Treatment of rheumatoid arthritis with PEGylated recombinant human soluble tumour necrosis factor receptor type I: a clinical update

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A recombinant form of the high affinity, natural inhibitor of tumour necrosis factor α (TNFα) is currently under development for the treatment of rheumatoid arthritis (RA).[1] This molecule is referred to as recombinant-methionyl soluble TNF-type I receptor (r-metHu-sTNF-RI or sTNF-RI). Recombinant sTNF-RI is an *Escherichia coli* derived recombinant, truncated, monomeric form of the 4-domain soluble TNF-type I receptor. For optimal delivery, a high molecular weight (30 kDa) PEG molecule is attached at the N-terminus (met 1) position to form the molecule intended for clinical investigations (PEG r-metHu-sTNF-RI or PEG sTNF-RI). PEG sTNF-RI, with an approximate molecular weight of 42 kDa, has been designed for long term chronic subcutaneous (SC) administration for the treatment of RA.

Preclinical studies to date demonstrate that PEG sTNF-RI is efficacious in rodent[2–4] and primate[5] models of acute and chronic inflammatory diseases, including *E coli* induced septic shock.[6] PEG sTNF-RI has demonstrated efficacy in predictive animal models of RA at doses as low as 0.3 mg/kg every other day.[2] The results of these and other[7–9] preclinical studies indicate that PEG sTNF-RI is a promising treatment for chronic inflammatory diseases.

Safety and pharmacokinetics study

Eighty two subjects with active (for at least six months), moderate to severe RA (as defined by the American College of Rheumatology) were enrolled into this randomised, double blind, placebo controlled, dose escalation trial of safety and pharmacokinetics.[10] Subjects were randomised to PEG sTNF-RI or placebo within one of two dose schedules. In schedule 1, subjects received a single dose of PEG sTNF-RI (100, 300, or 600 μg/kg) or placebo, followed six weeks later by weekly dosing for three weeks. In schedule 2, subjects received a single dose of PEG sTNF-RI (100, 300, or 600 μg/kg) or placebo every other week for six weeks. In addition, a group of subjects within schedules 1 and 2 received only a single dose of 1000 μg/kg on day 1.

A Safety Monitoring Committee reviewed the safety data after each dose cohort and made a recommendation for dose escalation or alternative action. In both schedule 1 and schedule 2, the decision to enroll subjects in the next higher dose cohort was based on all data available two weeks before the planned decision point, provided a minimum of four subjects receiving active medication had received at least one dose of PEG sTNF-RI. All dose levels of PEG sTNF-RI or placebo in both dose schedules were enrolled with subjects. A total of 66 subjects were given PEG sTNF-RI; 15 received placebo.

Subjects were mostly white (83%) and male (77%) with mean age about 54 years and mean body weight about 81 kg. The mean duration of RA before entry into the study was about 12 years, and 56% of subjects were positive for rheumatoid factor. Most subjects (59%) had used at least one disease modifying antirheumatic drug (DMARD) before entering the study. At entry to the study, 72% of subjects were being treated with non-steroidal anti-inflammatory drugs (NSAIDs), and 41% of subjects were being treated with corticosteroids.

No differences were observed in the incidence or severity of adverse events between the two dosing schedules, and no apparent dose response relation was noted between the incidence and severity of adverse events and dose of PEG sTNF-RI. Headache and RA flare were the most common adverse events, and the proportion of subjects who experienced injection site reactions was low. The incidence of infectious episodes (mostly upper respiratory infections (URIs)) was similar in PEG sTNF-RI treated subjects (21%) and placebo subjects (20%). Two serious adverse events were reported, both of which were unrelated to study drug. There were no treatment or dose related trends apparent in laboratory tests or vital sign values.

The pharmacokinetics of PEG sTNF-RI after single SC administration were dose independent in the range of 100 to 1000 μg/kg after single dose administration, and peak plasma concentrations were observed 48 to 96 hours after the dose.[11] The pharmacokinetics were characterised by a slow absorption rate (absorption half life of 25 hours), a limited volume of distribution (130 ml/kg), a low clearance rate (1.1 ml/h/kg), and a long elimination half life (83 hours). A twofold increase in trough levels was noted after weekly administration, and no accumulation occurred with bimonthly dosing. Compartmental analysis demonstrated that the plasma pharmacokinetics of PEG sTNF-RI were characterised as a linear, one compartment disposition model incorporating an adsorption model. These data suggest favourable pharmacokinetics for infrequent dosing (bimonthly or monthly) of PEG sTNF-RI. The pharmacokinetic profile of the one subject with persistent seroreactivity noted above did not seem to be different from that of other subjects.

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Table 1 Summary of phase 2 studies of PEG sTNF-RI

Study title	*Subjects (n)*	*Treatment regimens*
A randomised, placebo controlled, double blind, multicentre, dose finding study to evaluate the safety and efficacy of PEG sTNF-RI in patients with RA	395 enrolled (about 70 subjects per treatment arm)	Placebo, 50, 300, or 600 μg/kg PEG sTNF-RI every other week for 24 weeks *or* 1000 μg/kg for 12 weeks followed by 300 μg/kg for the next 12 weeks.
A randomised, placebo controlled, double blind, multicentre, dose finding study to evaluate the safety and efficacy of weekly administration of PEG sTNF-RI in patients with RA	194 enrolled (about 60 subjects per treatment arm)	Placebo, 400, or 800 μg/kg of PEG sTNF-RI weekly for 12 weeks.

Four subjects treated with PEG sTNF-RI were seroreactive to PEG sTNF-RI during the study.[12] Three subjects were considered to have an IgM anti-PEG sTNF-RI seroreactivity, and one subject was considered to have an IgG response. At the end of the study, one subject was still considered seroreactive, with an IgM, low titre, non-specific response. No neutralising antibodies were observed in these subjects. There did not seem to be any dose or time dependency, and the maximum titre was 1:400 (on day 22). No clinical symptoms or alteration of pharmacokinetics were associated with seroreactivity. No placebo subjects developed seroreactivity.

Although the small treatment group population evaluated in this study provided limited descriptive efficacy analyses, there seemed to be a trend toward decreases in tender/painful and swollen joints in subjects treated weekly with PEG sTNF-RI. No consistent changes were observed with bimonthly dosing. As most subjects in all treatment groups had normal baseline erythrocyte sedimentation rates (ESR) and C reactive protein (CRP) concentrations, no clear evidence of efficacy was apparent for these acute phase reactants.

Phase 2 studies

Two phase 2 studies of PEG sTNF-RI are in progress (see table 1). The primary objective of both of these studies is to assess the effect of PEG sTNF-RI dose (given SC) on safety and ACR_{20} response after 12 weeks of treatment of subjects with RA. Enrollment for these studies took an "all comers" approach to represent a "real world" RA patient population. Subjects were allowed to be receiving concurrent treatment with either methotrexate, sulfasalazine, or hydroxychloroquine. Certain combinations of these three drugs were also allowed (methotrexate+sulfasalazine; methotrexate+hydroxychloroquine; and methotrexate+sulfasalazine+hydroxychloroquine). Subjects were not allowed to be taking DMARDs at entry to the study. Doses for the studies were based on data from animal pharmacodynamic studies, from a pharmacokinetics study of TNF binding protein (TNFbp),[13] and from phase 1 trial data of PEG sTNF-RI.

At the time of this meeting, efficacy data were not available from the two studies. An interim analysis of safety data was performed. Analysis of adverse events showed no trends or adverse events of concern for the drug in this patient population. In the bimonthly dose groups, the incidence of URIs was 15% in the PEG sTNF-RI treated groups as compared with 5% in the placebo treated groups; no dose response in the incidence of URIs was noted, and no trend was observed in the weekly dosing groups. The incidence of injection site reactions (ISRs) was 13% to 18% in the PEG sTNF-RI treated groups as compared with 9% to 11% in the placebo treated groups; no dose response in the incidence of ISRs was noted. The incidence of withdrawals from study was 1% to 2%. No trends of concern were noted in serious adverse events or in clinical chemistry, haematology, or urine analysis parameters. Results are not yet available for assays of ANA, ACA, or anti-double stranded DNA. In the bimonthly group, approximately 5% of samples for antibodies against PEG sTNF-RI were seropositive in PEG sTNF-RI treated subjects. No neutralising antibodies have been found.

Future directions

TNF and interleukin 1 (IL1) are both central mediators in RA with overlapping, but differing, targets and effects. Combinations of agents that block the actions of TNF (such as PEG sTNF-RI) and IL1 (such as IL1 receptor antagonist (IL1ra)) may be useful in the treatment of RA. The objectives of combination treatment (defined as either: two or more specific anticytokines; or one or more specific anticytokines plus one or more non-specific agents) are improvement in disease control; reduction in dose of any of the agents; reduction in toxicity of non-specific agents; and reduction in impairment of the host's defences.

The ability of the combination of PEG sTNF-RI and IL1ra to modify the extent of skeletal damage and inflammation was tested in two studies of animal models of arthritis. In the first study,[14] adjuvant arthritic rats with established disease were given PEG sTNF-RI (3 mg/kg, IP, study days 9, 11, and 13) and IL1ra (100 mg/kg in hyaluronic acid slow release vehicle, SC, daily on days 8–14). The per cent inhibition of disease was measured for ankle swelling, histological bone resorption, final hind paw weights, relative spleen weights, and body weight. The effects of the anticytokines were additive for these parameters, for example, per cent inhibition of histological bone resportion for rats treated with PEG sTNF-RI, IL1ra, and the combination of the anticytokines were 56%, 43%, and 100%, respectively. The additive effect was noted in type II collagen arthritic rats, for example, final paw weights for rats treated with PEG sTNF-RI (1 mg/kg IP every other day), IL1ra (30 mg/kg SC daily in hyaluronic acid vehicle), and the combination of the anticytokines were 21%, 39%, and 58%, respectively.

In the second study,[15] male Lewis rats with mycobacteria induced adjuvant arthritis (AdA)

were treated with PEG sTNF-RI (0.25, 1, or 4 mg/kg/day SC), IL1ra (0.2, 1, or 5 mg/kg/h continuous SC infusion), or the combination of the anticytokines from days 9 to 16 after inoculation. The lowest doses of either agent alone did not inhibit inflammation (paw swelling) or bone destruction (loss of bone mineral density). The combination of these doses were synergistic, resulting in a (mean (SD)) 78% (24%) inhibition of paw swelling and a 64% (34%) inhibition of loss of bone mineral density. The results of these studies provide the preclinical rationale for investigating anticytokine combination treatment in clinical trials.

Conclusions

- PEG sTNF-RI is a new, second generation, soluble TNF receptor (p55) that is being evaluated in subjects with RA.
- Treatment of 67 subjects with doses ranging from 100 to 1000 μg/kg for up to four doses shows that PEG sTNF-RI was well tolerated.
- The pharmacokinetics of PEG sTNF-RI are dose and time linear, with a long half life.
- No clinical symptoms or alteration of pharmacokinetics were associated with seroreactivity to PEG sTNF-R1.
- Preliminary efficacy data support that PEG sTNF-RI acts to reduce the number of swollen and tender/painful joints.
- Additional trials are underway to define the optimum dose and schedule and to further evaluate the efficacy and safety of PEG sTNF-RI in subjects with RA.
- In animal studies, the combination of PEG sTNF-RI and IL1ra shows promise as a treatment of RA.

The authors thank Clifton Chunn and Aaron Van Etten for their editorial assistance.

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