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GP2015 as a promising therapy for Rheumatoid Arthritis

Abstract

Introduction: Rheumatoid arthritis is a common inflammatory joint disease with myriad systemic manifestations. Over the last 20 years its treatment has been revolutionised by the introduction of a number of different biologic drugs, including the TNF-receptor Fc fusion protein, Etanercept. However, these drugs are expensive and their widespread use puts a financial burden on health care systems. As many biologic treatments begin to come off patent new “biosimilar” versions are being developed which can lead to significant cost savings. GP2015 (Erelzi®) is the second biosimilar version of Etanercept which is licensed for the treatment of rheumatoid arthritis.

Areas covered: We discuss the Chemistry, pharmacokinetics and pharmacodynamics of GP2015 in relation to reference Etanercept. Preclinical trials have shown pharmacokinetic equivalence between GP2015 and the reference drug. The recently completed phase III, randomised, double blind EQUIRA study has shown equivalent efficacy and safety between GP2015 and Etanercept in patients with rheumatoid arthritis.

Expert opinion: GP2015 has shown equivalent efficacy and safety to reference Etanercept. With a growing number of biosimilar medications becoming available and another biosimilar Etanercept already being widely prescribed it is likely to be the cost of the drug that will determine if it is used widely.

Key words:

Biosimilar, Etanercept, GP2015, Immunogenicity, Pharmacodynamics, Pharmacokinetics, Rheumatoid arthritis, Safety, TNF inhibitor.

1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which affects around 0.5-1% of the population[1]. It causes cartilage and bone damage leading to progressive joint damage and disability. It also has a number of systemic manifestations including fatigue, anaemia, low grade fever and rheumatoid nodules, as well as more severe complications such as pulmonary fibrosis and vasculitis [2]. It can lead to excess mortality though increased cardiovascular risk[3] and an increased susceptibility to infection[4]. It has been estimated that RA costs the UK National Health Service £560 million in health care costs with an additional £1.8 billion cost to the economy through sick leave and work related disability[5].

The development of tumour necrosis factor-inhibitor (TNFi) treatment and subsequently, other biologic disease modifying anti-rheumatic drugs (bDMARDs), has revolutionised the treatment of RA[6]. A number of bDMARDs are currently licensed for the treatment of RA. These include the TNF-receptor fusion protein, Etanercept, and monoclonal antibodies, Infliximab, Adalimumab, Golimumab and Certolizumab Pegol; the anti-IL-6 receptor monoclonal antibody Tocilizumab, the anti CD-20 monoclonal antibody Rituximab and the T-cell co-stimulation inhibitor Abatacept [1]. The armamentarium has been further augmented by the recent introduction of the oral, small molecule, Janus Kinase (JAK) inhibitors Tofacitinib and Baricitinib.

Despite these advances, the high cost of these drugs places a significant financial burden on health care systems [7]. As the patents expire on a number of currently established, but expensive bDMARDs, new, more cost effective biosimilar treatments have emerged onto the market.

Development of biosimilar drugs involves the detailed analysis of multiple batches of the reference product to determine its structure and batch to batch variability in post translational protein modifications and impurity levels[8]. Biological drugs, such as Etanercept, are manufactured using recombinant DNA technologies in which the protein is produced within a host cell line[8]. Due to the inherent variability of biological systems, differences in post translational modification of the protein (eg glycosylation) can occur, even between batches of the same drug[8]. Therefore, when

a new competitor version for the reference drug is manufactured using a different recombinant DNA model, these post translational differences are highly likely to occur. This means that it will not be identical to the reference drug, hence the term biosimilar. These differences must be kept within strict limits set by regulatory bodies in order for new version to be approved for use[9, 10]. Variability of the reference product defines the target range for the development of a biosimilar product. Most regulatory agencies define pharmokinetic equivalence as when the 90% CIs for the ratio of geometric means for the area under the curve and maximal concentration between the bio-similar and reference product fall within the log-transformed range of 80-125%[10]. All biosimilar drugs undergo state of the art analysis to confirm their amino acid sequence and to confirm that higher order structures are the same as the reference product and that any variation in post-translational modification and impurity is within the predefined range to determine “biosimilarity”.

2 Overview of the biosimilar market

Biosimilar drugs for both infliximab[11] and etanercept [12], and also rituximab[13] have recently come onto the market. SB4 (Benepali®) was the first Etanercept biosimilar approved for use in the EU in early 2016. It has demonstrated pharmacokinetic equivalence with reference etanercept [14]. In a 52-week Phase III randomised confirmatory trial in RA it has shown comparable efficacy and safety to the reference drug [12].

3 Introduction to the compound and chemistry

Etanercept is a fully humanised dimeric fusion protein consisting of the extra-cellular ligand binding domain of the 75kDa TNF receptor 2 linked to the Fc portion of human immunoglobulin G1 (IgG1). It competitively binds soluble and membrane bound TNF, which is over-expressed in RA. Etanercept was first licenced in the USA for the treatment of RA in 1998 [15, 16] and Europe in 2000[17]. GP2015 (Erelzi®) is the second Etanercept biosimilar to be approved for use in the same indications as the reference product including RA, psoriasis, psoriatic arthritis and ankylosing spondylitis [18]. GP2015 is produced using recombinant DNA technology and a Chinese hamster ovary mammalian expression system from a single gene encoding

the same amino acid sequence as originator Etanercept (Enbrel®) [8]. Further analytical characterisation of the molecule confirmed that it has the same amino-acid sequence, higher order structure and comparable levels of biological activity and impurities as the reference. [8]

4 Pharmacodynamics

Etanercept binds specifically to TNF, which plays a pivotal role in RA[19], and to lymphotoxin-α (LT-α)[20], the role of which in RA is unclear. By inhibiting the binding of TNF (and LT-α) to TNF-Receptor 1 and TNF-Receptor 2 expressing cells, Etanercept biologically inactivates TNF and modulates biological responses induced or regulated by TNF. The functional characterisation programme of GP2015 included both binding and cell-based assays. The real-time binding of GP2015 and Etanercept to TNF in a surface plasmon resonance (SPR)-based assay demonstrated complete overlap[21, 22]. The intrinsic binding affinities determined by ELISA of the two Etanercept products to human C1q and a range of human Fcγ receptors and FcRn likewise exhibited a high level of comparability[21]. Moreover, there was complete overlap of the values reported for GP2015 and Etanercept in the Luciferase reporter-gene assay (RGA), which assesses binding and functional neutralization of TNF[21]. Of note, the range of values for TNF neutralization across multiple batches of GP2015 was much narrower than that for originator Etanercept. Cell-based assays were used to assess the ability of GP2015 or Etanercept to inhibit TNF-induced apoptosis of target cells, complement-dependent cytotoxicity (CDC) activity and antibody-dependent cell-mediated cytotoxicity (ADCC) [20, 23]. The activity of effector caspases-3 and -7 in U937 cells undergoing apoptosis was measured demonstrating a comparable inhibition of apoptosis induced by TNF and complete overlap of values for the neutralization of LT-α [21]. The cytotoxic effects of GP2015 were analysed in transmembrane TNF-bearing cells via Fc-dependent mechanisms. Originator Etanercept exhibited higher activity than GP2015 in the ADCC assay, whereas values for CDC activity were slightly lower for Etanercept compared with GP2015[21].

5 Pharmacokinetics and metabolism

The final GP2015 formulation was determined in a pilot study in rabbits[21]. In the main preclinical PK study, three groups of rabbits received 8 mg/kg subcutaneous (sc) GP2015 in the pre-selected 50 mM citrate/25 mM lysine buffer, or GP2015 in an Enbrel-like buffer (25 mM phosphate/25 mM arginine HCl), or commercially available reference Etanercept (Enbrel®). This 2-week study showed almost complete overlap of the serum concentration–time curves for the 3 groups. Values of AUC, Cmax, tmax, and elimination t1/2 were within the bioequivalence margins of 80–125%[24]. Furthermore, when GP2015 was formulated in Enbrel-like buffer the PK profiles were also comparable, reinforcing the biosimilarity of GP2015 to reference Etanercept[21]. In cynomolgus monkeys, following administration of GP2015, sc reference Etanercept 15 mg/kg and a vehicle control group (the formulation buffer used for GP2015) once every 3 days, serum Etanercept concentrations increased steadily, showing some accumulation after repeat dosing both for reference Etanercept and GP2015 which was markedly reduced by day 28. There were no appreciable gender-related PK differences and overall exposure to GP2015 and Etanercept was similar.

Finally, PK of GP2015 was assessed in two randomised, two-sequence, two-period, crossover studies conducted in healthy male subjects[15]. In the bioequivalence study[15, 25] subjects were randomised to receive a single 50 mg sc injection of GP2015 or reference Etanercept. Following a wash-out period of at least 35 days after dosing, subjects underwent cross-over and received a single sc injection of GP2015 or Etanercept originator. The mean serum concentration time profiles were similar between GP2015 and reference Etanercept. The geometric mean ratios of GP2015/Etanercept for Cmax, AUC0–t last, AUC0–inf were within the predefined bioequivalence range of 80–125%. Among the secondary endpoints, the mean t½ for GP2015 and Etanercept were 104.7 h and 110.7 h, respectively and median tmax was 58.3 h and 59.8 h, respectively. Also, the mean Cmax, AUC0–tlast and AUC0–inf were similar for both treatment administrations. The delivery study[15, 26] compared the administration of GP2015 by autoinjector (AI) or prefilled syringes (PFS) and demonstrated comparable serum concentration-time profiles of both AI and PFS treatment administrations of serum concentration-time profiles.

6 Clinical efficacy

6.1 Preclinical studies

The effects of GP2015 and reference Etanercept were indistinguishable in inhibiting Tg197 human TNF transgenic mouse model of polyarthritis[27]. Based on the findings of a pilot dose-ranging study a dosage of originator Etanercept 10 mg/kg by intra peritoneal (i.p) injection produced sub-therapeutic clinical response in terms of clinical symptoms and was used in a subsequent comparative study with GP2015[21]. Treatment was initiated after the onset of arthritis (sixth week of age) and was continued over 4 weeks. The effects of reference Etanercept and GP2015 were indistinguishable. Age-related arthritis progression as assessed by arthritic scores was confirmed in this model. Distinct pathological severity changes started from week 6 in the control group (when treatment was initiated) and progressed to advanced arthritis by week 10 in the group that received only vehicle. During the course of the study, there were no marked differences between GP2015 and Etanercept (both 10 mg/kg i.p.) in terms of changes in arthritic scores. At the 10mg/kg dosage, both regimens were inferior to Etanercept 30 mg/kg i.p. and superior to control (vehicle) to a similar extent. Histopathological findings paralleled changes in arthritis scores and, overall, GP2015 10 mg/kg produced similar improvements in histopathological scores as Etanercept 10 mg/kg.

6.2 Phase III studies

The equivalent efficacy and comparable safety and immunogenicity of GP2015 and Etanercept was previously assessed in a phase III study in patients with psoriasis[28]. Furthermore, the randomised, double-blind, phase III study, EQUIRA (NCT02638259)[29] compared the efficacy and safety of GP2015 versus originator Etanercept in patients with moderate-to-severe RA and an inadequate response to DMARDs. Patients aged ≥ 18 years with active RA who had an inadequate clinical response to methotrexate (MTX) at a dose of 10 – 25 mg/week, were randomised

1:1 to self-administer 50 mg GP2015 (n=170) or reference Etanercept (n=156) subcutaneously, once weekly, for 24 weeks. All patients continued to receive concomitant MTX (10 – 25 mg/week), at a stable dose throughout the study and folic acid (≥ 5 mg/week until end of study). The primary endpoint was change from baseline in the clinical composite disease activity score-C-reactive protein (DAS28-CRP[30]) at week 24. In the per-protocol set, GP2015 was determined to be equivalent to reference Etanercept in the least squares (LS) mean change from baseline to week 24 in DAS28-CRP, as the 95% CI was within the pre-specified equivalence margin of -0.6; 0.6 (LS mean difference between GP2015 vs Enbrel: -0.07, 95% CI: -0.26, 0.12(Sandoz personal communication)). At week 24, the American College of Rheumatology (ACR) response rates[31] (i.e. 20%/50%/70% improvement in tender and swollen joint counts and 3 of 5 other clinical parameters) were an ACR 20 of 88.8% for GP2015 vs 93.6 in the Etanercept group, ACR 50 was 63.9% vs 71.2% and ACR 70 was 33.7% vs 42.9% respectively. The mean change from baseline in DAS28-CRP scores were comparable between GP2015 and originator Etanercept groups at -2.78 in the GP2015 group and -2.81 in the Etanercept group[29].

7 Safety and tolerability

No signs of local intolerance were observed in PK studies in rabbits and no other obvious adverse effects with regard to clinical observations or body weight were recorded. Toxicity as well as toxicokinetics of GP2015 was compared to Etanercept in cynomolgus monkeys using the same model of the reference drug[21]. Toxicological profiles were comparable, with injection-site reactions presenting as the main toxicity for both GP2015 and reference Etanercept. Histopathological changes at the injection site were also assessed and they correlated with decreased exposure to either GP2015 or Etanercept alongside the production of anti-drug antibodies (ADAs). Across all PK studies in humans, GP2015 was well tolerated. The incidence of injection site reactions was low and similar in healthy volunteers after administration of GP2015 or reference Etanercept[25, 26]. Treatment related adverse effects from pharmacokinetic studies of GP2015 are summarised in Table 1. Tolerability and safety profile of GP2015 in patients with psoriasis in the EGALITY study was generally similar to that of reference Etanercept [28]. Likewise, in the

EQUIRA study[29], over 24 weeks the safety profile was comparable between GP2015 and Etanercept. In the GP2015 (n=186) vs reference Etanercept (n=190) groups (safety set), adverse events (AEs) occurred in 43.5% vs 49.5% patients, respectively. Serious AE (SAE) occurred in 0.5% vs 2.6% patients, respectively (Sandoz personal communication). Injection site reactions, as a part of all AEs, were reported in 7.0% of patients in GP2015 and 18.4% of patients in Etanercept group (Sandoz personal communication). In the EGALITY study switching between GP2015 and reference Etanercept, and vice versa, did not appear to impact the efficacy of either agent in terms of PASI response rates or all other efficacy parameters. Treatment safety and immunogenicity were similar between the pooled continued and pooled switched treatments, indicating that there are no effects on clinical data of multiple switches between GP2015 and originator Etanercept[32] .

[21]**Table 1.** Treatment related adverse events from the phase III EGALITY study with 531 patients monitored over 52 weeks (adapted from Griffiths et al 2017[28]).

Adverse event	**Continued GP2015 N = 164**	**Continued ETN N = 171**	**Switched GP2015 N = 100**		**Switched ETN N = 96**
Any TEAE	98 (60)	98 (57)	61 (61)		57 (59)
Any SAE	7 (4)	7 (4)	6 (6)		6 (6)
Any treatment-related TEAE	34 (21)	33 (19)	22 (22)		20 (21)
Discontinuations due to TEAE	11 (7)	8 (5)	2 (2)		5 (5)
Deaths	0	1 (1)	0		0
Upper respiratory tract infections	37 (23)	34 (20)	21 (21)		20 (30)
Raised AST/ALT/GGT	17 (10)	3 (2)	5 (5)		4 (4)
Musculoskeletal pain	13 (8)	13 (8)	7 (7)		12 (13)
Lower respiratory tract infections	8 (5)	5 (3)	4 (4)		2 (2)
Constitutional symptoms	7 (4)	16 (9)	13 (13)		5 (5)
Raised blood pressure	7 (4)	9 (5)	7 (7)		2 (2)
Gastrointestinal symptoms	5 (3)	8 (5)	4 (4)		9 (9)
Lymphadenopathy	4 (2)	0	1 (1)		1 (1)
Cough	3 (2)	2 (1)	3 (3)		0
Herpes simplex	2 (1)	2 (1)	4 (4)		1 (1)
Urinary tract infections	2 (1)	3 (2)	4		1 (1)
Mouth symptoms	5 (3)	4 (2)	3 (3)		6 (6)
Skin abnormalities	3 (2)	11 (6)	5 (5)		2 (2)
Hyperuricaemia	0	1 (1)	2 (2)		0
Diabetes mellitus	0	0	1 (1)		2 (2)

Switched GP2015: Switched to treatment sequence ETN>GP2015>ETN in period 2 and continued with ETN in extension period. Switched ETN: Switched to treatment sequence GP2015>ETN>GP2015 in period 2 and continued with GP2015 in extension period.

AE, adverse event; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; ETN, etanercept originator product; GGT, gamma-glutamyltransferase; SAE, serious adverse event; TEAE, treatment-emergent adverse event. Data represented by numbers (percentage).

8 Immunogenicity of GP2015

In the preclinical PK study in cynomolgus monkey the development of ADAs was only confirmed in four, out of 12 animals (two in both Etanercept and GP2015 groups)[21]. Moreover, by day 28 there were reductions in Cmax, AUC, and elimination t1/2 consistent with increased ADA clearance. The formation of anti-drug antibodies was further assessed in the bioequivalence study using a three-step procedure comprising a validated electrochemiluminescence assay for binding antibodies and a validated competitive ligand-binding neutralization antibody assay. This approach used a single, highly-specific and sensitive assay to detect antibodies against both the bio- similar and the reference molecule, even in the presence of circulating drug product. Among all healthy volunteers (n=216), anti-etanercept antibodies were detected in just three subjects on Day 65, after the second treatment period. All three subjects (enrolled in the same study) had received GP2015 in the first treatment period and reference Etanercept in the second treatment period. Titres were near the detection limit and none of the detected binding anti-etanercept antibodies were neutralising[8]. In the EGALITY study five patients (1.9%) in the reference Etanercept group (n=267) had a confirmed transiently positive low titre non-neutralising ADA result within the first 4 weeks of treatment, whereas one patient (1%) who was switched from originator Etanercept to GP2015 (n=90) showed a confirmed positive low titre non-neutralising ADA result at week 36 (patient was receiving GP2015 for 12 weeks at the time of the finding)[28]. In patients with RA treated with GP2015 very

low titres of ADAs were transiently detected, however at week 24 none of the patients had significant levels detected[29].

9 Conclusion

GP2015 (Erelzi®) is a new biosimilar version of Etanercept which has been approved for the treatment of RA. It has shown equivalent pharmacokinetics and pharmacodynamics and safety and tolerability to the reference product.

10 Expert Opinion

GP2015 has demonstrated equivalent efficacy and safety to originator Etanercept. As with all biosimilar medications the main benefit will likely be a reduced cost and an increase in competition for the originator, which will help to drive down costs across the range of targeted therapies and thus improve access to the available treatment options. The list price for this new drug will be the key factor in determining whether it is widely prescribed as there are a growing number of equivalent drugs coming onto the market with an additional etanercept biosimilar (Benepali®) already being widely prescribed. At present we do not have head to head data comparing the efficacy and safety of emerging biosimilars, although comparing the totality of the evidence approach used in the development of these drugs would suggest that significant differences are unlikely. In the next few years the success of GP2015 will be determined by a number of factors including the confidence placed in it by physicians, nurses, pharmacists and patients through increased experience, its ease of administration and the quality of its autoinjector device and its cost relative to its direct competitors. Given the current financial climate, the price is likely to be the key determinant in whether it is widely prescribed.

Drug Name: GP2015 (Etanercept biosimilar)

Phase: Phase III
Indication: Rheumatoid arthritis
Pharmacological decription/mechanism of action: fully humanised dimeric fusion protein consisting of the extra-cellular ligand binding domain of the 75kDa TNF receptor 2 linked to the Fc portion of human immunoglobulin G1 (IgG1). Binds and inactivates TNF and LTα
Route of administration: Subcutaneous injection
Pivotal trials: EQUIRA (NCT02638259). Randomised, double-blind, phase III study showing equivalent efficacy and safety to reference Etanercept.

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