis). An example where an adverse effect may occur is lung tissue (e.g., tuberculosis)[10,11].

On the other hand, thresholds of the therapeutic window for each tissue/fluid depend on the surplus of TNF in the tissue/fluid to be compensated, and on the physiologically normal levels of TNF in the particular tissue/fluid. It can be hypothesized with high confidence that the thresholds of TNF levels and the therapeutic window vary at the different locations of an organism.

A third issue: both thresholds of the therapeutic window are likely to vary across indications, across individuals, and with time within an individual. This underlines the difficulties of quantitatively determining the therapeutic window, similarly to the situation with other drugs (e.g., antibiotics).

PHARMACOKINETIC PROPERTIES OF TNF ANTAGONISTS

The therapeutic window paradigm and the cascade of events following administration of TNF antagonists provide the context in which their pharmacokinetic properties will be reviewed. Only publicly available information has been used for this review.

In principle, when a therapeutic window situation is encountered, dosage regimens that lead to smooth concentration-time profiles are preferred to acute dosage regimens yielding large peak-to-trough concentration ratios at steady state. Excessively high peaks and/or exposure at steady state increase the risk of overcompensating existing TNF and consequently lower an organism's defense potential against infection. Inadequate TNF antagonist exposure may lead to suboptimal efficacy.

Adalimumab (Humira®) is a recombinant human IgG1 monoclonal antibody specific for human TNF-α. It is approved for use in adults with moderate to severely active RA and is being investigated for the treatment of psoriasis, psoriatic arthritis, and other indications. Pharmacokinetic data for adalimumab have been published in healthy volunteers and patients with RA[12-17].

Etanercept (Enbrel®) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa (p75) TNF receptor (TNFR), linked to the Fc portion of human IgG1. It is approved for use in adults with moderate to severely active RA, juvenile RA (JRA), psoriatic arthritis, and ankylosing spondylitis (AS). A recent filing to the US Food and Drug Administration was submitted for the use of etanercept in the treatment of psoriasis. Etanercept is the TNF antagonist with probably the best characterized pharmacokinetic properties. Pharmacokinetic data for the drug have been published in healthy volunteers and patients with RA, JRA, AS, and psoriasis[18-28].

Infliximab (Remicade®) is a chimeric IgG1k monoclonal antibody composed of the human constant and murine variable regions. It is approved for use in adults with moderate to severely active RA and moderate to severely active Crohn's disease. Infliximab is being investigated for the treatment of psoriasis and other indications. Pharmacokinetic data for infliximab have been published in patients with Crohn's disease, psoriasis, and RA[29-37].

Details about the dosage and administration, binding, molecular weight, and bioavailability of the 3 drugs are given in Table 1. A direct comparison of the exposure measures of the TNF antagonists considered here is made possible by the similarity in their molecular weights and binding characteristics.

Adalimumab is administered subcutaneously by a uniform multiple dosing regimen with dosing period of one (QW) or 2 (every other week, EOW) weeks. Etanercept is administered subcutaneously (SC) by quasi-uniform (twice weekly) or uniform (QW) multiple dosing regimen with dosing period one week. Infliximab is administered by a short (2 h) intravenous (IV) infusion using a combination of a loading dosing scheme (Weeks 0, 2, 6) and a uniform maintenance dosing scheme with dosing period 4 or 8 weeks.

The combination of slow absorption rate following SC administration, slow elimination rate, and the appropriate dosing frequencies of etanercept and adalimumab yields smooth and uniform concentration-time profiles at steady state. In contrast, with infliximab's IV route of administration the extreme loading doses (630-2100 mg delivered within 6 weeks for a 70 kg individual) and the fairly high maintenance doses (210 mg to 700 mg for 70

Table 1. Properties of TNF antagonists related to their pharmacokinetics

Drug	Variable	Value	Reference	Note
Adalimumab	Dose & administration	SC injection		
	RA	40 mg EOW or QW	12	Approved
	Psoriasis	80 mg loading dose, 40 mg EOW or QW	14	Psoriasis doses used in clinical trials
	Molecular wt, kDa	148	12	
	Binding Kd, M	$7.05* 10^{-11}$	13	TNF-alpha only
		$1*10^{-10}$	17	
	Volume of distribution, l			
	Steady state	(4.7-6.0)[b]	12	
Etanercept	Dose & administration	SC injection		
	RA, PsA, AS	25 mg BIW, 50 mg QW	18	Approved
	JRA	0.4 mg/kg BIW, 0.8 mg/kg QW	25	
	Psoriasis	25 mg QW, 25 mg BIW, 50 mg QW, 50 mg BIW	24	Psoriasis doses used in clinical trials
	Molecular wt, kDa	150	18	
	Binding Kd, M	$3.35*10^{-11}$	19	TNF-alpha and TNF-beta
	Apparent vol. of distribution d, l			
	Single 25 mg dose	12 ± 6[c]	21	Healthy subjects
	Population mean	16.1 (14.3-18.2)[a]	22	RA
		22.5 (13.9-30.7)[a]	23	Psoriasis
Infliximab	Dose & administration	2h IV infusion		
	RA	3-10 mg/kg at 0,2,6 & every 4-8 wks	27	Approved
	Crohn's disease	5 mg/kg at wks 0,2,6	31	Approved
	Psoriasis	3 & 5 mg/kg at wks 0,2,6	31	Doses tested in clinical trials
	Molecular wt, kDa	149	27	—
	Volume of distribution 1			
	RA at steady rate	4.27 ± 2.5[a]	34	5 mg/kg
		3.13 ± 0.72[a]	34	10 mg/kg
		4.12	31	3 mg/kg
		4.09	31	10 mg/kg
		(3-5)[b]	36	—
		3	5	5 mg/kg
		3	5	10 mg/kg

[a]Estimate (95% CI from population pharmacokinetic analysis), [b]Interval. [c]Mean ± SD. [d]Volume divided by bioavailability, V/F; F~50% for etanercept 20.

kg individual) create acute concentration-time profiles with very high peaks and low minimums and hence high peak-to-trough ratios.

In the context of the therapeutic window paradigm, the smoothness of the steady-state concentration-time profiles of etanercept and adalimumab is a very desirable quality. Moreover, the risk of exceeding the maximum tolerated concentrations leading to excessive binding of TNF is minimized. However, the resulting therapy is not suboptimal as the concentrations are kept above the minimum efficacious levels at all times.

A comparison of exposure measures after multiple dosing and/or at steady state shows the maximum infliximab concentrations after 3 mg/kg infusions at steady state are about 40 times greater than the maximum observed etanercept steady-state concentrations (with the 25 mg BIW dose) and roughly 13 times greater than the measured maximum adalimumab steady-state concentrations (with the 40 mg EOW dose). For the 5 mg/kg and 10 mg/kg infliximab infusions, these ratios grow to about 64 and 120 times for etanercept and roughly 20 and 40 times for adalimumab, respectively. Such an acute overexposure by infliximab bears the risk of binding all or most of the TNF in the organism, rendering it susceptible to infections.

If we consider another important exposure measure, the average steady concentration levels derived from the areas under the curve and the dosing periods of the drugs, infliximab 3, 5, and 10 mg/kg produce 4–7, 15–17, and 30 times higher exposures, respectively, than etanercept 25 mg BIW. Adalimumab 40 mg EOW average steady-state concentrations are 2–3 times lower than infliximab 3 mg/kg, but still 2–3 times higher than etanercept 25 mg BIW. These considerations show that the risk of overexposure is highest with infliximab, medium with adalimumab, and lowest with etanercept.

To evaluate the effect of the potential overexposure by TNF antagonists, the primary indicator analyzed should be the incidence of infection events. However, the increased susceptibility to infections will also be expressed in an earlier onset of infections (especially for a loading dose-maintenance dose scheme as with infliximab), and in increased frequency of infection episodes over the time of anti-TNF therapy. Careful analysis of

adverse event databases for the 3 TNF antagonists is needed. As more patients are treated with TNF antagonists, comparative reviews are emerging[10,11].

If we consider the other extreme exposure measure, the minimum concentration at steady state, several authors (as well as the infliximab package insert) state that with the 3 mg/kg infliximab dose, 25% of the subjects have levels below the quantification limits at the end of the dosing period. This is compared to minimum steady concentrations of about 1.5 mg/l for etanercept (25 mg BIW) and 3.8 mg/l for adalimumab (40 mg EOW). These numbers indicate that 3 mg/kg infliximab may be subtherapeutic at the end of the 8 week dosing period. A suboptimal dosage regimen in the clinic will result not only in recurrence of disease symptoms, but also in increased doses administered and/or shortened administration periods during prolonged therapy. The latter can also be a sign of antibody development or occurrence of other tolerance mechanisms. Analysis of the clinical databases will show whether a relationship exists between the frequencies of such events and the TNF antagonist exposure.

As indicated, the penetration and distribution of TNF antagonists to the eventual sites of action and adverse effects is of critical importance for the efficacy and safety profiles of the drugs. The pharmacokinetic parameter that characterizes drug distribution is the volume of distribution at steady state. Infliximab has the lowest volume of distribution, 3 to 5 liters, which coincides with or is slightly above the physiological volume of human serum. This indicates that infliximab distributes little outside the blood circulation and into the inflamed tissues — a circumstance mentioned in the package insert of the drug as well. Adalimumab's volume of distribution is marginally higher (4.7–6 l), pointing to slightly improved distribution properties. Etanercept has the highest volume of distribution at steady state, between 7 and 12 liters, accounting for a bioavailability of 60%. These values show that more than one-half of the drug amount distributes outside serum, presumably in extravascular tissues and fluids. Analysis of the TNF antagonist binding outside serum as well as generation of data for the concentration-time profiles of the drugs in various target tissues and fluids (such as synovial fluid, psoriatic lesions, and gut mucosa) will help clarify the meaning and the effect of the observed differences in the volumes of distribution. Unfortunately, very limited data are available regarding the concentration-time profiles of the TNF antagonists outside serum. It has been reported that adalimumab concentrations in the synovial fluid from 5 RA subjects were 31–96% of those in serum (adalimumab patient information sheet).

A note of caution is due for all 3 TNF antagonists when reviewing their pharmacokinetic properties. The concentration levels for these drugs are measured using ELISA. Due to the existing interferences and the presence of endogenous TNF receptors, significant baseline concentrations are often detected. These baseline levels are both different between individuals and variable with time within an individual. Calculating pharmacokinetic parameters when baseline levels are present may be subject to error, especially for extrapolation (e.g., AUC to infinity or half-lives). In such circumstances, estimates from steady-state data are more robust and should be preferred to those following single doses.

Population pharmacokinetic analyses derived from large datasets with sparse sampling typical for the clinical setting yield the best quality pharmacokinetic parameter estimates, compared to values obtained from studies in small numbers of subjects with intensive sampling schemes and conventional PK analysis techniques.

Of the 3 TNF antagonists reviewed, the dose-exposure-response relationship of etanercept has undergone the most comprehensive analysis, which resulted in 3 published population PK/PD models in RA, JRA, AS, and psoriasis. The pharmacokinetic and pharmacodynamic information about infliximab in the public domain is patchy and scattered; no large scale population PK/PD studies have been published, despite the significant number of patients treated with this drug and the significant accumulated databases. The PK and PK/PD data for adalimumab are starting to appear as this drug's development program goes forward.

CONCLUSIONS

The underlying differences in pharmacokinetics are prime factors for consideration when differentiating efficacy and safety characteristics between the 3 TNF antagonists. This is the result of a causal relationship between exposure (i.e., pharmacokinetics) and response (i.e., efficacy and safety); this hypothesis is widely accepted in clinical pharmacokinetics and supported by extensive clinical data for this class of drugs. The differences in the observed concentration-time profiles and exposure characteristics derived from them are induced either by differences of the inherent properties of the molecules (such as binding to various receptors, absorption and clearance mechanisms and rates, etc.), or by the differences in the dosage and administration regimens of the drugs (such as dose magnitude, administration frequency, route of administration, etc.).

The dose-exposure-response cascade of the TNF antagonists shows that: (1) their PK properties should be interpreted in the context of the therapeutic window paradigm; and (2) the exposure of tissues and fluids is a primary determinant of the drug action/adverse action. Efforts should be made to evaluate the pharmacokinetics of the TNF antagonists in tissues/fluids of interest at the sites of inflammation (e.g., synovium, gut mucosa, skin lesions) and sites of potential adverse effects (e.g., the lungs).

Data presented here are based on hypotheses derived from relationships typical for clinical pharmacokinetics and widely validated with numerous drugs. For the TNF antagonists, further research is needed to improve quantitative understanding of dose-exposure-response relationships and subsystems of the cascade depicted in Figure 1.

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