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Review

The effect of tumor necrosis factor antagonists on mood and mental health-associated quality of life: Novel hypothesis-driven treatments for bipolar depression?

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ABSTRACT

Bipolar disorder (BD) is associated with high rates of morbidity, comorbidity, disability, economic and human capital costs as well as premature mortality. Although, the past decade has witnessed substantial progress in the treatment of BD, high rates of non-recovery, inter-episodic symptomatology, and episode recurrence remain an ongoing deficiency. Conventional treatments for BD are capable of alleviating 'surface-based' symptomatology yet no agent is disease-modifying. Translational research initiatives provide evidence that mood disorder symptomatology is subserved by disturbances in interacting immuno-inflammatory, metabolic, and neuroendocrine networks. Numerous studies document elevated pro-inflammatory circulating cytokines [e.g. interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α)], in individuals with BD as compared to healthy volunteers. Elevated peripheral levels of TNF-α and its receptors (i.e. TNF-R1 and TNF-R2) are a frequent findings across depressive and manic states and may persist into euthymia. As such, TNF-α may constitute a trait marker of BD. Other markers of inflammation including acute phase reactants (e.g. C-reactive protein) and vascular adhesion molecules (e.g. intercellular adhesion molecule-1) are also altered in BD. Herein, we review supporting evidence for the hypothesis that disturbances in inflammatory homeostasis, as marked by elevated TNF-α levels, are salient to the pathophysiology of BD and provide a platform for novel drug discovery. In this review, we propose that TNF-α modulation is a target for disease-modifying treatment of BD. To support this hypothesis, we review evidence from clinical trials evaluating the efficacy of TNF-α antagonists (i.e. adalimumab, etanercept, and infliximab) on depressive symptoms and mental health-associated quality of life measures.

Contents

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Bipolar disorders (BD) are highly prevalent syndromes associated with a high rate of non-recovery, recurrence, and inter-episodic dysfunction. Results from Canadian and US cross-national epidemiological studies indicate that approximately 2–4% of the general population is affected (Regier et al., 1990; McIntyre and Konarski, 2004b; McIntyre and O'Donovan, 2004; McIntyre et al., 2006a,b). Bipolar disorder is a chronic mental illness defined by the presence of a manic episode, nevertheless, phenomenological studies emphasize that depressive symptoms dominate the longitudinal course and disproportionately account for the burden of illness in BD (Judd and Akiskal, 2003; Martinez-Aran et al., 2004; Robinson et al., 2006). Identifying novel treatments for bipolar depression is a pressing need as approved evidence-based treatment options are limited (i.e. quetiapine and combination of olanzapine and fluoxetine). Most agents approved for the treatment of BD are indicated for the management of hypo/mania (i.e. risperidone, olanzapine, quetiapine, ziprazidone, lithium, carbamazepine, divalproex, chlorpromazine, and arapiprazole) (Yatham et al., 2006).

Although currently available pharmacological treatments are frequently capable of alleviating 'surface-based' symptomatology of BD, no agent has been developed and approved based on disease pathophysiology. The major hindrance towards the development of disease-modifying therapies has been the absence of a comprehensive experimental (e.g. animal) model (O'Neil and Moore, 2003; Holsboer, 1999; Everette and Toman, 1959).

The widely accepted hypothesis that mood disorders are subserved by abnormalities in the monoamine system gathered momentum over 50 years ago following serendipitous observations that amine modulation induced disturbance in mood. For example, separate lines of evidence documented that reserpine was associated with depressive symptom induction while iproniazid treatment in patients with tuberculosis led to elevated mood (Everette and Toman, 1959). The primary pharmacodynamic target of most antidepressants today continues to be the monoaminergic system.

In summary, parsing out other mediating factors that compromise (or protect) neuronal and glial function may illuminate and refine existing models of BD and possibly provide a novel direction for development of disease-modifying therapy. The aim of this review is to propose that the tumor necrosis factor alpha (TNF-α) pathway is a promising treatment target for BD. Towards this aim we synthesize empirical evidence of TNF-α antagonists' mood altering properties.

1. Pro- and anti-inflammatory cytokines

Pro-inflammatory activation refers to the synthesis, secretion, and action of pro-inflammatory cytokines, chemokines, acute-phase reactants and cellular adhesion molecules (Raison et al., 2006). Cytokines are secreted regulator proteins that influence the survival, proliferation, differentiation, and effector function of tissue cells. Inflammatory cytokines coordinate the activities of many cell types leading to innate and acquired immune responses. Cytokines have many sites of production but relatively few cellular targets. Moreover, cytokines have high biological redundancy and pleiotropy (Dantzer, 2004; Dantzer et al., 2008). The primary mode of action of cytokines is autocrine and paracrine; nevertheless some cytokines [e.g. Interleukin-6 (Il-6)] have been documented to have an endocrine mechanism (Venters et al., 2000).

The innate immune system operates through a complex and highly regulated network of signaling processes in large part mediated by cytokines. Central to this network are the inflammatory cytokines, most notably interleukin-1 (IL-1), IL-6 and TNF-α. The activities of these inflammatory proteins are, in turn, subject to down-regulation by anti-inflammatory cytokines [e.g. IL-10, IL-1 receptor antagonist (IL-1RA)], ensuring efficient resolution of the inflammatory response once a pathogen has been eliminated (Brietzke and Kapczinski, 2008; Schiepers et al., 2005).

2. Cytokines in the central nervous system

Historically, the central nervous system (CNS) has been viewed as an 'immuno-privileged' site; it is now well established that the CNS synthesizes and is a target of immune effector systems (Brietzke and Kapczinski, 2008). The role of inflammatory

cytokines therefore is not limited to the peripheral system; cytokines act on and are produced by brain tissues (Brietzke and Kapczinski, 2008; Manji et al., 2003). Glial cells are the primary sources of inflammatory mediators (e.g. cytokines) that act on neural tissue (Vezzani et al., 2008). Cytokine receptors have been localized throughout the brain including regions known to participate in affective and cognitive processing (e.g. hippocampus, prefrontal cortex) (Licinio et al., 1998).

Peripherally derived cytokines traverse the blood-brain barrier (BBB) via: (a) leaky region in the BBB (i.e. circumventricular organs), and (b) active transport through a saturable transport protein. Communications between the periphery and CNS occurs via (a) activation of endothelial cells, which then release inflammatory mediators within the brain parenchyma, and (b) binding to cytokine receptors located on peripheral afferent nerve fibers (e.g. vagus nerve), which in turn, relay signals to brain nuclei (Raison et al., 2009).

3. Bipolar disorder is marked by cellular, neuronal, and glial abnormalities which may be the consequence of an aberrant immuno-inflammatory system

The explanatory insufficiency of the monoaminergic model is underscored by results documenting disparate cellular, neuronal, and glial abnormalities in BD. Alterations in neuronal plasticity, cellular resilience, and cytoarchitecture, along with regional abnormalities in neuronal and glial density and morphology provide support for the involvement of multi-systemic biological networks (Carlson et al., 2006; Manji and Lenox, 2000; Manji et al., 2003; Rajkowska, 2002). Reduction in glial cell number in the prefrontal cortex as well as signs of necrosis and apoptosis in oligodendrocytes of the frontal cortex and caudate nucleus are found in postmortem brain of individuals with BD (Macdonald et al., 2003; Brietzke and Kapczinski, 2008). Reports of smaller glial cells or larger nuclei in glial cells are hypothesized to be indicative of a compensatory mechanism resulting from the reduction of glial cell number in BD (Brietzke and Kapczinski, 2008; Brauch et al., 2006). It has been suggested that glial cell loss may differentiate BD from other neurodegenerative conditions that are marked by neuronal loss and increases in glial cell density (Brietzke and Kapczinski, 2008; Rajkowska, 2002).

In keeping with the view that BD is marked by multi-systemic abnormalities, it is not surprising that most individuals with BD treated with monoamine-based pharmacotherapy fail to achieve full symptomatic and functional recovery (Tohen et al., 2006; Judd et al., 2005).

4. Individuals with bipolar disorder are differentially affected by inflammatory-mediated medical comorbidity

Several lines of evidence provide support for the hypothesis that BD may be the consequence of an aberrant immuno-inflammatory system. Epidemiological and clinical studies have provided convergent evidence that individuals with BD are differentially affected by inflammatory-mediated medical comorbidity (McIntyre et al., 2006a,b, 2007b). For example, rates of overweight/obesity, abdominal obesity, type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease are increased relative to age- and sex-matched healthy control groups (McIntyre et al., 2005, 2006a, 2007a). The pertinacity of medical comorbidity in the BD population is underscored by observations that co-occurring medical syndromes are associated with a more complex BD presentation, non-recovery, recurrence, and decreased treatment response (Beyer et al., 2005; Thompson et al., 2006; Fagiolini et al., 2003). Moreover, results from mortality studies indicate that death due to cardiovascular disease is the single largest cause of excess and premature mortality in BD populations (Osby et al., 2001; Roshanaei-Moghaddam and Katon, 2009). In addition, preliminary evidence from genome-wide association studies suggests common susceptibility loci for BD and several inflammatory-mediated chronic medical disorders (2007). Further evidence also suggests that aberrant expression of inflammatory genes may be a discriminating mRNA signature in offspring of BD parents (Padmos et al., 2008). These findings point towards a pathophysiological overlap between BD and inflammatory-mediated conditions.

Interestingly, in 1887, the Austrian psychiatrist Wagner-Jauregg published a case series which comprised of 163 individuals manifesting psychotic symptoms that remitted following an infectious event (e.g. typhoid fever). This observation led to the development of malaria fever therapy for general paresis of the insane that involved the inoculation of malaria parasites. In 1927, Wagner-Jauregg was awarded the Nobel Prize in Medicine for his novel treatment. It could be hypothesized that alterations in the inflammatory homeostasis mediated the therapeutic benefit afforded by malaria treatment (Kapczinski et al., 2008; McEwen and Stellar, 1993).

5. Animal models of 'cytokine-induced sickness behavior' resemble the phenotypic presentation of depressive symptoms in humans

Animal models of 'cytokine-induced sickness behavior' resemble the phenotypic presentation of depressive symptoms in humans. Experimental injection of pro-inflammatory cytokines, primarily those involved in innate immune function (e.g. TNF-α, IL-1β, IL-6), into rodents induces 'sickness behavior', a syndrome phenotypically similar to depressive symptoms that include anorexia, sleep disturbance, neurocognitive impairment, fatigue, and reduced self-care behaviour (Dantzer, 2004). Preclinical evidence indicates that cytokine antagonism can attenuate the development of behavioural changes following immune activation (Miller, 2009; Dantzer et al., 2008). Moreover, TNF-α receptor (i.e. TNF-R1 or TNF-R2) knockout mice show an antidepressant-like response on the forced swim test (Birgitte et al., 2006).

6. Pro-inflammatory activation in both healthy and medically as well as psychiatrically ill individuals is associated with disturbances in affective, cognitive, and somatic function

In human subjects, the injection of endotoxin (i.e. *Salmonella typhi* vaccine, a stimulator of the inflammatory system particularly the secretion of TNF-α, IL-1β, IL-6) into healthy volunteers is associated with an induction of depressive symptoms and cognitive disturbance (Reichenberg et al., 2001). The clinical use of cytokine therapy has been demonstrated to induce and/or intensify affective symptomatology (Reichenberg et al., 2005; Asnis and De La, 2005). For example, interferon alpha (INF-α) therapy in patients infected with hepatitis C virus is associated with depression onset that is attenuated with antidepressant pretreatment (Capuron and Miller, 2004). Abnormalities in pro-inflammatory cytokine production in individuals with BD have been documented *ex vivo* and *in vivo* throughout the past decade. For example, cultured blood monocytes from individuals with BD that are exposed to lipopolysaccharide (LPS) *in vitro* are characterized by low IL-1β and high IL-6 production as compared to healthy monocytes (Knijff et al., 2007).

Increased concentrations of circulating TNF-α (Kim et al., 2007; Ortiz-Dominguez et al., 2007; O'Brien et al., 2006) and IL-6 (Kim et al., 2007; Ortiz-Dominguez et al., 2007; O'Brien et al., 2006) in serum and/or plasma as well as its receptor expression (Haack et al., 1999; Rapaport et al., 1999; Maes et al., 1995) are frequently reported. The pathophysiology of BD may be subserved by an

imbalance between pro- and anti-inflammatory cytokines. For example, increases in pro- to anti-inflammatory cytokine ratios, including TNF-α/IL-4, IL-2/IL-4, INFγ/IL-4, are reported in manic states (Kim et al., 2007). The concentration of cytokines in the cerebral spinal fluid (CSF) of individuals with BD remains to be investigated. It is well known, however, that pro-inflammatory cytokines, including TNF-α and TNF receptors, are expressed in brain tissue (Tarkowski et al., 2003). Preliminary evidence, has documented abnormalities in pro-inflammatory cytokines concentrations in CSF of individuals with major depressive disorder (Levine et al., 1999; Stubner et al., 1999).

7. Converging evidence points towards pro-inflammatory cytokine elevations in bipolar disorder, most notably in TNF-α as compared to unaffected populations

Converging evidence points towards elevated concentrations of TNF-α in BD as a molecular target for novel treatment development (Brietzke and Kapczinski, 2008). Abnormally high circulating TNF-α levels are consistently reported during depressive (O'Brien et al., 2006; Ortiz-Dominguez et al., 2007) and manic states (O'Brien et al., 2006; Kim et al., 2007; Ortiz-Dominguez et al., 2007) with no significant difference between the two affective states (O'Brien et al., 2006; Ortiz-Dominguez et al., 2007). Our preliminary results show that TNF-α may persist into states of euthymia (Soczynska et al., 2008). Increased mRNA expression of TNF-α and TNF receptors in BD as well as BD offspring provide further support for scrutinizing the TNF pathway in this patient population (Padmos et al., 2008). The TNFA*2 allele and TNF-α-G308A polymorphism is also found in individuals with BD (Czerski et al., 2008; Pae et al., 2004; Meira-Lima et al., 2003).

Reports of elevations in other (equally) pro-inflammatory cytokines and chemokines in BD are consistent with the ability of TNF-α to induce the production of IL-1β (Ortiz-Dominguez et al., 2007; Padmos et al., 2008; Papiol et al., 2004), IL-6 (Ortiz-Dominguez et al., 2007; O'Brien et al., 2006; Rapaport et al., 1999; Maes et al., 1995), and the chemokine IL-8 (O'Brien et al., 2006; Brennan and McInnes, 2008).

The abnormalities reported across studies in IL-1β are somewhat conflicting in BD but may be the result of underlying phasic differences. A higher IL-1β mRNA expression in BD (Padmos et al., 2008) as well as an overexpression of the −511 polymophism for the IL-1β gene is found in BD as compared to healthy controls (Papiol et al., 2004). A trend towards a low production of IL-1β as well as significantly decreased IL-1β/IL-6 ratio by monocytes stimulated by LPS was found in non-lithium-treated patients with BD as compared to healthy monocytes (Knijff et al., 2007), while no significant elevations in IL-1β were detected in non-stimulated monocytes (Knijff et al., 2007). Comparisons between manic and depressive phases of BD indicate that mania is marked by lower levels of IL-1β as compared to depressive states in medication-free individuals as compared to healthy volunteers (Ortiz-Dominguez et al., 2007).

Higher IL-6 mRNA expression (Padmos et al., 2008) and elevated levels of circulating IL-6 are reported in BD during depressive (Ortiz-Dominguez et al., 2007) and manic states (O'Brien et al., 2006; Kim et al., 2007). A trend towards increased IL-6 production by monocytes under LPS stimulated and non-stimulated conditions in patients with BD as compared to healthy monocytyes is also reported (Knijff et al., 2007). Studies evaluating state specific IL-6 abnormalities show conflicting results. For example, increased IL-6 levels are reported in manic but not bipolar depressed individuals (O'Brien et al., 2006), whereas elevated IL-6 levels are also reported in bipolar depressed (Ortiz-Dominguez et al., 2007) but not mania (Ortiz-Dominguez et al., 2007; Maes et al., 1995). Results of IL-8 levels in BD are limited to one study reporting elevated levels in bipolar depression and mania as compared to healthy controls. No significant differences were detected between the two affective states on levels of circulating IL-8 (O'Brien et al., 2006).

Abnormalities in the 'inflammatory homeostatic network' in BD are not limited to pro-inflammatory cytokines. Alterations in acute phase reactants and anti-inflammatory cytokines are a replicated finding (Cunha et al., 2008; De et al., 2006a,b; Dickerson et al., 2007; Hornig et al., 1998; Huang and Lin, 2007; Wadee et al., 2002). Increased serum levels of the acute phase reactant, C-reactive protein are reported across heterogeneous BD populations (Cunha et al., 2008; Dickerson et al., 2007; Huang and Lin, 2007; Wadee et al., 2002). Alterations in circulating anti-inflammatory cytokines including IL-1RA, IL-4, and IL-10 are documented (Kim et al., 2004a, 2007; Ortiz-Dominguez et al., 2007; Boufidou et al., 2004). Abnormally high levels of other cytokines such as IL-2 (Breunis et al., 2003; Ortiz-Dominguez et al., 2007; Liu et al., 2004; Boufidou et al., 2004) and its soluble receptor (Breunis et al., 2003; Tsai et al., 2001, 1999; Maes et al., 1995), interferon-gamma (INF-γ) (Su et al., 2002; Liu et al., 2004; Kim et al., 2004b), and transforming growth factor-beta (TGF-β) (Kim et al., 2004b) have also been elucidated. (See Appendix A, Table 1 for summary of review).

8. Psychotropic agents used to treat bipolar disorder have the capacity to alter pro-inflammatory cytokines and attenuate or restore inflammatory homeostasis

In keeping with the view that a neurotoxic process occurs in mood syndromes, numerous investigations have explored the effect of disparate conventional pharmacological treatments for BD on the production of pro-inflammatory cytokines as well as their gene expression (Rybakowski, 2000; Pollmacher et al., 2000). For example, lithium and antipsychotic treatment have been demonstrated to reduce gene expression of TNF-α, IL-1β, and IL-6, and restore inflammatory homeostasis (Boufidou et al., 2004; Padmos et al., 2008). Taken together, psychotropic agents used to treat BD have the capacity to alter pro-inflammatory cytokines and attenuate or restore inflammatory homeostasis.

A pilot study evaluating the anti-inflammatory, celecoxib, as an adjunctive treatment for BD in a double-blind, randomized, placebo-controlled study provided suggestive evidence of a modest rapid-onset antidepressant effect in individuals with BD exhibiting depressive or mixed symptomatology (Kauer-Sant'anna et al., 2008). Preliminary evidence with other immune-targeted therapies have shown antidepressant properties. For example, open-label acetylsalicylic acid when added to fluoxetine led to increased remission rates in individuals with major depression who were previously non-responsive to fluoxetine monotherapy (Mendlewicz et al., 2006). A shortened onset of action (i.e. within 1 week) was also reported with acetylsalicylic acid in this patient sample (Mendlewicz et al., 2006).

9. Allostasis in bipolar disorder: a disease of cumulative allostatic states

Although the causal factors that subserve dysregulation of the immuno-inflammatory network in BD are unknown, several interacting networks, including the hypothalamic–pituitary–adrenal-axis (HPA-axis), neurotransmitter metabolism, growth factors, arachidonic acid, insulin-like growth factor 1 (IGF-1), and as well as insulin signaling are proposed. (Kapczinski et al., 2008; Cassidy et al., 1998; Diehl and Gershon, 1992).

Allostasis is broadly defined as the capacity of a system to achieve stability through change. The term 'allostatic load' has been defined as the physiologic toll that is required for adaptation and may be a consequence of cumulative and multi-systemic changes (Kapczinski et al., 2008). It has been hypothesized that BD

is a disease of cumulative allostatic states where in the allostatic load increases progressively as stressors, mood episodes, and comorbidity (Kapczinski et al., 2008). Moreover, supporting empirical evidence documents that the HPA-axis, oxidative balance, and immuno-inflammatory systems are biological mediators of allostasis.

Consequently, allostatic processes lead to disturbances in systemic homeostasis with resultant 'end-organ damage'. For example, pro-inflammatory cytokine activation may mediate neurocognitive deficits and residual symptomatology as well as 'stress sensitive' medical comorbidity (e.g. cardiovascular disease) in BD (Smith, 1991; Kapczinski et al., 2008; Raju, 1998; Wagner-Jauregg, 1994; Dantzer, 2004).

10. Mediators of allostasis in bipolar disorder: a focus on tumor necrosis factor alpha

10.1. Hypothalamic–pituitary–adrenal-axis

Abnormalities in the HPA-axis are well documented in BD and are marked by elevated levels of cortisol and 'dexamethasone suppression test' non-suppression (Swann et al., 1992; Watson et al., 2004). Recent reports provide support for T-cell relative resistance to glucocorticoids and altered glucocorticoid-signaling cascades in BD (Knijff et al., 2006; Spiliotaki et al., 2006). Moreover, TNF-α is associated with increases in cortisol production in human adult adrenocortical cell cultures (Stolte et al., 2008). It is also documented that patients with BD have higher levels of cortisol independent of illness phase (i.e. depression, mania/hypomania, and euthymia) as compared to healthy controls (Huang and Lin, 2007; Dickerson et al., 2007).

Cortisol administered at levels commensurate with stress provocation to phagocytes *in vitro* significantly inhibits LPS-induced expression of the pro-inflammatory cytokine TNF-α and interleukin-12 (IL-12) (subunit p35) and of inducible nitric oxide synthase (iNOS) expression (Stolte et al., 2008). Under basal conditions, *in vitro* incubation with cortisol and dexamethasone increases TNF-α production in blood cells of depressed inpatients responsive to antidepressant treatment. Levels of TNF-α decreased after 6 weeks of antidepressant treatment (Heiser et al., 2008).

10.2. Neurotransmitter metabolism

Cytokines have the capacity to influence the synthesis of neurotransmitters including the release and reuptake of monoamines (Miller et al., 2009; Miller, 2009). A prominent mechanism by which cytokines influence neurotransmitter metabolism is via activation of indoleamine 2,3-dioxygenase (IDO) enzyme. Activation of IDO is consequent to cytokine-stimulated immuno-inflammatory signaling pathways, including signal transducer and activator of transcription 1a (STAT1a), interferon regulatory factor (IRF)-1, NF-kappaB, and p38 mitogen activated protein kinase (MAPK). Activated IDO breaks down the serotonin precursor tryptophan into kynurenine (KYN), with resultant serotonin depletion (Miller et al., 2009; Miller, 2009; Dantzer et al., 2008). Moreover, decreased peripheral circulating tryptophan and increased KYN have been associated with IFNα-induced depression (37). Systemic administration of LPS induces expression of IDO in rat cortex and hippocampus and is paralleled by increased central TNF-α and IL-6 expression (Connor et al., 2008).

10.3. Glutamate excitotoxicity

In the CNS, TNF-α plays a facilitator role in glutamate excitotoxicity, both directly and indirectly by inhibiting glial glutamate transporters located on astrocytes. Additionally, TNF-α directly affects glutamate transmission by increasing expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on synapses. Increases in TNF-α mRNA and TNF-R1 expression have been observed in hippocampal dentate gyrus cultures treated with glutamate (Figiel and Dzwonek, 2007).

TNF-α has been implicated in neuroprotection against glutamate-induced excitotoxicity via NF-kappaB-dependent up-regulation of K2.2 channels. The expression of K(Ca)2.2 channel was up-regulated by TNF-α treatment in a time-dependent manner whereas the expression of K(Ca)2.1 and K(Ca)2.3 channels was not altered. The increase in K(Ca)2.2 channel expression after TNF-α treatment was shown to be dependent on TNF-R2 and NF-kappaB activation (Dolga et al., 2008).

10.4. Omega-6 and -3 fatty acids: arachidonic acid versus docosahexaenoic acid

Broadly defined omega-6 fatty acids (e.g. arachidonic acid) promote inflammation, whereas omega-3 fatty acids (e.g. eicosapentaenoic acid and docosahexaenoic acid) have anti-inflammatory properties (Kang and Weylandt, 2008). Arachidonic acid along with docosahexaenoic acid (DHA) constitute approximately 20% of fatty acids in the mammalian brain (Rapoport, 2008).

Arachidonic acid gives rise to the eicosanoid family of mediators (e.g. prostaglandins, thromboxanes, and leukotrienes), which regulate inflammatory cytokines. Consumption of long-chain n-3 polyunsaturated fatty acids decreases production of arachidonic acid-derived eicosanoids as well as the production of TNF-α, IL-1β, and IL-6 as well as the expression of adhesion molecules involved in inflammatory cascades (Calder, 2006).

Moreover, commonly used therapies for BD (e.g. lamotrigine, divalproex, carbemazepine, lithium) selectively target the arachidonic acid cascade in the rat brain (Lee et al., 2007). Anti-manic agents are reported to decrease turnover of arachidonic acid in phospholipids and expression of calcium-dependent arachidonic acid-selective cytosolic phospholipase A(2) (cPLA(2)) in rat brain (Lee et al., 2007). In contrast, increases cPLA(2) expression and arachidonic acid turnover. It has been hypothesized that switching from bipolar depression to mania may be mediated by increased arachidonic acid recycling and metabolism in the brain (Lee et al., 2008).

11. Neuroplasticity

11.1. Brain derived neurotrophic factor

Abnormalities in growth factors such as brain derived neurotrophic factor (BDNF), which regulates neurotrophism and neuroplasticity via its effects on neuronal differentiation, proliferation, and structure as well as synaptogenesis are documented in BD (Mattson et al., 2004; Xu et al., 2003). BDNF levels are negatively correlated with the severity of mood symptoms in BD (Hado-Vieira et al., 2007; Shimizu et al., 2003; Cunha et al., 2006; Frey et al., 2006). Recent evidence suggests that TNF-α levels may be higher in late-stage BD (versus early-stage) contemporaneous with decreased BDNF levels (Kauer-Sant'anna et al., 2008).

11.2. Insulin and insulin-like growth factor signaling

The binding of TNF-α to its receptor inhibits neuronal survival signals, mediated by IGF-1, without directly inducing neurotoxicity. The amount (10 pg/mL) of TNF-α required to inhibit neuronal survival pathways is one-hundredth of the amount needed to cause direct cytotoxicity (Venters et al., 2000). Activation of TNF-α receptors inhibits the phosphorylation of tyrosine-residues in the major docking protein, insulin receptor substrate 2 (IRS2), thereby

inhibiting the downstream ability of IGF-1 to activate the survival enzyme, phosphatidylinositol 3′ kinase (PI3 kinase) (Venters et al., 2000).

TNF-α is overexpressed in the adipose tissues of rodents and humans (Uysal et al., 1997; Hotamisligil et al., 1993) and has the capacity to block the action of insulin via insulin-stimulated tyrosine kinase activity of the insulin receptor (Uysal et al., 1997; Feinstein et al., 1993; Hotamisligil et al., 1994). Down-regulation of the insulin-sensitive glucose transporter Glut4 expression is also associated with TNF-α (Nieto-Vazquez et al., 2008; Hotamisligil et al., 1993; Stephens and Pekala, 1991; Cornelius et al., 1989).

Obese mice lacking either TNF-α or its receptors are protected from developing insulin resistance (Hotamisligil, 2003). Direct exposure to TNF-α inhibits insulin signaling in cells via insulin receptor substrate (IRS) proteins (Hotamisligil, 2003). The mechanisms affecting IRS involve proteasome-mediated degradation, phosphatase mediated dephosphorylation, and serine phosphorylation of IRS-1, which antagonizes insulin-stimulated tyrosine phosphorylation of IRS-1 and insulin receptor activity (White, 2003; Pirola et al., 2004; Rui et al., 2001).

11.3. Cellular and neural adhesion molecules

Several lines of evidence suggest that cell and neural adhesion molecules are salient to both structural and synaptic plasticity in BD. Using quantitative real-time polymerase chain reaction (PCR) technique in peripheral blood cells of individuals with BD, a reduced expression of neural cell adhesion molecule-140 mRNA was observed in a current depressive state, while comparable expression was observed in a remitted state to that of healthy controls (Wakabayashi et al., 2008). Increased intercellular adhesion molecule-1 (ICAM-1) immuno-reactivity in gray and white matter of the anterior cingulate cortex is also reported in postmortem tissue from individuals with BD (Thomas et al., 2004). TNF-α is capable of inducing cell surface expressions ICAM-1 as well as vascular cell adhesion molecule-1 (VCAM-1) in human microvascular endothelial cells from lung blood vessels (Matsuda et al., 2008). Up-regulation of VCAM-1 expression on the human neural stem cells and increased neural stem cell-endothelial interaction are also reported with TNF-α stimulation (Mueller et al., 2006).

12. Tumor necrosis factor alpha

12.1. Tumor necrosis factor alpha physiology

TNF-α is a 157 amino acid pro-inflammatory cytokine that was identified in 1975 as the factor in serum isolated from endotoxin-treated mice that induced necrosis of a methylcholanthrene-induced murine sarcoma (Carswell et al., 1975). TNF-α is synthesized and secreted by macrophages, lymphocytes, neutrophils, and structural cells including fibroblasts, smooth muscle cells, astrocytes, and microglia. The synthesis and secretion of TNF-α is increased in response to injury, infection, and inflammatory stimuli (Old, 1985; Tracey et al., 2008).

TNF-α is initially released from cells as a soluble cytokine (sTNF, a homotrimer of 17 kDa) after being enzymatically cleaved from its cell surface-bound precursor [transmembrane TNF (tmTNF), a homotrimer of 26-kDa monomers] by TNF-α-converting enzyme (TACE). Both sTNF and tmTNF ligands are biologically active and exert their effects by binding to TNF receptors: TNF-R1 (p55, CD120a) and TNF-R2 (p75, CD120b). Both TNF receptors are membrane glycoproteins that specifically bind TNF-α and lymphotoxin alpha-3 (LTα3) (Tracey et al., 2008; Brietzke and Kapczinski, 2008). TNF-R1 is abundantly expressed in most cell types except on erythrocytes, whereas TNF-R2 is generally inducible and preferentially expressed on hematopoietic cells. TNF-R1 meditates apoptosis, cytokine production and activation of the transcription factor NF-kappaB resulting in subsequent activation of specific inflammatory genes. Activation of TNF-R1 has been shown to trigger a dual signaling cascade leading to apoptosis, proliferation, differentiation, or survival of different cell types. Reverse signaling can be initiated by TNF-α antagonist binding to TNF-R2 or cell surface tmTNF, resulting in cytokine suppression or apoptosis. Soluble TNF receptors (sTNF-R1 and sTNF-R2) can be released from a TNF-responsive cell following enzymatic cleavage (Tracey et al., 2008; Brietzke and Kapczinski, 2008). Binding of TNF-α to its receptor TNF-R1 activates an intracellular cascade that results in recruitment of the TNF receptor associated death domain (TRADD). This adapter protein subsequently recruits Fas-associated death domain (FADD) that leads to caspase-3 activation, which directly participates in cell degradation (Brietzke and Kapczinski, 2008; Tracey et al., 2008) (See Fig. 1).

12.2. The pleiotropic functions of tumor necrosis factor alpha

TNF-α has pleiotropic functions capable of exerting a salutary as well as a detrimental effect on inflammatory homeostasis in both innate and adaptive immune responses. TNF-α plays a critical role in lymphoid tissue development and has both antiviral and cytotoxic effects. For example, acute modest elevations of TNF-α concentrations augment host defense mechanisms while chronically elevated TNF-α may contribute to subsequent end-organ damage (e.g. arthritis) (Tracey et al., 2008). The capacity of TNF-α to induce multi-organ damage occurs via its pro-inflammatory effects on vascular endothelium (Pober, 1988). The expression of pro-inflammatory cytokines is not random, but is controlled by a hierarchical inflammatory network. TNF-α works in collaboration with other pro-inflammatory cytokines (e.g. IL-1 and IL-6) and chemokines (e.g. IL-8). This process is further facilitated by the up-regulation of key integrins and adhesion molecules, including E-selectin and VCAM-1, on endothelium (Brennan and McInnes, 2008). Importantly, antagonism of TNF-α bioactivity in cell cultures reduces the spontaneous production of both IL-1 protein and *IL-1B* mRNA, neutralizes IL-1 bioactivity (Brennan et al., 1989), and inhibits the expression of IL-6 and IL-8 (Butler et al., 1995; Brennan and McInnes, 2008).

13. Tumor necrosis factor alpha and cognition in bipolar disorder

Cognitive deficits are well documented in BD persisting across affective and euthymic states. Several identified risk factors for cognitive dysfunction include the number of depressive and manic episodes, number of hospitalizations, and duration of illness. Deficits in verbal memory and executive function are the most consistently replicated abnormalities in euthymic BD individuals (Leonard, 2001).

The association between neurocognitive function and pro-inflammatory cytokine activation has not been well elucidated in BD. Nevertheless, pro-inflammatory cytokines impair spatial learning and disrupt memory formation in rodents (Chen et al., 2008). In humans, the effect of peripheral inflammation on the CNS and neurocognitive function has been evaluated with functional magnetic resonance brain imaging (fMRI). Healthy males subjected to a typhoid vaccination showed markedly perturbed neural reactivity within the substantia nigra, which was associated with psychomotor slowing. Moreover, healthy males with higher levels of circulating IL-6 had significantly slower reaction time responses (Brydon et al., 2008).

Several neurodegenerative disorders, including Alzheimer's disease, have been linked to alterations in inflammatory networks, including elevated peripheral IL-1β and TNF-α (McCoy and Tansey, 2008). In Alzheimer's disease, beta amyloid accumulation stimulates production of TNF-α by microglia as well as reactive

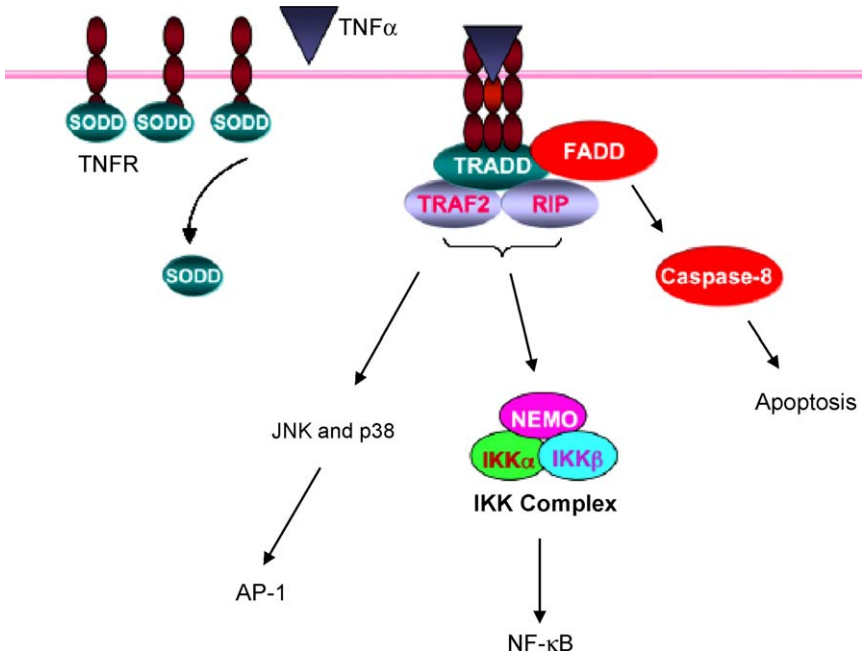

Fig. 1. The general aspects of TNF-α pathway. Stimulation of the TNF-α receptor complex recruits downstream adaptor molecules such as TRADD, RIP, TRAF2, and FADD, which lead to activation of NF-κB and AP-1 transcription factors, and apoptosis The balance among different signaling outcomes of NF-κB, JNK, and caspase activation determines the cell survival or death.
Adapted with permission from Li and Lin (2008).

oxygen species which subsequently participate in activation of apoptosis (Larson and Dunn, 2001). It has also been reported that TNF-α levels in CSF of patients with Alzheimer's disease are elevated 25-fold on average as compared to controls and are associated with cognitive decline (Tarkowski et al., 2003).

Increased CSF levels of TNF-α have also been reported in individuals with HIV-associated dementia as compared to those without dementia (Angelopoulos et al., 2008). Preliminary evidence from our group indicates that TNF-α, IL-8, INFγ, and IL-1RA concentrations are significantly associated with deficits in verbal learning and memory in euthymic individuals with BD (Soczynska et al., 2008).

14. Tumor necrosis factor antagonists

Binding of TNF antagonists can induce reverse signaling through the membrane-anchored ligand and trigger cell activation, and cytokine suppression or apoptosis (Tracey et al., 2008). Currently there are three Food and Drug Administration approved TNF-α antagonists: adalimumab (Humira), a fully human monoclonal antibody, infliximab (Remicade), a chimeric monoclonal antibody, and etanercept (Enbrel), a soluble receptor construct (Tracey et al., 2008; Segal et al., 2008). Several other TNF-α antagonists are in clinical development (e.g. certolizumab and golimumab) (Not specified, 2002). The agents are indicated for the treatment of disparate immuno-inflammatory disorders (e.g. rheumatoid arthritis and Crohn's disease). It is hypothesized that TNF antagonist therapy may offer broad-spectrum symptomatic benefits for mood disorders across affective, cognitive, and somatic domains (see Padmos et al., 2008; Ortiz-Dominguez et al., 2007; Papiol et al., 2004; Knijff et al., 2007; Liu et al., 2004; Kim et al., 2004a; Rapaport et al., 1999; Boufidou et al., 2004; Rapaport, 1994; Breunis et al., 2003; Tsai et al., 2001; Maes et al., 1995; Tsai et al., 1999; Kim et al., 2004b; Kim et al., 2007; O'Brien et al., 2006; Su et al., 2002; Kim et al., 2002; Czerski et al., 2008; Pae et al., 2004; Meira-Lima et al., 2003; Cunha et al., 2008; Dickerson et al., 2007; Huang and Lin, 2007; Wadee et al., 2002; Hornig et al., 1998; Haack et al., 1999; Rapaport and Manji, 2001; Haack et al., 1999; Himmerich et al., 2005; Haack et al., 1999; Table 1 for molecular structures and Tables 2–3 for review of clinical and mechanistic profiles).

15. Adalimumab (Humira)

Adalimumab is a recombinant human IgG1 monoclonal antibody for TNF-α that consists of 1330 amino acids with a molecular weight of 149 kD. It is supplied in single-use, 1 mL pre-filled glass syringes, and also 2 mL glass vials as a sterile, preservative-free solution for subcutaneous administration. Adalimumab solution is clear and colorless, with a pH of approximately 5.2. The solution contains 40 mg of adalimumab with additional non-active ingredients; 4.93 mg sodium chloride, 069 mg monobasic sodium phosphate dehydrate, 1.22 mg monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and water for injection (Not specified, 2002)

Adalimumab specifically binds to the cell surface and blocks TNF-α receptors p55 and p75. It does not bind to or inactivate lymphotoxin (formerly known as TNFβ). Adalimumab also modulates biological responses mediated by TNF-α such as regulating levels of cellular adhesion molecules responsible for leukocyte migration [Endothelial-leukocyte adhesion molecule-1 (ELAM-1), VCAM-1, and ICAM-1. In patients with rheumatoid arthritis, adalimumab injection decreases acute phase reactants (i.e. C-reactive protein). Decreases in serum levels of matrix metalloproteinases (i.e. MMP-1 and MMp-3) have also been documented (Not specified, 2002).

The C_{max} and T_{max} of adalimumab are 4.7 ± 1.6 μg/mL and 131 ± 56 h, respectively, following a single subcutaneous injection to healthy adults. The pharmacokinetics of adalimumab are linear within the dose range of 0.5–10.0 mg/kg and its absolute bioavailability averages approximately 64%. The distribution volume (V_{ss}) of adalimumab has been documented to be 4.7–6.0 L. The systemic clearance is approximately 12 mL/h and a half-life of approximately 14 days. The serum levels at steady state increase in a dose-dependent manner following 20, 40, and 80 mg every other week. There is no evidence of changes in clearance after repeated administration across multiple years (i.e. >2 years) (Kimel et al., 2008).

16. Adalimumab, mood symptoms, and quality of life (see Table 4 for review)

The effect of adalimumab maintenance therapy on health-related quality of life as well as depressive symptoms has been evaluated in patients with moderate to severe Crohn's disease in a randomized, double-blind clinical trial. Following open-label adalimumab treatment of 80 mg at baseline and 40 mg at week 2, patients were randomized to adalimumab maintenance treatment at week 4 (40 mg every other week or 40 mg weekly) or placebo (open-label treatment only). Significant improvement in health-related quality of life was observed following 4 weeks of open-label adalimumab induction therapy. Patients who continued on adalimumab maintenance of 40 mg every other week as well as weekly reported less depression on the Zung Self-Rating Depression Scale, and greater physical and mental health component summary scores on the The Short Form (36) Health Survey (SF-36) from weeks 12 to 56 (Loftus et al., 2008).

Results from a 2-year, randomized, comparator-controlled trial evaluating combination therapy with adalimumab (40 mg s/c eow) and methotrexate (MXT) or MXT monotherapy (initial dose 7.5 mg/week and increased as needed to a maximum of 20 mg/week) in patients with rheumatoid arthritis reported significant improvements in quality of life [i.e. SF-36 item] and somatic symptom measures (Kimel et al., 2008). Improvements in SF-36 mental health score as well as mental health component summary (MCS) score were reported at weeks 12, 52 and 104 in both treatment groups, with scores comparable to that of the US general population across all post-baseline time points. Social function was also significantly improved at weeks 52 and 104 in both treatment groups with comparable scores to that of the US general population. Correlational analyses provide support for a weak association between the MCS score and disability index ($r = 0.33$) and disease activity ($r = -0.21$), while a strong association was found between the physical component summary (PCS) score and disability index ($r = -0.65$) and moderate association with disease activity ($r = -0.42$) (Kimel et al., 2008).

A 5-year, randomized, placebo-controlled study evaluating the efficacy of adalimumab (40 mg eow) on pain, fatigue and stiffness in patients with ankylosing spondylitis reported significant improvements in pain and fatigue which occurred within 2 weeks and were maintained at 12 and 24 weeks. The SF-36 bodily pain and vitality scores significantly improved at 12 and 24 weeks. Pain, fatigue, stiffness and physical function were significantly correlated with overall quality of life on the Ankylosing Spondylitis Quality of Life questionnaire (ASQOL) (Revicki et al., 2008). An earlier 3-year, open-label, health outcomes extension study with adalimumab (40 mg eow) for rheumatoid arthritis reported significant improvement in all subdomains of the SF-36 at week 26 (i.e. physical functioning, bodily pain, role-physical, role-emotional, general health, mental health, vitality, and social functioning) as well as in overall utility as measured with Health Utilities Index-3 (Mittendorf et al., 2007). Youths et al. evaluated patients from 3 randomized placebo-controlled trials with adalimumab plus MXT or placebo plus standard therapy for rheumatoid arthritis. The authors reported significant and consistent reductions in fatigue scores in adalimumab-treated patients across the 3 clinical trials (Yount et al., 2007).

17. Etanercept (Enbrel)

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa (p75) TNF receptor (TNF-R) linked to the Fc portion of the human IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system. It consists of 934 amino acids and has a molecular weight of approximately 150 kDa (Tracey et al., 2008).

Etanercept is supplied as a sterile, white, preservative-free, lyophilized powder for parental administration after reconstitution with 1 mL of the supplied sterile bacteriostatic water for injection (BWFI), USP (containing 0.9% benzyl alcohol). Each vial of etanercept contains 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine. Etanercept has FDA approval for the treatment of moderate to sever rheumatoid arthritis, polyarticular-course of juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more Disease-Modifying Antirheumatic Drugs (DMARDs, e.g. MXT), and finally for active arthritis in patients with proriatic arthritis (Tracey et al., 2008).

Single subcutaneous injection of 25 mg of etanercept into patients with rheumatoid arthritis ($n = 25$), documented a half-life of 102 ± 30 h with a clearance of 160 ± 80 mL/h. A maximum serum concentration was 1.1 ± 0.6 mcg/mL and time to C_{max} of 69 ± 34 h was observed following a single 25 mg dose. An increase in mean Cmax (2.4 ± 1.0 mcg/mL) was reported in patients with rheumatoid arthritis after 6 months of biweekly injections of 25 mg doses. Repeated dosing has also been documented to increase peak serum concentration by two to sevenfold and increase AUC fourfold (Tracey et al., 2008; Goldenberg, 1999).

18. Etanercept, mood and cognitive symptoms (see Table 5 for review)

We identified one randomized, double-blind, placebo-controlled trial with etanercept (Tyring et al., 2006) and one open-label effectiveness study that included depression outcomes (Gelfand et al., 2008); the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HAMD). Secondly, we identified one open-label study with etanercept in individuals with Alzheimer's disease (Tobinick et al., 2006).

The first trial enrolled patients with plaque psoriasis ($n = 618$) who were randomized to either etanercept (50 mg twice weekly) or placebo for 12 weeks. Subjects receiving active treatment exhibited 47% reduction in psoriatic measures and at least a 50% improvement in HAMD and BDI at 12 weeks. Clinically meaningful improvements in fatigue were also reported. Significant improvement in depressive symptoms was less correlated with objective measures of skin clearance or joint pain (Tyring et al., 2006). Following the double-blind phase, subjects ($n = 591$) entered an open-label treatment with etanercept (50 mg twice weekly). Mean BDI improvements were comparable across the etanercept/etanercept and placebo/etanercept groups (4.0 units vs. 4.5 units, respectively) at 24 weeks. The percentage of BDI responders (>50% change from baseline) increased to comparable levels in both groups (58% and 55%, respectively). Improvement in HAMD scores (i.e. 1.7 units from baseline) at week 24 were similar to the improvement observed during the double-blind phase in the etanercept group and the percentage of HAMD responders also increased to similar levels in the two groups (45% vs. 46%, respectively). The HAMD and BDI improvements as well as responder rates were sustained in both groups up to week 96 (Krishnan et al., 2007).

The second study enrolled patients with moderate to severe plaque psoriasis ($n = 2546$) who received open-label etanercept (50 mg twice weekly) for 12 weeks followed by 12 weeks of 50 mg once weekly. Significant improvement in mean BDI scores was reported at 12 weeks and maintained at 24 weeks. Significant improvements in vitality and quality of life were also reported (Gelfand et al., 2008). Significant improvement at 6 months of open-label etanercept treatment has been reported in patients with Alzheimer's disease on measures of Mini Mental State

Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the Severe Impairment Battery (SIB) (Tobinick and Gross, 2008). A single case report with etanercept also reported rapid cognitive improvement beginning within 2 h in a patient with late-onset Alzheimer's disease (Tobinick and Gross, 2008).

19. Infliximab (Remicade)

Infliximab is a chimeric IgG1k monoclonal antibody for TNF-α with a molecular weight of 150 kDa. It is composed of human constant and murine variable regions of the antibody. Infliximab is supplied as a sterile, white, lyophilized powder for intravenous injection; following reconstitution with 10 mL of sterile water for injection it has a pH of approximately 7.2. Each single-use vile contains 100 mg of infliximab, 50 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg d dibasic sodium phosphate, dehydrate, with no added preservatives (Tracey et al., 2008).

Infliximab binds with high affinity to the soluble and transmembrane forms of TNF-α and inhibits binding of TNF-α with its receptors. TNF-α induces the production of other pro-inflammatory cytokines such as IL-1β and IL-6; as a result, infliximab directly blocks TNF-α activity and indirectly via other inflammatory cytokines (Tracey et al., 2008; Klotz et al., 2007).

Treatment with infliximab reduces the access of inflammatory cells into inflamed areas in particular inflamed joints or intestine areas in patients with rheumatoid arthritis and Crohn's disease, respectively. Moreover, infliximab reduces the expression of cellular adhesion molecules, such as E-elastin, ICAM-1, and VCAM-1, as well as chemokines (i.e. IL-8 and MCP-1) and tissue degradation molecules (MMP-1 and MMP-3) (Gonzalez-Gay et al., 2006). Decreases in serum IL-6 and C-reactive protein have also been reported following infliximab treatment (Visvanathan et al., 2008; Tanaka et al., 2008).

Single intravenous (IV) infusion of infliximab results in a linear increase between the maximum serum concentration and dose of administration (3–20 mg/kg). Infliximab is primarily distributed in the vascular compartment and its volume of distribution at steady state is independent of dose. Single dose infusion of 3–10 mg/kg indicates that the median terminal half-life is 8.0–9.5 days. Repeated infusions of infliximab at 2 and 6 weeks result in predictable concentration-time profiles following each treatment. No systemic accumulation occurs at 4- or 8-week intervals with 3–10 mg/kg dosing. At 8 weeks, mean serum concentrations of infliximab range from 0.5 to 6 mcg/mL (Tracey et al., 2008; Klotz et al., 2007) (see Tables 1 and 2 for clinical and biochemical profiles and refer to Fig. 2 for structures of anti-TNF antagonists).

20. Infliximab and mood symptoms (see Table 6 for review)

One clinical trial with infliximab was identified on clinicaltrials.gov (NCT00463580) for treatment resistant depression including bipolar and unipolar disorder. Infliximab, single-dose, has been shown to reduce fatigue and depressive scores as well as improve quality of life at 4 weeks in patients with Crohn's disease (Persoons et al., 2005). Specific measures of depression were identified in three open-label studies (Persoons et al., 2005; Tookman et al., 2008; Minderhoud et al., 2007).

In a single-dose study of infliximab, Persoons et al. reported that the presence of depression (24%) at baseline significantly predicted lower remission rates (29% vs. 70%) at 4 weeks as compared to subjects without depression. A significant decrease in time to retreatment was also reported for subjects with depression. Furthermore, a significantly smaller proportion of subjects met criteria for depression at 4 weeks (16% vs. 24%) as compared to baseline (Persoons et al., 2005). Minderhoud et al. in a single-blinded study enrolled patients with Crohn's disease ($n = 14$), each of whom received placebo (i.e. saline) at baseline, followed by infliximab (5 mg/kg) at 2 weeks. A significant effect of infliximab

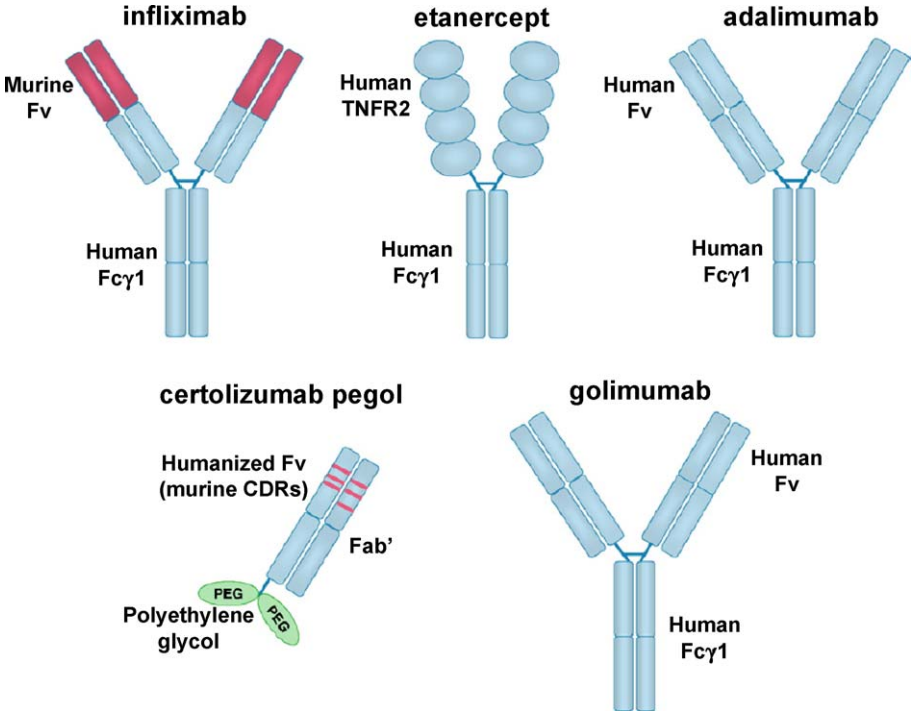

Fig. 2. Tumor necrosis factor alpha signaling. Simplified diagrams of the molecular structures of 5 TNF antagonists. Infliximab is a mouse/human chimeric monoclonal anti-TNFantibody of IgG1 isotype. Adalimumab and golimumab are fully human IgG1 monoclonal anti-TNF antibodies. Etanercept is a fusion protein of TNFR2 (p75) and the Fc region of human IgG1. Certolizumab is a PEGylated Fab' fragment of a humanized IgG1 monoclonal anti-TNF antibody. Figure adapted with permission from Tracey et al. (2008).

infusion was observed on the Center of Epidemiological Studies Depression scale (CES-D) at 4 weeks, an effect not seen in the placebo group (Persoons et al., 2005). Finally, Tookman et al. enrolled patients with advanced cancer ($n = 17$) in an open-label pilot study with infliximab and found improvements in fatigue as well as anxiety and depression subscores (Tookman et al., 2008).

Taken together, the results provide support that TNF-α antagonists may offer therapeutic benefit for somatic, cognitive, and affective symptoms associated with mood disorders

21. Safety and toxicity concerns

The major risk associated with TNF-antagonists is an increased propensity for infections. As a result, treatment should not be initiated in patients who demonstrate evidence of acute or chronic infections. Patients must be monitored closely for clinical presentations suggestive of infection while receiving a TNF-antagonist. Allergic reactions have been reported in approximately 1% of patients; serious allergic reactions are rare. Moreover, although rare, patients treated with TNF-antagonists may develop antibodies against the biologic agent and very rarely develop a lupus-like syndrome. Other rare side-effects include: increased risk of serious infections, risk of demyelinating disorders (e.g. multiple sclerosis), decrease in WBC and RBC count, and less than 1% risk of developing malignancy has been reported (Huang et al., 2008; Callen, 2007; Hochberg et al., 2005). Common side-effects include: mild skin reaction at the injection site (itchiness, redness, and mild swelling), nausea, abdominal pain, headache, rash, and upper respiratory tract infections (such as sinusitis) (Segal et al., 2008) (see Appendix A for side-effects with Adalimumab, Table 7).

22. Conclusions

Available clinical trials provide preliminary support that TNF-α antagonists offer therapeutic benefit for depressive and cognitive symptoms in non-psychiatric populations. Moreover, improvements in fatigue, vitality and other somatic symptoms are well documented with available TNF-α antagonists. The efficacy of these agents in mood disorders remains to be determined, although it can be reasonably surmised that similar benefits may be observed in primary mood disorder populations. A pressing need in BD is to identify treatments that directly target pathophysiological abnormalities are hypothesized to be central to the disorder. Testing TNF-α antagonists as a treatment for depressive symptoms of BD may provide preliminary support for a new class of potentially disease-modifying treatments.

Future research vistas include: (1) parsing out components of the inflammatory network that are state versus trait related; (2) whether there a linear association between the severity of psychopathology and detectable levels of pro-inflammatory cytokines (e.g. TNF-α); (3) do elevated levels of pro-inflammatory cytokines alter brain activation patterns or CNS anatomical structure in BD; (4) do pro-inflammatory cytokines subserve the medical comorbidity that differentially affects BD populations; (5) do psychosocial treatments for BD affect components of the inflammatory network, and (6) does the use of cytokine based therapies normalize inflammatory homeostasis coincident with symptomatic improvement in BD?

Conflict of interest

Joanna K. Soczynska has previously received travel honoraria from "Organon and Wyeth". Roger S. McIntyre is on the Advisory Board for "Astra Zeneca, Bristol-Myers Squibb, France Foundation, GlaxcoSmithKline, Jaanssen-Ortho, Solvay/Wyeth, Eli Lilly, Organon, Lundbeck, Biovail, Pfizer, and Shire" and is on the Speakers Bureau for Janssen-Ortho, Astra-Zeneca, Eli Lilly, Lundbeck, and Biovail". Dr. McIntyre is also involved in CME Activities with "Astra Zeneca, Bristol-Myers Squibb, France Foundation, I3CME, Solvay/Wyeth, and Physicians' Postgraduate Press".

Sidney H. Kennedy is on the Advisory Board for ANS, AstraZeneca, Biovail, Eli Lilly, Janssen, Lundbeck, Organon, Servier, and Wyeth. Dr. Kennedy has conducted clinical trials with ANS, Biovail, Eli Lilly, Pfizer, Servier, and Wyeth. Dr. Kennedy also acknowledges that he has received honoraria from: ANS, AstraZeneca, Biovail, Eli Lilly, Lundbeck, Servier, and Wyeth. Sidney H. Kennedy has received research grants from "CHIR, NARSAD, OMHF, OPGRS, and Stanley Foundation". Benjamin I. Goldstein is a consultant for Solvay Pharmaceuticals.

Appendix A

Tables 1–7

Table 1
Summary of research studies documenting cytokine abnormalities in bipolar disorder.

	IL-1β	IL-1RA	IL-2	sIL-2R	IL-4	IL-6	sIL-6R	IL-8	IL-10	IL-12	TNFα	TNF-R1	TNF-R2	IFNγ	TGFβ	IL-6/ IL-4	TNFα/ IL-4	IL-2 /IL-4	IFNγ/ TGFβ	IFNγ/ IL-4	IL-1/ IL-6	IL-4/ TGFβ	CRP
BD I/II vs. HC	↑*↑+^ ●+●`	●+●+	●'	↑ ●	ND	↑* ●`●`ND	●		●`ND		↑*↑+↑+ ●+			●`ND							↓`↓		
Depression vs. HC	●		↓	↑	●	↑ ●	●	↑	●		↑↑												●
Mania vs. HC	↓	↑	↓ ●●`	↑↑↑↑	↑↑↓` ●	↑↑` ● ND	↑ ●●●	↑	●`●●	●	↑↑↑`			↑↓`↓ ●`	↓	↑`	↑`	↑`	↑	↑↑`		↑	↑↑↑ ●
Euthymia vs. HC		↑	↑↓` ●`●	↑ ●●	●	↓`	●		↓` ●`●					↓`↓`↓									●
Mania vs. Depression	↓		●	↑	↑	↓ ●●`		●	●		●●										●`		↑ ●>
Mania vs. Euthymia	●			↑↑ ●		●`	●●		●`					●`							●`		↑↑ ●>
Depression vs. Euthymia	●			●		↑*●`															●`		●●>
References	(Padmos et al., 2008; Ortiz-Dominguez et al., 2007; Papiol et al., 2004) (Knijff et al., 2007)	(Liu et al., 2004; Kim et al., 2004a; Papiol et al., 2004)	(Rapaport et al., 1999;; Ortiz-Dominguez et al., 2007; Liu et al., 2004;Boufidou et al., 2004) (Rapaport 1994)	(Rapaport et al., 1999; Breunis et al., 2003; Tsai et al., 2001;; Maes et al., 1995; Rapaport, 1994; Tsai et al., 1999)	(Ortiz-Dominguez et al., 2007; Liu et al., 2004; Kim et al., 2004b;)	(Padmos et al., 2008; Rapaport et al., 1999; Kim et al., 2007; Ortiz-Dominguez et al., 2007; O'Brien et al., 2006;Boufidou et al., 2004;; Maes et al., 1995; Knijff et al., 2007)	(Rapaport et al., 1999; O'Brien et al., 2006; Tsai et al., 2001; Tsai et al., 1999; Maes et al., 1995)	(O'Brien et al., 2006)	(Rapaport et al., 1999; O'Brien et al., 2006; Liu et al., 2004; Boufidou et al., 2004;Su et al., 2002)	(Kim et al., 2002)	(Padmos et al., 2008; Czerski et al., 2008;; Ortiz-Dominguez et al., 2007; O'Brien et al., 2006;; Pae et al., 2004; Meira-Lima et al., 2003)			(Liu et al., 2004; Kim et al., 2004b; Boufidou et al., 2004;; Su et al., 2002) (Rapaport et al., 1999;	(Kim et al., 2004b)	(Kim et al., 2007)	(Kim et al., 2007)	(Kim et al., 2007)	(Kim et al., 2004b)	(Kim et al., 2007; Kim et al., 2004b)	(Knijff et al., 2007)	(Kim et al., 2004b)	(Cunha et al., 2008; Dickerson et al., 2007; Huang et al., 2007; Wadee et al., 2002; Hornig et al., 1998)

NOTE: Each mark denotes an individual study finding: ↑ higher concentrations; ↓ lower concentrations; ● non-significant differences; ND not detected * cytokine mRNA expression;+ specific cytokine polymorphism/genotype(s)/haplotype(s); ^ interleukin-1 cluster ` stimulated production from monocytes; > positive detection in serum/plasma; Li-lithium; Carb- Carbamazepine, Cloza-Clozapine, Benz-Benzodiazepine, Hal- Haloperidol, Ami-Amitryptyline, Amisu- Amisulpride; Quet- quetipaine; Risp- risperidone; Olanz- olanzapine; VP- sodium valproate; AP- antipsychotic; TAU- treatment as usual

Table 1 (*Continued*)

	IL-1β	IL-1RA	IL-2	sIL-2R	IL-4	IL-6	sIL-6R	IL-8	IL-10	IL-12	TNFα	TNF-R1	TNF-R2	IFNγ	TGFβ	IL-6/ IL-4	TNFα/ IL-4	IL-2 / IL-4	IFNγ/ TGFβ	IFNγ/ IL-4	IL-1/ IL-6	IL-4/ TGFβ	CRP
Treatment vs. baseline *(repeated measures)*			↓` ●● `	●●●	●● `	↓`↓` ●	●●		↓`	↓	↑ ●`	↑	↑	↓` ●● `	↑	●`	●`	●`	●	↑↓ ●		●	
BD Treated vs. BD Untreated *(independent samples)*	↑` ●*	●●●●	● `	↑ ●●●● ●● `		↑>↓` ●*●>●> ●>●>			● `		↑↑↓* ●●●	●●●●●	↑↑↑ ●●	● `							↑↑`		↓>
Bipolar treated vs. HC	↑* ●`	↑	↓` ●`	● `	●	↑*↓` ● `			↓` ●		●*			↑↓`							↑●`		
HC treated *in vitro*	↓`		↓`		↑`	↓` ● `			↑`					↓`									
Type of Treatment Intervention	Li or AP; Li (↑); Li (↓)	Clo Hal Ami Li Benz ; L i, Carb, VP and AP (↑)	L i, Carb, VP and AP ; VPA, Li, Li +VP and risp, quet, amisu, olanz; Li; Li ; Li (↓); Li (↓); Li (↓)	Clo (↑) Hal Ami Li Benz ; VP ; Li ; Li; Li	VP Li LI+V Pand AP (optio nal); VP, Li, Li +VP and risp, quet, amis ul, olanz ; Li (↑)	Li or AP; Clo Hal Ami Li ↑> Benz ; VP, Li, Li +VP and risp, quet, amisu, olanz (↑); VP; Li (↓); Li (↓); Li (↓); Li (↓)	VP; Li		TAU; L i, Carb, VP and AP; Li (↑); Li (↓); Li (↓)	TAU (↓)	Li or AP; Clo Hal Ami Li (↑) Benz(↑); VP, Li, Li+VP and risp, quet, amisu, olanz; Li or Carb(↑)	Clo Hal Ami Li Benz ; Li or Carb (↑)	Clo(↑) Hal Ami Li(↑) Benz(↑); Li or Carb(↑)	TAU; VP Li LI+ VP and AP (optio al); L i, Carb, VP and AP(↑); VP, Li, Li +VP and risp, quet, amisu, olanz; Li (↓); Li (↓); Li (↓)	VP Li LI+ VP and AP (optional)	VP, Li, Li+ VP and risp, quet, amisu, olanz	VP, Li, Li+ VP and risp, quet, amisu,ol anz	VP, Li, Li+ VP and risp, quet, amisu,ol anz	VP, Li, LI+VP and AP (optional)	VP, Li LI+VP and AP (optional); VP, Li, Li +VP and risp, quet, amisul, olanz (↑)	Li	VP Li LI+VP and AP (optional)	Li
References	(Padmos et al., 2008;) (Knijff et al., 2007)	(Liu et al., 2004; Kim et al., 2004a; Haack et al., 1999)	(Kim et al., 2007;; Liu et al., 2004; Boufidou et al., 2004; Rapaport & Manji, 2001) Rappaport 1994; (Rapaport et al., 1999)	(Rapaport et al., 1999; Breunis et al., 2003;Haack et al., 1999; Maes et al., 1995; Rapaport, 1994;)	(Kim et al., 2007; ; Liu et al., 2004; Kim et al., 2004 b; Rapaport et al., 2001)	(Padmos et al., 2008;; Kim et al., 2007; Boufidou et al., 2004; Rapaport et al., 2001; Haack et al., 1999; Maes et al., 1995; Knijff et al., 2007)	(Rapaport et al., 1999; ;Maes et al., 1995)		(Liu et al., 2004; Boufidou et al., 2004; Rapaport et al., 2001; Su et al., 2002)	(Kim et al., 2002)	(Padmos et al., 2008; Czerski et al., 2008; Kim et al., 2007; Himmerich, Koethe, Schuld, Yassouridis, & Pollmacher, 20Haack et al., 1999;	(Himmerich et al., 2005; Haack et al., 1999)	(Himmerich et al., 2005; Haack et al., 1999)	(Kim et al., 2007; Liu et al., 2004; Kim et al., 2004b; Boufidou et al., 2004; Rapaport et al., 2001;; Su et al., 2002)	(Kim et al., 2004b)	(Kim et al., 2007)	(Kim et al., 2007)	(Kim et al., 2007)	(Kim et al., 2004b)	(Kim et al., 2007; Kim et al., 2004b)	(Knijff et al., 2007)	(Kim et al., 2004b)	(Horn ig et al., 1998)

NOTE: Each mark denotes an individual study finding: ↑ higher concentrations; ↓ lower concentrations; ● non-significant differences; ND not detected * cytokine mRNA expression;+ specific cytokine polymorphism/genotype(s)/haplotype(s); ^ interleukin-1 cluster ` stimulated production from monocytes; > positive detection in serum/plasma; Li-lithium; Carb- Carbamazepine, Cloza-Clozapine, Benz-Benzodiazepine, Hal- Haloperidol, Ami-Amitryptyline, Amisu- Amisulpride; Quet- quetipaine; Risp- risperidone; Olanz- olanzapine; VP- sodium valproate; AP- antipsychotic; TAU- treatment as usual

Table 2
Clinical profile of TNF antagonists.

	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab	References
Brand name	REMICADE	ENBREL	HUMIRA	NA	NA	Enbrel PI, Humira PI, Remicade PI
Synonyms/historical	cA2	p75TNFR-Fc	D2E7	CDP87O	CNTO-148	
EU registration	RA, PsA, AS, CD, UC, Ps	RA, PsA, AS, JIA, Ps	RA, PsA, AS, CD, Ps	NA	NA	Enbrel PI, Humira PI, Remicade PI
US registration	RA, PsA, AS, CD, UC, Ps	RA, PsA, AS, JIA, Ps	RA, PsA, AS, CD	NA	NA	Enbrel PI, Humira PI, Remicade PI
Efficacy in RA	+++	+++	+++	+++	+++	Enbrel PI, Furst, 2005, Haraoui, 2005, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
Efficacy in PsA	+++	+++	+++	ND	ND	Enbrel PI, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
Efficacy in AS	+++	+++	+++	ND	ND	Enbrel PI, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
Efficacy in CD	+++	–	+++	++	ND	Haraoui, 2005, Sandbom, 2001, Schreiber, 2005
Efficacy in UC	+++	ND	ND	ND	ND	Rutgeerts et al., 2005
Efficacy in Ps	+++	++	+++	ND	ND	Gordon, 2006, Gottlieb, 2004, Leonardi, 2003
Efficacy in JIA	++	++	ND	ND	ND	Carrasco et al., 2004, Furst, 2005
Efficacy in Wegener's granulomatosis	++	–	ND	ND	ND	Lamprecht et al., 2002, WGET Research Group, 2005
Efficacy in sarcoidosis	++	–	ND	ND	ND	Baughman et al., 2006, Utz, 2003
Administration	IV	SC	SC	SC	SC	Enbrel PI, Furst, 2005, Haraoui, 2005, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
Dosages	3–10 mg/kg; q4–8w	25 mg biw; 50 mg qw	40 mg eow; 40 mg qw	100, 200 or 400 mg q4w	50 or 100 mg q2w or q4w	Enbrel PI, Furst, 2005, Haraoui, 2005, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
Pharmacokinetics						
Half-life (t 1/2)	8–10 days	4 days	10–20 days	~14 days	7–20 days	Enbrel PI, Humira PI, Remicade PI, Weir, 2006, Zhou et al., 2007
Volume of distribution (V_{ss})	4.3 +– 2.5 L[a]	8.0 L[b]	4.7–6.0 L[c]	ND	6.9 L[d]	Enbrel PI, Furst 2006, Humira PI, Nestorov, 2005a, Remicade PI, Weisman et al., 2003, Zhou et al., 2004, Zhou et al., 2007
Clearance (C_L)	11 mL/h[a]	72 +/– 5 mL/h[e]	12 mL/h[c]	ND	16.7 mL/h[f]	Enbrel PI, Furst, 2006, Humira PI, Nestorov, 2005a, Remicade PI, Zhou et al., 2004, Zhou et al., 2007
C_{max}	118 μg/mL[a]	1.1 +/– 0.6 μg/mL[e]	4.7 +/– 1.6 μg/mL[g]	ND	70.8 +/– l8.9 μg/mL[h]	Enbrel PI, Furst, 2006, Humira PI, Nestorov, 2005a, Remicade PI, Zhou, 2005, Zhou et al., 2007
Immunogenicity						
RA monotherapy	+++	+	+	ND	ND	Anderson, 2005, Baert, 2003, Enbrel PI, Humira PI, Remicade PI
RA with MTX	+	+/–	+/–	ND	ND	Anderson, 2005, Baert, 2003, Enbrel PI, Humira PI, Remicade PI
CD monotherapy	+++	+	+	+	ND	Anderson, 2005, Baert, 2003, Enbrel PI, Humira PI, Remicade PI

AS is ankylosing spondylitis; biw, twice a week; CD, Crohn's disease; IV, intravenous; JIA, juvenile idiopathic arthritis; MTX, methotrexate; NA, not applicable; ND, no data available; Ps, psoriasis; PsA, psoriatic arthritis; qw, every week; eow, every other week; RA, rheumatoid arthritis; SC, subcutaneous; UC, ulcerative colitis; +/–, very weak; +, weak; ++, moderate; +++, strong.
Table adapted from Tracey et al. (2008).

[a] 5 mg/kg IV.

[b] V_{ss} (volume of distribution at steady state) estimated as the sum of $V_c + V_p$ for the volumes of distribution in the central and peripheral compartments, respectively, from a 2-compartment population pharmacokinetic model based on 10 studies with 2–25 mg IV or SC single dose or biw.

[c] 0.25–10 mg/kg IV.

[d] V_{ss} (volume of distribution at steady state) estimated as the sum of $V_c + V_p$ for the volumes of distribution in the central and peripheral compartments, respectively, from a 2-compartment population pharmacokinetic model based on data from 0.1 to 10 mg/kg IV.

[e] Based on data from 2 to 20 mg IV and 2 to 50 mg s/c.

[f] 0.1–10 mg IV.

[g] 40 mg s/c.

[h] 3 mg/kg IV.

Table 3
Biochemical and mechanistic profile of TNF antagonists.

	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab	References
Class	Monoclonal antibody	Fc-fusion protein	Monoclonal antibody	Monoclonal antibody fragment	Monoclonal antibody	Enbrel PI, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
Structure	Mo/Hu chimeric IgGlκ	Hu sTNFR2-Fcγl	Hu IgGlκ	PEG-Hu IgGlκ Fab[1]	Hu IgGlκ	Enbrel PI, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
Molecular weight (kDa)	150	150	150	~95	150	Enbrel PI, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
Specificity	TNF	TNF/LT	TNF	TNF	TNF	Enbrel PI, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
TNF ligands	sTNF, tmTNF	sTNF, tmTNF,	sTNF, tmTNF	sTNF, tmTNF	sTNF, tmTNF	Enbrel PI, Humira PI, Kay et al., 2006, Remicade PI, Weir, 2006
LT ligands	–	LTα3, LTα2β1	–	–	–	Browning, 1995, Crowe, 1994, Scallon, 2002, Ware, 2005, Williams-Abbott, 1997
Neutralization potency						
sTNF (low conc)	++	+++	++	ND	ND	Kaymakcalan, 2006b
sTNF (high conc)	+++	+++	+++	+++	ND	Enbrel PI, Humira PI, Gramlick, 2006, Kay et al., 2006, Kaymakcalan, 2006b, Kohno, 2005a, Remicade PI, Van den Brande, 2003, Weir, 2006
tmTNF binding	+++	++	+++	+++	ND	Fossati, 2005a, Kaymakcalan, 2006a,b, Lugering, 2001, Mitoma, 2004, Scallon, 2002, Shen, 2005, van den Brande, 2003
tmTNF neutralization	+++	++	+++	+++	ND	Gramlick, 2006, Shen, 2005
Reverse signaling (apoptosis)	+++	++/–	+++	–	ND	Catrina, 2005, Chaudhary, 2006, Di Sabatino, 2004, Eissner, 2000, Fossati 2005b, Lugering, 2001, Shen, 2005, van den Brande, 2003
Reverse signaling (cytokine suppression)	+++	++/–	+++	+++	ND	Nesbitt, 2006, Kirchner, 2004, Mitoma, 2004, 2005, Scallon, 2002, Shen, 2005
FcγR binding						
Drug–TNF complexes 1:1 ratio	++	–	++	ND	ND	Kaymakcalan, 2006a, Kohno, 2005b
Drug–TNF complexes >10:1 ratio	–	–	–	ND	ND	Kaymakcalan, 2006a
CDC	+++	++/–	+++	–	ND	Fossati, 2005a, Gramlick, 2006, Kohno, 2005a, Scallon, 1995, van den Brande, 2003
ADCC	+++	++/–	+++	–	ND	Fossati, 2005a, Gramlick, 2006, Scallon, 1995, van den Brande, 2003

ADCC is antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; Hu, human; IgG, immunoglobulin G; LT, lymphotoxin; Mo, mouse; ND, no data available; PEG, polyethylene glycol; sTNF, soluble TNF; tmTNF, transmembrane TNF; TNF, tumor necrosis factor; +/–, very weak; +, weak; ++, moderate; +++, strong.

Table 4
Summary of studies Kimel et al., 2008; Revicki et al., 2008; documenting effects adalimumab on mood symptoms and quality of life.

Author	Diagnosis	Age	Study Design	Treatment (Tx)	Measures	Results
Kimel et al. (2008)	RA: *n*=525; US General population: → (*n*=1982) 1998 National Survey of Functional Health Status (NSFHS) and → (*n*=33556) 2001 wave of Medical Expenditures Panel Survey (MEPS)	45-54 years; Adalimumab+MXT: 51.9 ± 14.0 Placebo+MXT: 52.1 ± 13.1	Subanalysis from PREMIER trial. Two-year, multi-site, double-blind, comparator-controlled Phase III trial	• Adalimumab 40 mg s/c eow + MTX (*n*=268) • MTX + placebo oral weekly *(initial dose 7.5mg/week, increased as needed to a maximum of 20 mg/week)* • *(*Not included in the analysis: *Adalimumab 40 mg s/c eow + placebo (n=274))* • *Concomitant medications*: Folic acid (5 to 10 mg/week) (*n*=525)	Medical Outcomes Study Short Form-36 health survey (SF-36) Summary Scores: Physical component summary Score (PCS) Mental Component Summary Score (MCS); Health Assessment Questionnaire Disability Index (HAQ-DI); 28-joint Disease Activity Scores (DAS28)	**Baseline vs. general population** ○ significantly lower scores on all subscales of SF-36 (including mental health, role-limitations emotional, vitality, and social function); ○ significantly lower PCS and MCS: ▪ PCS strongly associated with HAQ-DI and moderately with DAS28 (*r*=-0.65 and -0.42) ▪ MCS weakly associated with HAQ-DI and DAS28 (*r*=-0.33 and -0.21) **Adalimumab+MXT vs. baseline** ○ significant improvement in vitality, physical function, and bodily pain at week 12 and sustained at week 52, and 104 **Treatment groups *vs. general population*** **Vitality** ○ similar scores at week 12 in Adalimumab+MXT and significantly higher scores at week 52 and 104 in both treatment groups **Mental Health** ○ similar scores at week 12, 52, and 104 in both treatment groups **Bodily Pain** ○ significantly higher scores at week 52 and 104 in Adalimumab+MXT and similar scores at week 104 in MXT+placebo **General Health and Social Function** ○ similar scores at week 52 and 104 in both treatment groups **Physical function, Role-limitations physical and Role-limitations emotional** ○ significantly lower scores at week 12, 52 and 104 in both treatment groups **PCS** • improved in both groups at week 12 and 52 but were significantly lower than those for the general population • similar to the general population at week 104 for Adalimumab + MTX **MCS** • significantly improved at week 12 and 52 but were lower than those in the general population in both treatment groups • similar to the general population at week 104 for Adalimumab + MXT and significantly greater for the MXT + placebo group
Revicki et al.(2008)	AS: *n*=315	Adalimumab: 41.7 ± 11.7 Placebo: 43.4 ± 11.3	Five-year, open – label, Adalimumab Trial Evaluating Long-term Safety and Efficacy for AS (ATLAS); Initial 24-week, multi-site, randomized, double-blind, placebo-controlled period	• Adalimumab 40 mg s/c eow (*n*=208) • Placebo (*n*=107)	SF-36 Bath AS Disease Activity Index (BASDAI) Bath AS Functional index (BASFI) AS Quality of Life Questionnaire (ASQOL) Patient reported outcomes (PRO)	**Significant improvements from baseline** **Pain and Fatigue** • back pain, nocturnal pain, and fatigue improved within 2 weeks and were sustained at 12 and 24 weeks. • SF-36 bodily pain and vitality improved at 12 weeks and sustained at 24 weeks **Pain, Fatigue, Stiffness, Physical Function and Quality of Life** • pain, fatigue, and stiffness were significantly correlated with ASQOL • longitudinal regression models for ASQOL scores demonstrated significant association between changes in pain, fatigue and stiffness with changes in overall HRQOL

Table 4 (*Continued*)

Mittendorf et al (2007)	Longstanding RA who had received adalimumab therapy during 1 of 6 Phase I-III studies: *n*=505	55 (22-82)	Three-year, open – label, health outcomes extension study Initial 26 weeks of randomized, double-blind, placebo-controlled period *(analyzed as a subgroup)* Subjects included from 6 trials	Adalimumab 40 mg s/c eow	SF-36 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Health Utilities Index-3 (HUI3)	**Significant improvements from baseline and placebo** **Health Related Quality of Life** • all sub-domains of SF-36 at week 26 and sustained for 3 years (i.e. physical functioning, bodily pain, role-physical, role-emotional, general health, mental health, vitality, and social functioning) **MCS and PCS** • significant improvement at 26 weeks but were not significant at 3 years **Fatigue** • improvements observed at week 12 and maintained for 3 years **Health Utilities** • increase from baseline in overall utility at week 26 and sustained for up to 3 years **Mental Health and Physical Function** • the SF-36 mental health sub-domain score was mildly correlated with physical function or clinical response, and moderately correlated with fatigue (Spearman correlation =-0.272, 0.162, -0.154, and 0.513, respectively)
Yount et al (2007) *(extracted from abstract)*	RA: *n*=1526	NA	Subjects included from 3 randomized placebo-controlled trials of Adalimumab versus placebo plus methotrexate or placebo plus standard therapy	Adalimumab 40 mg s/c eow MXT + placebo or standard therapy + placebo	FACIT-Fatigue	**Fatigue** • significantly and consistently reduced in adalimumab-treated subjects in the 3 clinical trials • adalimumab-treated subjects reported statistically significantly less fatigue at all time points post-baseline relative to MXT + placebo

Table 5
Summary of studies Gelfand et al., 2008; Tobinick and Gross, 2008; Braun et al., 2007; Krishnan et al., 2007; De et al., 2006b; Tyring et al., 2006; Moreland et al., 2006; Tobinick et al., 2006; documenting effects etanercept on mood symptoms and quality of life.

Author	Diagnosis	Age	Study Design	Treatment (Tx)	Measures	Results
Gelfand et al. (2008)	Moderate-severe plaque psoriasis: *n*=2546	Continuous group: 45.8 ± 13.6, Interrupted group: 44.9 ± 13.6	The Etanercept Assessment of Safety and Effectiveness (EASE) study 24-week, open-label, multisite, randomized, phase III trial Subjects received treatment for 12 weeks then either continued etanercept for another 12 weeks or interrupted (single round of discontinuation and retreatment) Continuous therapy: *n*=1272 Interrupted therapy: *n*=1274	12 weeks: Etanercept (50 mg s/c twice weekly); Week 12-24: Etanercept (50 mg s/c once weekly)	Beck Depression Inventory (BDI), SF-36- vitality; Dermatology Life Quality Index (DLQI), European Quality of Life Group Feeling Thermometer (EuroQoL-FT), Patient Global Assessment of Psoriasis (PtGA), Patient satisfaction survey	**Depression** • etanercept-treated subjects in both the continuous and interrupted group significantly improved in BDI scores at 12 weeks (mean= 8.1 and 8.3 vs. 5.77 and 5.87, respectively) and maintained at 24 weeks **Vitality** • significant improvements in vitality at 12 weeks and maintained at 24 weeks in both continuous and interrupted groups **Quality of Life** • significant improvements in EroQoL-FT at 12 weeks and maintained at 24 weeks in both continuous and interrupted groups
Tobinick and Gross (2008)	AD: *n*=1	male - 81 years	Case Report	Etanercept (25 mg/week for 5 weeks, perispinal administration)	Montreal Cognitive Assessment Test (MOCA) (e.g. Trails B, copy cube, draw clock)	**Cognitive Function** • rapid (after two hours) and sustained (at 7 weeks, 14 days after last dose of etanercept) improvement in visuospatial/executive function following etanercept administration
Braun et al. (2007)	AS: *n*=356	18 - 70 years Etanercept 50 mg: 41 years Etanercept 25 mg: 40 years Placebo : 40 years	12-week, double-blind, placebo controlled multicenter study	Etanercept 50 mg (QW s/c): *n*=155 Etanercept 25 mg (BIW s/c): *n*=40 Placebo: *n*=40	SF-36 BASFI BASDAI-fatigue item EuroQOL-5D (EQ-5D) EQ-5D visual analog scale (VAS), EQ-5D utility	**Quality of Life** **EQ-5D** • almost two-thirds (65%) of patients reported problems with anxiety or depression at baseline • significant improvement VAS in both treatment groups from week 2 to 12 as compared to placebo • significant improvement in utility from week 2 to 12 in QW and 8 to 12 weeks for BIW treatment groups as compared to placebo **SF-36** • significant improvement at 12 weeks of treatment in both groups • as well as in all sub-domains (physical functioning, vitality, social functioning, bodily pain, mental and general health, role limitations-physical and role-limitations-emotional) with the exception of role limitation-emotional for 25 mg BIW group **Fatigue** • significant improvements for both treatment groups at 8 to 12 weeks
Krishnan et al. (2007)	Plaque Psoriasis: *n*=591	NA	See Tyring et al. (2006) for results from double-blind phase. Second phase after week 12, open-label etanercept for 84 weeks	Etanercept 50 mg s/c twice weekly *n*=233: etanercept/etanercept group (EE) *n*=231: placebo/etanercept group (PE)	FACIT-Fatigue item BDI HAMD	**Fatigue** • subjects in the PE improved 5.0 units from baseline in the fatigue score at 24 weeks which was sustained up to 96 weeks • 58% of subjects in the PE and 52% in the EE group were 'fatigue-responders' (≥3 units from baseline) and sustained up to 96 weeks

Table 5 (*Continued*)

Krishnan et al. (2007)b						**Depression** • mean BDI improvements were comparable (EE: 4.0 units and PE: 4.5 units) at week 24 and sustained up to 96 weeks • percentage of BDI responders (> 50%) increased to a similar level in both groups (EE: 58% and PE: 55%) as did the proportion of subjects with minimal symptoms of depression (85% vs. 88%, respectively). • subjects in the PE group had similar improvements (mean improvement of 1.7 units) in HAMD scores compared to subjects in the etanercept group during the double-blind phase and were sustained for up to 96 weeks • percentage of HAMD responders (> 50%) increased to similar levels (EE: 45% and PE: 46%) as did the proportion of subjects with no symptoms of depression (86% and 87%, respectively)
De Felice et al. (2006)	Psoriatic arthritis *n*=71	18-75 (50.5) years	Open-label, initial 12 week, followed by a maintenance dose for 12 weeks	12 Weeks: Etanercept 50 mg s/c twice weekly Maintenance: Etanercept 25 mg s/c twice-weekly	Ritchie index (RI) Psoriasis area and severity index (PASI) DLQI, Skinder-29, Psoriasis Disability Index (PDI) Health Assessment Questionnaire (HAQ)	**Quality of life** • DLQI, Skinder-29, PDI and HAQ scores showed fast and consistent improvement in mean scores at 12 and 24 weeks. • measures of HAQ showed significant reduction in disability and increase in functional capacity at 24 weeks
Tyring et al. (2006)	Active clinically stable, Psoriasis *n*=620	>18	12 week, randomized, double-blind, placebo-controlled multisite trial Individuals with a history of psychiatric disease were excluded	Etanercept 50 mg s/c twice weekly *n*=311 Placebo *n*=309	HAMD BDI FACIT-Fatigue DLQI PASI	**Depression** • at baseline, 33% (*n*=102) of etanercept and 35% (*n*=106) of placebo group met criteria for mild or moderate to severe depression on BDI and 25% (*n*=77) vs. 26% (*n*=80) on the HAMD, respectively • significant improvements in BDI (mean difference of 1.8 units) and HAMD (1.5 vs. 0.4 units) scores were at 12 weeks • significantly greater proportion of BDI responders at 4 weeks (45% vs. 36%) which increased (55% vs. 39%) at 12 weeks • significantly greater proportion of HAMD responders (45% vs. 32%) at 12 weeks **Quality of life** • significant improvements in quality of life were reported in 69% of etanercept-treated subjects as compared with 22% of placebo-treated subjects at 12 weeks **Fatigue** • significant improvement (i.e. 5 points) on the FACIT-fatigue scale as compared to placebo (i.e. 1.9 points) at 12 weeks

Tyring et al. (2006)						**Depression, Fatigue and Psoriasis Severity** • improvements in HAMD at 12 weeks were significantly correlated with DLQI (r=0.4), fatigue (r=0.34), and non-significant correlation with PASI or PASI items (joint pain, skin pain, itching) • improvements in FACIT-Fatigue were significantly correlated with BDI, HAMD, DLQI, joint pain, skin pain, and itching
Moreland et al. (2006)	RA: (i) Recent-onset RA (n=304) (ii) Established RA (n=131)		2 multicenter, randomized, double-blind clinical trials for 12 months followed by open-label 12 month period	(i) Recent-onset RA: Randomized: Etanercept 25 mg s/c twice weekly or MXT 20 mg weekly Open-label: Etanercept 25 mg s/c or Etanercept + MXT (ii) Established RA: Randomized: Etanercept 25 mg s/c twice weekly or placebo Open-label: Etanercept 25 mg s/c	HAQ- fatigue	**Fatigue** • significant improvement in fatigue in patients with recent-onset RA at 2, 4 and 8 weeks with a continued reduction up to 44 months. • significant reduction in fatigue in established RA in the double-blind phase with an immediate reduction in fatigue scores after switch from placebo to etanercept at 6 months and sustained up to 46 months
Tobinick at al. (2006)	Mild to severe AD: n=15	76.7	6 month, prospective, open-label, pilot study	Etanercept, (perispinal, 25-50mg/ once weekly) Concomitant mediations: memantine, or a cholinesterase inhibitor, antidepressants (n=3), risperidone (n=1), gabapentin (n=1), olanzapine (n=1)	Mini Mental Status Examination (MMSE) AD Assessment Scale-Cognitive Subscale (ADAS-Cog) Severe Impairment Battery (SIB)	**Cognitive Function** • significant improvement with treatment in cognitive function in MMSE, ADAS-Cog and SIB at one month though 6 months.
Kaufman (2005)	psoriatic arthritis and BD: n=1	Female - 21 years	Case Report	Etanercept (25 mg BIW)	no formal scales used	**Mania** • etanercept was a possible catalyst of a manic episode with psychotic symptoms in an initially euthymic female with BD. • etanercept was discontinued and patient was stabilized on valproic acid (500 mg), oxcarbazepine (600 mg bid), ziprasidone (80 mg) and clonazepam (0.5 mg bid). The patient remained stable for 8 months

Table 6
Summary of studies Tookman et al., 2008; Bassukas et al., 2008; Minderhoud et al., 2007; Persoons et al., 2005; St Clair et al., 2004; documenting effects infliximab on mood symptoms and quality of life.

Author	Diagnosis	Age	Study Design	Treatment (Tx)	Measures	Results
Tookman et al. (2008)	Advanced cancer outpatients, *n*=17	NA	Open-label, pilot study; injection at baseline and if there was observable clinical benefit, every 4 weeks thereafter until clinical benefit was lost	Infliximab (5 mg)	Fatigue Severity Scale (FSS) Karnofsky Performance Status (KPS) Hospital Anxiety and Depression Scale (HADS) VAS Laboratory measures: *c*-reactive protein, erythrocyte sedimentation rate (ESR), TNF-α, IL-6, and leptin	**Fatigue** • improvements in fatigue were observed at week 4 in 9 out of 14 patients, while changes in performance status were reported in 3 out of 15 patients. **Anxiety and Depression** • improvement in anxiety and depression subscores were documented in 7 out of 15 patients **Laboratory outcomes** • majority of patients had modest improvements in serum *c*-reactive protein, ESR, and leptin
Bassukas et al (2007)	*n*=3 Psoriasis and BD Psoriasis and recurrent depression with psychotic symptoms Severe psoriasis with BD and borderline personality disorder	 male- 21 years female- 49 years male - 47 years	Case Report	Infliximab (5 mg/kg body weight) olanzapine (15 mg/d) venlafaxine (300 mg/d) and olanzapine (10 mg/d) risperidone (5 mg/d), lithium carbonate (blood levels: 0.69 mEq/L) and venlafaxine (150 mg/d)	PASI	**Depressive and Affective symptoms** • treatment with infliximab for 12 months was associated with improved psoriasis (PASI improved by 95%) and stabilization of BD symptoms • treatment with infliximab for 10 months was associated with improvement in residual depressive symptoms and psoriasis (PASI improved by 75%) • treatment with infliximab was associated with improvement in psoriasis (PASI improved by 55% at 3 months) and affective symptoms
Minderhoud et al. (2007)	CD: *n*=14	32.2 ± 8.6	Single-blind within-subjects design All subjects received placebo at baseline and infliximab after 2 weeks. Subjects were then followed for 4 weeks after last infliximab infusion. Patients with fistulae (*n*=5) received an extra dose of infliximab at week 4.	Infliximab (5 mg/kg)	Center for Epidemiological Studies Depression Scale (CES-D) Multi-dimensional Fatigue Inventory (MFI-20) Quality of life-Inflammatory Bowel Disease Questionnaire (QOL-IBDQ) Laboratory measures: TNF-α, IL-6, Il-10, and Il-18 were also assessed	**Depression** • significant improvement in depression as measured with the CES-D was reported at week 4 **Fatigue** • treatment with infliximab was associated with a drop in fatigue scores after 7 days and was sustained until study endpoint (week 4) **Quality of Life** • mean QOL-IBDQ score increased significantly at 4 weeks compared to baseline **Laboratory outcomes** • no correlation between severity of fatigue and the level of cytokines observed

Persoons et al (2005)	CD: *n*=100	34 ± 11	4-week, open-label single dose. Patients were subsequently followed-up clinically until next flare or at 9 months	Infliximab (5 ir 10 mg/kg, i.v.)	Patient Health Questionnaire 9-item (PHQ-9)- depression module for DSM-IV HADS Visual Analogue scale-Sleep, Toronto Alexithymia Scale 20 item (TAS-20) Social Support List-Interactions (SSL-I), CD Activity Index (CDAI)	**Depression** • presence of MDD (24%) at baseline significantly predicted lower remission (29% vs. 70%) at 4 weeks and significantly decreased time to retreatment (Relative hazard 2.27 95% CI 1.36-3.79) • at week 4 a significantly smaller proportion of patients met criteria for depression (16%) **Anxiety** • patients with possible anxiety were also less likely to achieve remission. **Social Support** • there was a negative relationship between social support and sleep and time to retreatment in patients with anxiety **Laboratory Measures** • the median c-reactive protein level was significantly higher (46.1 mg/L) in patients with MDD as compared to non-depressed (8 mg/L) patients
St. Clair et al (2004)	RA: *n*=1049	18-75 years	54-week, multicenter, 3 arm, parallel group, placebo-controlled trial. Randomly assigned in a 4:5:5 ratio to 3 treatment arms. Infusions were given at week 0, 2 and 6, and every 8 week thereafter through week 46.	MXT-Placebo (n=282), MXT- infliximab 3 mg/kg (*n*=359), MXT- infliximab 6 mg/kg (*n*=363); Maintenance MTX doses escalated to 20 mg/week	American College of Rheumatology improvement (ACR-N) DAS28 HAQ SF-36	**Quality of Life** • improvement in physical function on the HAQ and SF-36 was higher for combination of MXT-infliximab as compared to MXT therapy alone • changes in the mental health component of the SF-36 were not reported
Lichtenstein et. al. (2002)	CD: *n*=105	18-65 years	Multicenter, single-dose, randomized, placebo-controlled, double-blind: patients were followed-up for 14 weeks Non-responders at week 4 were offered open-label treatment with 10 mg/kg of infliximab. Patients who achieved at least a 70-point decrease from baseline in CDAI score at week 8 (during blinded or open-label) were eligible to participate in repeated treatment phase Repeated Treatment Phase: Randomized to receive placebo or infliximab 10 mg/kg at week 12, 20, 28	Infliximab (single dose; 5,10, or 20 mg/kg) (combined n=82) Placebo: (*n*=23) Most patients also received stable does of mesalamine, corticosteroids, azathioprine, or 6-meracaptopurine	IBDQ CDAI	**Quality of Life** • infliximab- treated subjects experienced significant improvement in overall quality of life, as well all on 4 dimensions of the IBDQ at 4 weeks (i.e. Bowel, Social, Emotional, and Systemic) • significant proportion of infliximab-treated patients scored in the 'almost normal' or 'normal' functioning on an itemized analysis of the IBDQ as compared to placebo. *Emotional* not frustrated, impatient, or restless (27%), not depressed or discouraged (46%), not worried or anxious (48%), not angry as a result of bowel problem (56%), extremely or well satisfied with personal life (23%); *Systemic* not feeling fatigued or tired and worn out (20%), full of energy (17%), generally well (35%); *Social* able to attend school or work (58%), and none or hardly any difficulty playing sports or games (41%)

Table 7
Number and percentage of subjects with ≥1% treatment-emergent adverse events at least possibly related to study drug during the control period in rheumatoid arthritis (RA) studies (studies RA I, RA II, RA III, RA IV, and RA V) [*Extracted from Compendium of Pharmaceuticals and Specialties (CPS)*].

Organ class (SOC)	Adalimumab 40 mg s/c eow *n* = 1247 (%)	All Adalimumab *n* = 1922 (%)	Placebo (not DE013) *n* = 690 (%)
Gastrointestinal disorders			
Nausea	80 (6.4)	112 (5.8)	12 (1.7)
Diarrhea	47 (3.8)	60 (3.1)	17 (2.5)
Abdominal pain	22 (1.8)	29 (1.5)	5 (0.7)
Abdominal pain upper	20 (1.6)	25 (1.3)	0 (0.0)
Mouth ulceration	17 (1.4)	24 (1.2)	5 (0.7)
Dyspepsia	14 (1.1)	21 (1.1)	4 (0.6)
Vomiting	16 (1.3)	20 (1.0)	5 (0.7)
General disorders and administration site conditions			
Injection site irritation	74 (5.9)	122 (6.3)	61 (8.8)
Injection site reaction	49 (3.9)	67 (3.5)	3 (0.4)
Injection site pain	36 (2.9)	63 (3.3)	24 (3.5)
Injection site erythema	36 (2.9)	60 (3.1)	2 (0.3)
Fatigue	37 (3.0)	58 (3.0)	7 (1.0)
Injection site rash	17 (1.4)	22 (1.1)	2 (0.3)
Influenza like illness	15 (1.2)	21 (1.1)	2 (0.3)
Pyrexia	13 (1.0)	20 (1.0)	1 (0.1)
Infections and infestations			
Nasopharyngitis	61 (4.9)	95 (4.9)	10 (1.5)
Upper respiratory infection	72 (5.8)	93 (4.8)	15 (2.2)
Sinusitis	46 (3.7)	55 (2.9)	17 (2.5)
Herpes simplex	33 (2.6)	48 (2.5)	6 (0.9)
Urinary tract infection	31 (2.5)	44 (2.3)	6 (0.9)
Bronchitis	19 (1.5)	29 (1.5)	8 (1.2)
Herpes zoster	17 (1.4)	23 (1.2)	8 (1.2)
Influenza	16 (1.3)	21 (1.1)	7 (1.0)
Pneumonia	17 (1.4)	21 (1.1)	3 (0.4)
Investigations			
Lymphocyte count decreased	11 (0.9)	38 (2.0)	11 (1.6)
Alanine aminotransferase increased	27 (2.2)	33 (1.7)	4 (0.6)
Liver function test abnormal	19 (1.5)	22 (1.1)	4 (0.6)
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis	11 (0.9)	28 (1.5)	7 (1.0)
Nervous system disorders			
Headache	75 (6.0)	124 (6.5)	14 (2.0)
Dizziness	23 (1.8)	32 (1.7)	6 (0.9)
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain	33 (2.6)	44 (2.3)	9 (1.3)
Cough	31 (2.5)	42 (2.2)	4 (0.6)
Skin and subcutaneous tissue disorders			
Rash	44 (3.5)	66 (3.4)	9 (1.3)
Pruritus	28 (2.2)	43 (2.2)	4 (0.6)
Alopecia	22 (1.8)	28 (1.5)	2 (0.3)
Rash pruritic	14 (1.1)	22 (1.1)	0 (0.0)

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