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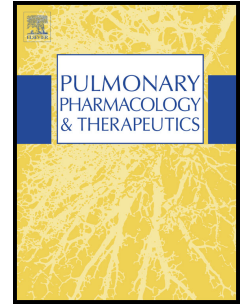
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TNF- α inhibitors in asthma and COPD: we must not throw the baby out with the bath water

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Abstract

Tumor necrosis factor (TNF)- α , a pleiotropic cytokine that exerts a variety of effects, such as growth promotion, growth inhibition, angiogenesis, cytotoxicity, inflammation, and immunomodulation, has been implicated in several inflammatory conditions. It plays a significant role in many inflammatory diseases of lung. Given that there is significant literature supporting the pathobiologic role of TNF- α in asthma, mainly in severe refractory asthma, and COPD, TNF- α inhibitors (infliximab, golimumab and etanercept) are now regarded as potential new medications in asthma and COPD management. The studies reported in literature indicate that TNF- α inhibitors are effective in a relatively small subgroup of patients with severe asthma, possibly defined by an increased TNF axis, but they seem to be ineffective in COPD, although an observational study demonstrated that TNF- α inhibitors were associated with a reduction in the rate of COPD hospitalisation among patients with COPD receiving these agents to treat their rheumatoid arthritis. These findings require a smart approach because there is still good reason to target TNF- α , perhaps in a more carefully selected patient group. TNF- α treatment should therefore not be thrown out, or abandoned. Indeed, since severe asthma and COPD are heterogeneous diseases that have characteristics that occur with different phenotypes remained poorly characterized and little known about the underlying pathobiology contributing to them, it is likely that definition of these phenotypes and choice of the right outcome measure will allow us to understand which kind of patients can benefit from TNF- α inhibitors.

Introduction

Tumor necrosis factor (TNF)- α , a pleiotropic cytokine that exerts a variety of effects, such as growth promotion, growth inhibition, angiogenesis, cytotoxicity, inflammation, and immunomodulation [1], has been implicated in several inflammatory conditions [2-6].

This cytokine is produced predominantly by activated macrophages but also by other immune (lymphocytes, natural killer cells, mast cells) as well as stromal (endothelial cells, fibroblasts, microglial cells) cells. TNF is synthesized as a monomeric type-2 transmembrane protein (tmTNF) that is inserted into the membrane as a homotrimer and cleaved by the matrix metalloprotease TNF- α converting enzyme (TACE; ADAM17) to a soluble circulating trimer (solTNF); both tmTNF and solTNF are biologically active [7, 8]. The balance between tmTNF and solTNF signaling is influenced by cell type, activation status of the cell, the stimulus eliciting TNF production, TACE activity, and expression of endogenous TACE inhibitors leading to divergent TNF-mediated effects on cellular viability [9, 10].

TNF- α receptors and signaling

The actions of TNF- α are mediated as well as regulated by its ubiquitously expressed TNF receptors 1 (TNF-R1, Tnfrsf1a) and 2 (TNF-R2, Tnfrsf1b), which are membrane glycoprotein receptors that specifically bind TNF and homotrimers of lymphotoxin A, but the two receptors differ in their expression profiles, ligand affinity, cytoplasmic tail structure, and downstream signaling pathway activation [11]. TNF-R1 is expressed in most cell types, and can be activated by binding of either solTNF or tmTNF, with a preference for solTNF; whereas TNF-R2 is expressed primarily by cells of the immune system and by endothelial cells, and is preferentially activated by tmTNF [12]. The cytoplasmic domains of these receptors are unrelated and are linked to different intracellular signalling pathways.

TNF-R1 and TNF-R2 are assumed to use different intracellular signaling pathways and may thus mediate different functions Multiple experimental

approaches have shown that TNF-R1 initiates the majority of biological functions of TNF- α [13, 14]. The binding of TNF to TNF-R1 leads to the recruitment of TRADD (TNF-R1-associated death domain protein) into the receptor complex. TRADD subsequently recruits other effector proteins into the complex. FADD/MORT1 (FAS-associated death domain protein), TRAF2 (TNF receptor associated factor 2), and the death domain kinase RIP (receptor interacting protein) have been shown to interact directly with TRADD. While FADD/MORT1 is essential for TNF-induced apoptosis through activating a caspase cascade, RIP and TRAF2 are critical in the activation of nuclear factor- κ B (NF- κ B) and activator protein 1 (AP-1), which regulate the expression of numerous immune and inflammatory response genes. Both transcription factors are activated through protein kinase cascades culminating in the phosphorylation of yet-to-be-identified I κ B kinases and the molecularly characterized c-jun N-terminal kinases (JNK), respectively. In addition, it has been reported that RIP mediates TNF-induced necrotic cell death. For TNF-R2 signaling, it is known that the occupancy of TNF-R2 by TNF leads to the recruitment of TRAF1 and TRAF2 as well as inhibitors of apoptosis protein 1 and 2 (cIAP1 and cIAP2). However, because most of the research effort from many laboratories is devoted to the study of TNF-R1 signaling, it is less clear how these molecules correlate to transduce the diverse TNF signals through TNF-R2.

Until recently, the prevailing theory was that the majority of the biological effects mediated by TNF- α are achieved through its interaction with TNF-R1 where the TNF-R2 plays a minor role in binding and redistributing the ligand to TNF-R1 in a process coined "ligand passing" [15]. However, there is accumulating evidence that signaling through the TNF-R2 influences a number of pro-inflammatory responses, including the activation of T cells [16-18], myofibroblasts [19], inhibition of angiogenesis and tumor suppression [20]. The proteinase TACE can also cleave TNF-R1 and TNF-R2 to yield soluble TNF receptors (sTNF-R) that act as competitive non-signalling agonists for TNF. sTNF-Rs show a higher degree of affinity for the cytokine than the corresponding bound forms. When TNF is bound to these soluble receptors, it

can no longer interact with the membrane forms and, therefore, it has been speculated that the presence of the soluble forms may constitute a way of regulating TNF actions [21].

TNF and its receptors may have a number of physiological and pathological roles. TNF- α acts as an endogenous mediator of pro-inflammatory cytokine stimulation and other cellular responses, including lymphocyte activation and migration, and cell proliferation, differentiation and apoptosis [22-24]. Moreover, TNF- α can induce reactive oxygen species (ROS) [24, 25] and stimulate the induction of various genes involved in inflammation [26-28] including interleukin-8 (IL-8). TNF- α also depletes cellular glutathione (GSH), a cellular antioxidant [29].

Role of TNF- α in asthma and COPD

TNF- α plays a significant role in many inflammatory diseases of lung. Of the various pulmonary diseases, it is implicated in asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), acute lung injury and acute respiratory distress syndrome [30]. Figure 1 illustrates the putative role of TNF- α in the pathogenesis of asthma and COPD.

TNF- α is expressed in asthmatic airways and may play a key role in amplifying asthmatic inflammation through the activation of NF- κ B, AP-1 and other transcription factors [31]. Elevated levels of TNF- α have been observed in induced sputum and in bronchoalveolar lavage fluid (BALF) from asthmatic patients and up-regulated TNF expression has been detected in alveolar macrophages, mast cells, and bronchial epithelial cells [32-39]. TNF- α induces the expression of multiple airway epithelial cell genes, including cytokines (IL-5, IL-6, IL-8, G-CSF, GM-CSF), chemokines (eotaxin, MCP-1, RANTES), adhesion molecules (ICAM-1), extracellular matrix glycoproteins (tenascin), neuropeptides (endothelin-1), mucins (MUC-1, MUC-2, MUC-5AC), and cytosolic phospholipase A2 [40-51]. TNF- α increases the adhesion of activated eosinophils to respiratory epithelial cell cultures and promotes neutrophil chemotaxis, adherence, and transendothelial and transepithelial migration [52-54]. IgE receptor activation induces TNF- α release from human lung tissue

and upregulates eosinophil TNF mRNA levels [55]. TNF- α causes transient bronchial hyperresponsiveness (BHR) [56] likely because it decreases M₂ muscarinic receptor expression and promotes recruitment of eosinophils, containing major basic protein, an M₂ antagonist [57]. It is widely accepted that airway hyperreactivity can be caused by dysfunction of neuronal M₂ muscarinic receptors that normally limit acetylcholine release from parasympathetic nerves [58]. Nonetheless, genetic polymorphism of the TNF- α gene on chromosome 6 is associated with asthma, asthma severity and BHR [59].

TNF- α is also believed to play a central role in the pathophysiology of COPD [60]. It is produced by alveolar macrophages, neutrophils, T cells, mast cells and epithelial cells following contact with different pollutants including cigarette smoke [61]. TNF- α has been shown in animal models to induce pathological features associated with COPD, such as an inflammatory cell infiltrate into the lungs, pulmonary fibrosis and emphysema [62, 63]. It enhances neutrophil chemotaxis and migration by inducing the expression of chemokine interleukin 8 (IL-8) and upregulating endothelial adhesion molecules [64, 65]. *In vivo*, elevated levels of TNF- α have been demonstrated in peripheral blood, bronchial biopsies, induced sputum and BALF of patients with stable COPD compared with control subjects [66-70]. TNF- α has been shown to correlate with body mass index (BMI) and cigarette smoke exposure [71, 72] and other inflammatory mediators [73] in COPD. A polymorphism of the promoter region of the TNF- α gene has been implicated in the occurrence, severity, and mortality risk of COPD [74-76].

Intriguingly, TNF- α levels in sputum increase significantly during acute exacerbations of COPD [77, 78]. TNF- α together with IL-1 β has been identified as key cytokine that is able to initiate inflammatory cascades during exacerbations of severe asthma [79] and COPD [80]. In particular, it has been reported that TNF- α is the initial and predictive cytokine released in the cascade following lipopolysaccharide (LPS) exposure [80].

Given the role of TNF in the pathogenesis of asthma and COPD, it is obvious to assume that TNF- α and/or its soluble receptor may be a target for reducing asthma and COPD inflammation.

TNF- α inhibitors

The therapeutic goal when administering TNF- α inhibitors is to eliminate the surplus of TNF- α in the blood and from sites of inflammation. Reduction should be made such that TNF- α levels do not fall below levels that may comprise an individual's immuno-competency. Once a TNF- α inhibitor is administered and absorbed from the site of administration, a number of interactions occur between tissue/fluids and blood. Upon reaching the target site the TNF inhibitors bind to soluble TNFs and TNF expressed on the surface of various cells triggering the pharmacologic mechanism of action. There are three commercially available biologic agents that inhibit TNF- α – etanercept, infliximab, and adalimumab. In addition, two other TNF inhibitors, certolizumab pegol and golimumab, are in development. Some recent review articles offer a thorough description of these drugs [81, 82].

Etanercept is a fully human dimeric fusion protein composed of a TNF- α type II receptor and the Fc portion of IgG1. It is administered as a subcutaneous injection. Etanercept is a receptor blocker that binds to free-floating and cell-bound TNF. Once bound to TNF, it prevents TNF actions at its usual receptor sites on T cells as well as other cells. Etanercept does not activate complement mediated cell lysis.

Infliximab is a chimeric monoclonal antibody (mAb) composed of the constant region of human immunoglobulin and two murine variable regions targeted to TNF- α . It has a chimeric binding site, which means that a portion of the protein is mouse derived and is recognized as foreign protein by the human immune system. This increases the potential for antibodies directed against infliximab, which might neutralize its effect. Indeed, chimeric antibodies are designed to minimize the human antimouse antibody (HAMA) antigenic response triggered by the antigenic part of the mouse component, while retaining a high specificity. However, although the immunogenicity profile is reduced, chimeric

antibodies such as infliximab can still trigger a human anti-chimeric antibodies (HACA) response [83]. This is similar to the HAMA response and reduces the antibody's efficacy. Infliximab, once bound to TNF- α , may activate complement mediated cell-lysis. Complement mediated cell lysis is believed to be responsible for the effectiveness in granulomatous diseases such as Crohn's disease and sarcoidosis.

Adalimumab is a recombinant human IgG1 mAb that is specific for human TNF. It was developed using phage display technology resulting in an antibody with human-derived heavy and light chain variable regions and human immunoglobulin G constant regions. Adalimumab is administered as a subcutaneous injection. The mechanism of action of adalimumab is the same as that of infliximab in that it binds to free floating and cell-bound TNF and may also induce complement mediated cell lysis.

The primary difference between the three TNF- α inhibitors is that the receptor blocker etanercept does not induce complement and has one binding site for TNF- α . The mABs are "classic" immunoglobulins with a Fc portion and two arms each with a binding site for TNF- α and both induce the complement cascade upon binding to TNF- α .

Certolizumab is a Fab1 fragment of an IgG1 mAb and lacks effector functions because it has no Fc region. Golimumab is IgG1 antibody, which is capable of complement fixation and Fc-receptor binding. It is fully human mABs.

Safety of TNF- α inhibitors

Given their mechanisms of action, it is possible that use of TNF- α inhibitors may predispose patients to an increased risk of serious and life-threatening infection, recrudescence of tuberculosis (TB), and reactivation of hepatitis B.

The anti-TNF- α therapies have subtly different side-effect profiles. Patients taking infliximab appear to have a higher risk of infection from histoplasmosis, coccidiomycosis or reactivation TB [84, 85]. Cases of TB were also reported in the studies of adalimumab, particularly at doses higher than those that were subsequently licensed, suggesting a dose–response effect. The reasons for this

remain unclear, but it is possible that, by virtue of their ability to fix complement, the monoclonal anti-TNF- α antibodies interfere with granuloma formation in a manner that is beneficial in Crohn's disease but detrimental in the reactivation of TB, whereas etanercept has neither of these effects. In any case, suppression of defense against infections also occurs with etanercept treatment, particularly against intracellular growing pathogens. Individual cases of a TB reactivation have also been described with the use of etanercept. Animal studies have suggested that partial rather than complete TNF blockade may allow preservation of the beneficial and anti-inflammatory functions of this cytokine in TB immunity [86].

The TNF- α inhibitors are contraindicated in patients with unstable congestive heart failure (CHF) and should be used only after other agents have failed in patients with a past history of CHF who are stable [87]. In particular, there have been reports of etanercept-induced CHF [88]. This event appears to be very rare, but therapy with etanercept for patients with unstable cardiac disease might be best avoided. This is a problem in COPD patients because the prevalence of CHF in patients with COPD is known to range from 20% to 32% [88].

The oncogenic potential of etanercept, particularly for lymphoma, is a much-debated issue. It may be dependent on the disease state that is being treated. Recent reports have suggested a slight (perhaps up to 3-fold) increase in the risk of lymphoma, particularly in patients with rheumatoid arthritis [89]. A recent meta-analysis involving infliximab and adalimumab demonstrated an increase risk of lymphoproliferative diseases and malignancies in patients treated with these agents [90].

Several patients treated with TNF antagonists have developed multiple sclerosis [91]. Others with multiple sclerosis have had exacerbations of their disease when treated with these agents.

At least 2 cases in which the use of infliximab has been associated with hepatotoxicity in the absence of other factors have been published [87]. No

similar reports of hepatotoxicity caused by etanercept or adalimumab have been published [87].

TNF- α inhibitors and asthma

Considering the critical role of TNF- α in the pathogenesis of asthma and the need for alternative treatments for those asthmatic patients with severe disease who are particularly resistant to conventional therapy, molecules targeted at blocking the effects of TNF- α are likely to constitute a considerable advance in the management of these difficult patients. Indeed, some trials have explored the possibility of using TNF- α inhibitors in asthmatic patients (table 1).

An uncontrolled study of etanercept 25 mg administered subcutaneously twice weekly for 12 weeks in 15 patients with severe asthma documented a significant (2.5 doubling concentration) improvement in methacholine BHR, a 240-mL improvement in Forced Expiratory Volume in 1 Second (FEV₁), and an improvement in asthma quality of life [92]. These findings were confirmed in a study that measured markers of TNF- α activity on peripheral-blood monocytes in 10 patients with refractory asthma, 10 patients with mild-to-moderate asthma, and 10 control subjects and also investigated the effects of treatment with etanercept (25 mg twice weekly) in the patients with refractory asthma. Antagonism of TNF- α with 10 weeks of etanercept therapy significantly reduced the expression of membrane-bound TNF- α by peripheral-blood monocytes and improved the provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀), the asthma-related quality of life, FEV₁, and symptom scores, as compared with placebo [93]. The baseline expression of membrane-bound TNF- α by peripheral-blood monocytes and the extent to which it was reduced by etanercept treatment were independently associated with the net improvement in both primary outcome measures.

Although these interesting data indicate a role for etanercept in the treatment of asthma, the results of other studies deny such a role. The administration of etanercept for 2 weeks to subjects with mild-to-moderate allergic asthma did not prevent pulmonary eosinophilia during the late phase response to

bronchoscopic segmental allergen challenge and, furthermore, TNF antagonism increased pulmonary IL-4 levels [94]. Data from a different study of etanercept administered once weekly for 12 weeks in 39 patients with severe corticosteroid refractory asthma demonstrated only a small but significant improvement in asthma control and systemic inflammation, as measured by serum albumin and CRP, with no improvements in the secondary endpoints of lung function, Peak Expiratory Flow (PEF) or BHR, supporting the view that if anti-TNF- α is to be effective in asthma, it will only be on a relatively small subgroup of patients, possibly defined by an increased TNF axis [95]. Minor adverse events, including injection site pain and skin rashes, were more frequent with etanercept than with placebo.

Only one study evaluated the effectiveness of infliximab. This mAb reduced diurnal PEF variability and, interestingly, the number of mild exacerbations encountered, but not morning PEF, in a trial of symptomatic patients with moderate asthma despite receiving inhaled corticosteroid (ICS) therapy [96]. There were no serious adverse events related to the study agent.

A trial that assessed the safety and efficacy of golimumab (50, 100, or 200 mg) through week 52 in a large population of patients with uncontrolled, severe persistent asthma was unable to demonstrate significant differences were observed for the change in percent-predicted FEV₁ or severe exacerbations through week 24 [97]. Unfortunately, an unfavourable risk/benefit profile led to early discontinuation of therapy with golimumab. 30.3% of patients treated with golimumab experienced serious adverse events, with serious infections occurring frequently. Moreover, one death and eight malignancies occurred in the golimumab groups. Nonetheless, careful examination of 53 nucleotide polymorphisms in 144 severe asthmatic subjects demonstrated a positive association between pharmacologic effect of golimumab and a common single nucleotide polymorphism (SNP) in 2 TNF receptor genes. Polymorphisms in TNF- α or ADAM17 did not associate with a positive effect of golimumab [98].

TNF- α inhibitors and COPD

In view of the similarities between chronic severe asthma and COPD, it has been suggested that blocking the biological effects of TNF- α may be beneficial in the treatment of COPD. Although randomised controlled trials to evaluate the effectiveness of TNF- α inhibitors in patients with COPD have been few, the results of the first studies seem to indicate that they are not really effective in this disease (table 2).

An exploratory study of infliximab treatment in patients with COPD did not show a short-term improvement in clinical or inflammatory parameters from infliximab treatment in patients with mild-to-moderate COPD, although patients so treated did demonstrate an increase in exhaled nitric oxide (eNO) [99]. Increased cough was reported by eight patients in the infliximab group.

In a larger dose-finding study, subjects with moderate to severe COPD received infliximab 3 mg/kg or 5 mg/kg or placebo at Weeks 0, 2, 6, 12, 18, and 24 and efficacy, health status, and safety were assessed through Week 44. No therapeutic benefit was observed in the primary outcome variable: health status as assessed by the Chronic Respiratory Questionnaire (CRQ) [100]. Similarly, no therapeutic benefit was noted in lung function, dyspnea, or in the incidence of moderate to severe COPD exacerbations. A modest trend toward improved 6-minute walk test (6-MWT) was demonstrated in the infliximab treatment groups, although this did not reach statistical or clinical significance. Higher proportions of infliximab-treated subjects discontinued the study agent due to adverse events (20–27%) than did placebo-treated subjects (9%). The most frequently reported adverse events in the combined infliximab treatment groups were COPD exacerbation, upper respiratory tract infection, sinusitis, pain, back pain, headache, and diarrhea. The Authors observed no opportunistic infections and no differences in the occurrence of infections requiring antibiotics, but they did find a higher incidence of pneumonia in infliximab-treated subjects and, although not statistically significant, more cases of cancer.

A recent small study population in cachectic patients with COPD revealed no change in levels of inflammatory markers in exhaled breath condensate (EBC) and minor effects on systemic inflammatory markers following treatment with

infliximab (5 mg/kg) administered to patients at weeks 0, 2 and 6 and evaluated at weeks 8 and 12, and followed through week 26 [101].

Nonetheless, an observational study conducted to evaluate the effectiveness of TNF- α antagonists in preventing COPD hospitalisations in a cohort of patients diagnosed with both rheumatoid arthritis and COPD identified from a health claims database, demonstrated that TNF- α inhibitors were associated with a reduction in the rate of COPD hospitalisation among patients with COPD receiving these agents to treat their rheumatoid arthritis [102]. This effect, however, was due exclusively to a reduction of 50% in the rate of COPD hospitalisation with etanercept. The other TNF- α inhibitor under study, namely infliximab, did not reduce the risk of COPD hospitalisation.

What can we learn from trials

The studies reported in literature indicate that TNF- α inhibitors are effective in a relatively small subgroup of patients with severe asthma, possibly defined by an increased TNF axis [103], but they seem to be ineffective in COPD, although in the study of Rennard et al. [100], the 6-MWT *post hoc* analyses suggested that cachectic individuals, as well as younger individuals, derived relatively greater benefit from treatment with infliximab. The discrepancy in the results obtained in two inflammatory diseases such as asthma and COPD have not been entirely unexpected. In fact, targeting of TNF- α is extremely effective in some inflammatory conditions (such as rheumatoid arthritis, inflammatory bowel disease and psoriasis), but has proved to be a less useful target in other conditions in which efficacy was expected, such as vasculitis, but even within rheumatoid arthritis, about one-third of patients show little response to this treatment for reasons that are still poorly understood.

Barnes has suggested that the failure of anti-TNF therapy is more likely a result of the fact that COPD is a highly complex inflammatory disease in which many other cytokines and mediators are involved, and that blocking a single cytokine does not have any effect, as other cytokines such as interleukin (IL)-1 β and IL-6 may play a similar role [104]. In the recent study of Sapey et al. [105] that aimed to know the relationships between this cytokine and its

antagonists in disease compared with healthy controls, TNF- α , sTNF-R1, and sTNF-R2 concentrations were not raised and TNF- α did not correlate with markers of disease suggesting that TNF- α is unlikely to be highly active in stable COPD. Nonetheless, it remains possible that TNF- α is quiescent when COPD is stable and only becomes biologically active (with increased concentrations) during exacerbations [106]. Indeed, the substantial increase in TNF- α production following LPS exposure and *in vivo* exacerbation studies suggests that the role of TNF- α may be more predominant in acute inflammatory episodes rather than in the chronic disease process [80]. Therefore, we completely agree with the opinion future studies may be better focused on the roles of anti-TNF therapies in preventing or modifying the severity of acute exacerbations. In any case, it must be mentioned that there is evidence of a subset of patients with polymorphisms of the TNF- α gene (that influence gene expression) who have an increased severity of COPD [107] or a mucus producing phenotype [108].

Although there have been no head-to-head trials, the literature seems to indicate that etanercept might be more effective than infliximab in asthma and COPD. Intriguingly, infliximab demonstrates clinical benefit in Crohn's disease whereas etanercept is ineffective. It is also interesting to note that infliximab appears to be less efficacious in smokers compared to non-smokers who suffer from Crohn's disease [109]. One might, therefore, speculate that, while the two drugs share a common therapeutic target, they might also differ in some aspects of their mode of action.

Although both infliximab and etanercept are potent neutralizers of TNF bioactivity, there are fundamental differences in their molecular structures, their binding specificities, and the manner in which they neutralize TNF. Infliximab, by virtue of being IgG1 antibodies, can activate complement and bind Fc receptor and it also can bind both monomeric and trimeric sTNF and tmTNF, whereas etanercept only binds TNF trimers and interacts with tmTNF with reduced avidity, compared with that of infliximab [82, 110-112].

Furthermore, infliximab forms stable complexes with soluble TNF- α , whereas etanercept tends to form relatively unstable complexes, allowing dissociation of

TNF- α and the potential to form a reservoir for binding TNF [110]. Infliximab, therefore, completely neutralizes TNF bioactivity, whereas freely diffusing etanercept might be considered to redistribute bioavailable TNF from sites of production to sites of lower concentration.

Another difference between etanercept and infliximab is the ability of etanercept to neutralize lymphotoxin, a property that is shared by its parent receptor TNF-R2 [110, 113]. Lymphotoxin A is involved in the normal development of lymphoid tissue and also acts as an inducer of the inflammatory response [114]. A further important consequence of the structural differences between these drugs is the fact that infliximab, but not etanercept, fixes complement, and therefore can lyse cells that express TNF- α on their surface [115]. Since TNF- α is initially expressed on the cell surface before being cleaved off by TACE, a wide range of cells, including T cells, may be susceptible. Indeed, preliminary reports appear to confirm this *in vivo*, with a decrease in absolute numbers of peripheral blood CD4+ T cells (which express interferon γ and TNF- α) in patients with ankylosing spondylitis treated with infliximab and a reciprocal increase with etanercept [116, 117]. All these substantial differences might explain why etanercept is more effective than infliximab in asthma and COPD.

Nonetheless Barnes believes that it is unlikely that any different results would be obtained with a different anti-TNF approach using etanercept, as the effects of blocking antibodies and soluble receptors are usually similar in terms of clinical efficacy in other inflammatory diseases [104]. Unquestionably this interpretation is correct. Nonetheless, we are convinced that although the overall results of published studies are perhaps disappointing, there is still good reason to target TNF- α , perhaps in a more carefully selected patient group. TNF- α treatment should therefore not be thrown out, or abandoned.

The true problem is that patients enrolled in the different trials have been considered as subjects of a general population with always the same characteristics since we consider severe asthma and also COPD as homogeneous diseases, and recruited using arbitrary clinical and physiological criteria. On the contrary, severe asthma and COPD are heterogeneous diseases

that have features that occur with different phenotypes remained poorly characterized and little known about the underlying pathobiology contributing to them [118, 119]. Considerable thought should be put into recruitment criteria with the emphasis more on identifying and including the at need population [120]. It is likely that definition of these phenotypes will allow us to study the correct patient population. If we will also be able to choose the right outcome measure we understand which kind of patients can benefit from TNF- α inhibitors.

We believe that the findings present in the literature require such an approach. Otherwise we could not consider a therapeutic option that in a well-identified group of patients would meet therapeutic needs not otherwise met. In other words, we could risk to throw the baby out with the bath water.

References

1. Aggarwal BB, Natarajan K. Tumor necrosis factors: developments during the last decade. *Eur Cytokine Netw* 1996;7:93-124
2. Sack M. Tumor necrosis factor- α in cardiovascular biology and the potential role for anti-tumor necrosis factor- α therapy in heart disease. *Pharmacol Ther* 2002;94:1231-5
3. Sarzi-Puttini P, Atzeni F, Shoenfeld Y, et al. TNF- α , rheumatoid arthritis, and heart failure: a rheumatological dilemma. *Autoimmun Rev* 2005;4:153-61
4. Kleyen CE, Griffiths CE. Infliximab for the treatment of psoriasis. *Expert Opin Biol Ther* 2006;6:797-805
5. Danese S, Semeraro S, Armuzzi A, et al. Biological therapies for inflammatory bowel disease: research drives clinics. *Mini Rev Med Chem* 2006;6:771-84
6. Cacquevel M, Lebeurrier N, Cheenne S, et al. Cytokines in neuroinflammation and Alzheimer's disease. *Curr Drug Targets* 2004;5:529-34
7. Aggarwal BB, Samanta A, Feldmann M. TNF α . In *Cytokine Reference* Edited by: Oppenheim J. London: Academic Press; 2000:414-34
8. MacEwan DJ. TNF receptor subtype signalling: differences and cellular consequences. *Cell Signal* 2002;14:477-92
9. Gearing AJ, Beckett P, Christodoulou M, et al. Processing of tumour necrosis factor- α precursor by metalloproteinases. *Nature* 1994;370:555-7

10. Smookler DS, Mohammed FF, Kassiri Z, et al. Tissue inhibitor of metalloproteinase 3 regulates TNF-dependent systemic inflammation. *J Immunol* 2006;176:721-5
11. Aggarwal BB, Samanta A, Feldmann M. TNF Receptors. In *Cytokine Reference* Edited by: Oppenheim JJ. London: Academic Press; 2000:1620-32
12. Grell M, Wajant H, Zimmermann G, et al. The type 1 receptor (CD120a) is the high-affinity receptor for soluble tumor necrosis factor. *Proc Natl Acad Sci USA* 1998;95:570-5
13. Liu ZG Molecular mechanism of TNF signaling and beyond. *Cell Res* 2005;15:24-7
14. Li H, Lin X Positive and negative signaling components involved in TNF α -induced NF- κ B activation. *Cytokine* 2008;41:1-8
15. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer* 2004;4:1-22
16. Kim EY, Teh HS. Critical role of TNF receptor type-2 (p75) as a costimulator for IL-2 induction and T cell survival: a functional link to CD28. *J Immunol* 2004;173:4500-9
17. Turner SJ, La Gruta NL, Stambas J, et al. Differential tumor necrosis factor receptor 2-mediated editing of virus-specific CD8⁺ effector T cells. *Proc Natl Acad Sci USA* 2004;101:3545-50
18. Kim EY, Priatel JJ, Teh SJ, et al. 2006. TNF receptor type 2 (p75) functions as a costimulator for antigen-driven T cell responses in vivo. *J Immunol* 2006;176:1026-35
19. Theiss AL, Simmons JG, Jobin C, et al. Tumor necrosis factor (TNF) α increases collagen accumulation and proliferation in intestinal myofibroblasts via TNF receptor 2. *J Biol Chem* 2005;280:36099-109
20. Zhao X, Mohaupt M, Jiang J, et al. Tumor necrosis factor receptor 2-mediated tumor suppression is nitric oxide dependent and involves angiostasis. *Cancer Res* 2007;67:4443-50
21. Aderka D, Engelmann H, Maor Y, et al. Stabilization of the bioactivity of tumor necrosis factor by its soluble receptors. *J Exp Med* 1992;175:323-9
22. Beutler BA. The role of tumor necrosis factor in health and disease, *J Rheumatol* 1999;57:16-21
23. Bradley JR. TNF-mediated inflammatory disease. *J Pathol* 2008;214:149-60
24. Shen HM, Pervaiz S. TNF receptor superfamily-induced cell death: redox-dependent execution. *FASEB J* 2006;20:1589-98
25. Vlahopoulos S, Boldogh I, Casola A, et al. Nuclear factor- κ B-dependent induction of interleukin-8 gene expression by tumor necrosis factor α : evidence for an antioxidant sensitive activating pathway distinct from nuclear translocation. *Blood* 1999;94:1878-89
26. Chen G, Goeddel DV. TNF-R1 signaling: a beautiful pathway. *Science* 2002;296:1634-5
27. Mukaida N, Mahe Y, Matsushima K. Cooperative interaction of NF- κ B and cis-regulatory enhancer binding protein-like factor binding elements in

- activating the IL-8 gene by pro-inflammatory cytokines. *J Biol Chem* 1990;265:21128-32
28. Russo MP, Bennett BL, Manning AM, et al. Differential requirement for NF- κ B-inducing kinase in the induction of NF- κ B by IL-1 β , TNF- α , and Fas. *Am J Physiol Cell Physiol* 2002;283:C347-57
 29. Witkamp R, Monshouwer M. Signal transduction in inflammatory processes, current and future therapeutic targets: a mini review. *Vet Q* 2000;22:11-6
 30. Mukhopadhyay S, Hoidal JR, Mukherjee TK. Role of TNF α in pulmonary pathophysiology. *Respir Res* 2006;7:125
 31. Kips JC, Tavernier JH, Joos GF, et al. The potential role of tumour necrosis factor α in asthma. *Clin Exp Allergy* 1993;23:247-50
 32. Gosset P, Tsicopoulos A, Wallaert B, et al. Increased secretion of tumor necrosis factor α and interleukin-6 by alveolar macrophages consecutive to the development of the late asthmatic reaction. *J Allergy Clin Immunol* 1991;561:561-71
 33. Gosset P, Tsicopoulos A, Wallaert B, et al. Tumor necrosis factor α and interleukin-6 production by human mononuclear phagocytes from allergic asthmatics after IgE-dependent stimulation. *Am Rev Respir Dis* 1992;146:768-74
 34. Cembrzynska-Nowak M, Szklarz E, Inglot A, et al. Elevated release of tumor necrosis factor- α and interferon- γ by bronchoalveolar leukocytes from patients with bronchial asthma. *Am Rev Respir Dis* 1993;147:291-5
 35. Ying S, Robinson D, Varney V, et al. TNF α mRNA expression in allergic inflammation. *Clin Exp Allergy* 1991;21:745-50
 36. Bradding P, Roberts JA, Britten KM, et al. Interleukin-4, -5, and -6 and tumor necrosis factor- α in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. *Am J Respir Cell Mol Biol* 1994;10:471-80
 37. Ackerman V, Marini M, Vittori E, et al. Detection of cytokines and their cellular sources in bronchial biopsy specimens from asthmatic patients. Relationship to atopic status, symptoms, and level of airway hyperresponsiveness. *Chest* 1994;105:687-96
 38. Keatings VM, Jatakanon A, Worsdell YM, et al. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997;155:542-8
 39. Obase Y, Shimoda T, Mitsuta K, et al. Correlation between airway hyperresponsiveness and airway inflammation in a young adult population: eosinophil, ECP, and cytokine levels in induced sputum. *Ann Allergy Asthma Immunol* 2001;86:304-10
 40. Lilly C, Nakamura H, Kesselman H, et al. Expression of eotaxin by human lung epithelial cells: induction by cytokines and inhibition by glucocorticoids. *J Clin Invest* 1997;99:1767-73
 41. Harkonen E, Virtanen I, Linnala A, et al. Modulation of fibronectin and tenascin production in human bronchial epithelial cells by inflammatory cytokines in vitro. *Am J Respir Cell Mol Biol* 1995;13:109-15
 42. Levine S, Larivee P, Logun C, et al. Tumor necrosis factor- α induces mucin hypersecretion and MUC-2 gene expression by human airway epithelial cells. *Am J Respir Cell Mol Biol* 1995;12:196-204

43. Tosi MF, Stark JM, Smith CW, et al. Induction of ICAM-1 expression on human airway epithelial cells by inflammatory cytokines: effects on neutrophil-epithelial cell adhesion. *Am J Respir Cell Mol Biol* 1992;7:214-21
44. Aubert JD, Juillerat-Jeanneret L, Leuenberger P. Expression of endothelin-1 in human broncho-epithelial and monocytic cell lines: influence of tumor necrosis factor α and dexamethasone. *Biochem Pharmacol* 1997;53:547-52
45. Salvi S, Semper A, Blomberg A, et al. Interleukin-5 production by human airway epithelial cells. *Am J Respir Cell Mol Biol* 1999;20:984-91
46. Richter M, Cantin AM, Beaulieu C, et al. Zinc chelators inhibit eotaxin, RANTES, and MCP-1 production in stimulated human airway epithelium and fibroblasts. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L719-29
47. Shirasaki H, Kanaizumi E, Watanabe K, et al. Tumor necrosis factor increases MUC1 mRNA in cultured human nasal epithelial cells. *Acta Otolaryngol* 2003;123:524-31
48. Adler KB, Fischer BM, Li H et al. Hypersecretion of mucin in response to inflammatory mediators by guinea pig tracheal epithelial cells in vitro is blocked by inhibition of nitric oxide synthase. *Am J Respir Cell Mol Biol* 1995;13:526-30
49. Song KS, Lee WJ, Chung KC, et al. Interleukin-1 β and tumor necrosis factor- α induce MUC5AC overexpression through a mechanism involving ERK/p38 mitogen-activated protein kinases-MSK1-CREB activation in human airway epithelial cells. *J Biol Chem* 2003;278:23243-50
50. Wu T, Ikezono T, Angus CW, et al. Tumor necrosis factor- α induces the 85-kDa cytosolic phospholipase A2 gene expression in human bronchial epithelial cells. *Biochim Biophys Acta* 1996;1310:175-84
51. Bedard M, McClure CD, Schiller NL, et al. Release of interleukin-8, interleukin-6, and colony stimulating factors by upper airway epithelial cells: implications for cystic fibrosis. *Am J Respir Cell Mol Biol* 1993;9:455-62
52. Smart SJ, Casale TB. TNF- α -induced transendothelial neutrophil migration is IL-8 dependent. *Am J Physiol* 1994;266:L238-45
53. Smart S, Casale T. Pulmonary epithelial cells facilitate TNF α -induced neutrophil chemotaxis. A role for cytokine networking. *J Immunol* 1994;152:4087-94
54. Godding V, Stark J, Sedgwick J, et al. Adhesion of activated eosinophils to respiratory epithelial cells is enhanced by tumor necrosis factor- α and interleukin-1 β . *Am J Respir Cell Mol Biol* 1995;13:555-62
55. Casale T, Costa J, Galli S. TNF α is important in human lung allergic reactions. *Am J Respir Cell Mol Biol* 1996;15:35-44
56. Thomas PS, Yates DH, Barnes PJ. Tumor necrosis factor- α increases airway responsiveness and sputum neutrophilia in normal human subjects. *Am J Respir Crit Care Med* 1995;152:76-80
57. Nie Z, Jacoby DB, Fryer AD. Etanercept prevents airway hyperresponsiveness by protecting neuronal M2 muscarinic receptors in antigen-challenged guinea pigs. *Br J Pharmacol* 2009;156:201-10

58. Fryer AD, Jacoby DB. Muscarinic receptors and control of airway smooth muscle. *Am J Respir Crit Care Med* 1998;158:S154-60
59. Aoki T, Hirota T, Tamari M, et al. An association between asthma and TNF-308G/A polymorphism: meta-analysis. *J Hum Genet* 2006;51:677-85
60. Chung A, Wang RD, Tai H, et al. Tumor necrosis factor- α drives 70% of cigarette smoke-induced emphysema in the mouse. *Am J Respir Crit Care Med* 2004;170:492-8
61. Chung KF. Cytokines in chronic obstructive pulmonary disease. *Eur Respir J* 2001;34:50s-9s
62. Lundblad LK, Thompson-Figueroa J, Leclair T, et al. Tumour necrosis factor- α overexpression in lung disease: a single cause behind a complex phenotype. *Am J Respir Crit Care Med* 2005;171:1363-70
63. Vuillemenot BR, Rodriguez JF, Hoyle GW. Lymphoid tissue and emphysema in the lungs of transgenic mice inducibly expressing tumour necrosis factor- α . *Am J Respir Cell Mol Biol* 2004;30:438-48
64. Rahman I, Gilmour PS, Jimenez LA, et al. Oxidative stress and TNF- α induce histone acetylation and NF- κ B/AP-1 activation in alveolar epithelial cells: potential mechanism in gene transcription in lung inflammation. *Mol Cell Biochem* 2002;234–235:239-48
65. Mackay F, Loetscher H, Stueber D, et al. Tumor necrosis factor α (TNF- α)-induced cell adhesion to human endothelial cells is under dominant control of one TNF receptor type, TNF-R55. *J Exp Med* 1993;177:1277-86
66. Di Francia M, Barbier D, Mege JL, et al. Tumor necrosis factor α levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;150:1453-5
67. Keatings VM, Barnes NC. Comparison of inflammatory cytokines in chronic obstructive pulmonary disease, asthma and controls. *Eur Respir Rev* 1997;7:146-50
68. Mueller R, Chanez P, Campbell AM, et al. Different cytokine patterns in bronchial biopsies in asthma and chronic bronchitis. *Respir Med* 1996;90:79-85
69. Keatings VM, Collins PD, Scott DM, et al. Differences in interleukin-8 and tumor necrosis factor- α in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am J Respir Crit Care Med* 1996;153:530-4
70. Daldegan MB, Teixeira MM, Talvani A. Concentration of CCL11, CXCL8 and TNF- α in sputum and plasma of patients undergoing asthma or chronic obstructive pulmonary disease exacerbation. *Braz J Med Biol Res* 2005;38:1359-65
71. Hacievliyagil SS, Gunen H, Mutlu LC, et al. Association between cytokines in induced sputum and severity of chronic obstructive pulmonary disease. *Respir Med* 2006;100:846-54
72. de Godoy I, Donahoe M, Calhoun WJ, et al. Elevated TNF α production by peripheral monocytes of weight losing COPD patients. *Am J Respir Crit Care Med* 1996;153:633-7
73. Sapey E, Bayley DL, Ahmad A, et al. Inter-relationships between inflammatory markers in stable COPD patients with bronchitis: the intra and inter patient variability. *Thorax* 2008;63:493-9

74. Sakao S, Tatsumi K, Igari H, et al. Association of tumor necrosis factor α gene promoter polymorphism with the presence of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:420-2
75. Sakao S, Tatsumi K, Igari H, et al. Association of tumor necrosis factor- α gene promoter polymorphism with low attenuation areas on high-resolution CT in patients with COPD. *Chest* 2002;122:416-20
76. Keatings V, Cave S, Henry M, et al. A Polymorphism in the tumor necrosis factor- α gene promoter region may predispose to a poor prognosis in COPD. *Chest* 2000;118:971-5
77. Sun G, Stacey MA, Vittori E, et al. Cellular and molecular characteristics of inflammation in chronic bronchitis. *Eur J Clin Invest* 1998;28:364-72
78. Aaron SD, Angel JB, Lunau M, et al. Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:349-55
79. Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;60:1012-18
80. Hackett TL, Holloway R, Holgate ST, et al. Dynamics of pro-inflammatory and anti-inflammatory cytokine release during acute inflammation in chronic obstructive pulmonary disease: an *ex vivo* study. *Respir Res* 2008;9:47
81. Jackson JM. TNF- α inhibitors. *Dermatol Ther* 2007;20:251-64
82. Tracey D, Klareskog L, Sasso EH, et al. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review *Pharmacol Ther* 2008;117:244-79
83. Hanauer SB. Safety of infliximab in clinical trials. *Aliment Pharmacol Ther* 1999;13:16-22
84. Nakelchik M, Mangino JE. Reactivation of histoplasmosis after treatment with infliximab. *Am J Med* 2002;112:78
85. Weisman MH. What are the risks of biologic therapy in rheumatoid arthritis? An update on safety. *J Rheumatol Suppl* 2002;65:33-8
86. Zganiacz A, Santosuosso M, Wang J et al. TNF- α is a critical negative regulator of type 1 immune activation during intracellular bacterial infection. *J Clin Invest* 2004;113:401-13
87. Callen JP. Complications and adverse reactions in the use of newer biologic agents. *Semin Cutan Med Surg* 2007;26:6-14
88. Dahlstrom U. Frequent noncardiac comorbidities in patients with chronic heart failure. *Eur J Heart Fail* 2005;7:309-16
89. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18, 572 patients. *Arthritis Rheum* 2004;50:1740-51
90. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275-85
91. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor α therapy for inflammatory arthritides. *Arthritis Rheum* 2001;44:2862-9

92. Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;60:1012-8
93. Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of tumor necrosis factor α in refractory asthma. *N Engl J Med* 2006;354:697-708
94. Rouhani FN, Meitin CA, Kaler M, et al. Effect of tumor necrosis factor antagonism on allergen-mediated asthmatic airway inflammation. *Respir Med* 2005;99:1175-82
95. Morjaria JB, Chauhan AJ, Babu KS, et al. The role of a soluble TNF α receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. *Thorax* 2008;63:584-91
96. Erin EM, Leaker BR, Nicholson GC, et al. The effects of a monoclonal antibody directed against tumor necrosis factor- α in asthma. *Am J Respir Crit Care Med* 2006;174:753-62
97. Wenzel SE, Barnes PJ, Bleecker ER, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor α blockade in severe persistent asthma. *Am J Respir Crit Care Med* 2009;179:549-58
98. Meyers DA, Hawkins GA, Wenzel SA, et al. Pharmacogenetic identification of increased responsiveness in severe asthma with anti-TNF (golimumab) therapy [abstract]. *J Allergy Clin Immunol* 2008;121:798
99. van der Vaart H, Koeter GH, Postma DS, et al. First study of infliximab treatment in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:465-9
100. Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate-to-severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:926-34
101. Dentener MA, Creutzberg EC, Pennings H-J, et al. Effect of infliximab on local and systemic inflammation in chronic obstructive pulmonary disease: a pilot study. *Respiration* 2008;76:275-82
102. Suissa S, Ernst P, Hudson M. TNF- α antagonists and the prevention of hospitalisation for chronic obstructive pulmonary disease. *Pulm Pharmacol Ther* 2008;21:234-38
103. Berry M, Brightling C, Pavord I, et al. TNF- α in asthma. *Curr Opin Pharmacol* 2007;7:279-82
104. Barnes PJ. Unexpected failure of anti-tumor necrosis factor therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:866-7
105. Sapey E, Ahmad A, Bayley D, et al. Imbalances between interleukin-1 and tumor necrosis factor agonists and antagonists in stable COPD. *J Clin Immunol* 2009;29:508-16
106. Dal Negro RW, Micheletto C, Tognella S, et al. A two stage logistic model based on the measurement of pro-inflammatory cytokines in bronchial secretions for assessing bacterial, viral and non-infectious origin of COPD exacerbations. *COPD* 2005;2:7-16
107. Gingo MR, Silveira LJ, Miller YE, et al. Tumour necrosis factor polymorphisms are associated with COPD. *Eur Respir J* 2008;31:1005-12

108. Wood AM, Simmonds MJ, Bayley DL, et al. The TNF α gene relates to clinical phenotype in α -1-antitrypsin deficiency. *Respir Res* 2008;9:52
109. Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? *Clin Infect Dis* 2005;41:S199-203
110. Scallon B, Cai A, Solowski N, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther* 2002;301:418-26
111. Mitoma H, Horiuchi T, Tsukamoto H. Binding activities of infliximab and etanercept to transmembrane tumor necrosis factor- α . *Gastroenterology* 2004;126:934-5
112. Mitoma H, Horiuchi T, Hatta N, et al. Infliximab induces potent anti-inflammatory responses by outside-to-inside signals through transmembrane TNF- α . *Gastroenterology* 2005;128:376-92
113. Gudbrandsdottir S, Larsen R, Sorensen LK, et al. TNF and LT binding capacities in the plasma of arthritis patients: effect of etanercept treatment in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2004;22:118-24
114. Pfeffer K. Biological functions of tumor necrosis factor cytokines and their receptors. *Cytokine Growth Factor Rev* 2003;14:185-91
115. Scallon BJ, Moore MA, Trinh H, et al. Chimeric anti-TNF- α monoclonal antibody cA2 binds recombinant transmembrane TNF- α and activates immune effector functions. *Cytokine* 1995;7:251-9
116. Zou J, Rudwaleit M, Brandt J, et al. Up regulation of the production of tumour necrosis factor α and interferon γ by T cells in ankylosing spondylitis during treatment with etanercept. *Ann Rheum Dis* 2003;62:561-4
117. Gratacós J, Collado A, Filella X, et al. Serum cytokines (IL-6, TNF- α , IL-1 β and IFN- γ) in ankylosing spondylitis: a close correlation between serum IL-6 and disease activity and severity. *Br J Rheumatol* 1994;33:927-31
118. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;368:804-13
119. Friedlander AL, Lynch D, Dyar LA, et al. Phenotypes of chronic obstructive pulmonary disease. *COPD* 2007;4:355-84
120. Berry MA, Pavord ID. Antagonism of tumour necrosis factor α in refractory asthma. *Thorax* 2008;63:571-2

Figure 1 - Putative role of TNF- α in the pathogenesis of asthma and COPD.

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Table 1 - Summary of studies of TNF- α inhibitors in asthma

Study	No patients and asthma severity	Design	Treatment	Outcomes	Results
Howarth et al. [92]	17 patients with severe asthma	Open label uncontrolled	Etanercept 12 wk	1° ACQ 2° FEV ₁ , FVC, and morning and evening PEF, BHR	Improvement ACQ, FEV ₁ , FVC, morning and evening PEF, and BHR
Berry et al. [93]	10 patients with refractory asthma, and 10 patients with mild-to-moderate asthma	Randomized placebo controlled crossover	Etanercept 10 wk	1° BHR and AQLQ 2° FEV ₁ , eNO, sputum cell counts	Improvement AQLQ, FEV ₁ , BHR ↓ sputum histamine
Morjaria et al. [95]	39 patients with severe corticosteroid refractory asthma	Randomized placebo controlled parallel group	Etanercept 12 wk	1° AQLQ 2° ACQ, FEV ₁ , PEF, BHR, exacerbations	No benefit compared with placebo
Rouhani et al. [94]	26 patients with mild-to-moderate allergic asthma/inhaled β_2 -agonists only	Segmental allergen challenge	Etanercept 2 wk	Markers of inflammation BHR	Increased TNF-R2 in BAL, no change in BHR
Erin et al. [96]	38 patients with moderate asthma/inhaled corticosteroids only	Randomized placebo controlled parallel group	Infliximab 6 wk	1° morning PEF 2° FEV ₁ , exacerbations, sputum markers	No change in morning PEF ↓ PEF variability ↓ exacerbations
Wenzel et al. [97]	231 patients with severe and uncontrolled asthma/high-dose inhaled corticosteroids and long-acting β_2 -agonists	Randomized, double-blind, placebo-controlled	Golimumab 52 wk	1° FEV ₁ , exacerbations 2° AQLQ, rescue medication	No benefit compared with placebo

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BHR, bronchial hyperresponsiveness; eNO, exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

Table 2 - Summary of studies of TNF- α inhibitors in COPD

Study	No patients and COPD severity	Design	Treatment	Outcomes	Results
van der Vaart et al. [99]	14 current smokers with mild-to-moderate COPD	Randomized, double-blind, placebo-controlled	Infliximab 6 wk	Sputum samples, spirometry, diffusion capacity, eNO, REE, CCQ, SGRQ, BHR	No benefit compared with placebo
Rennard et al. [100]	157 patients with moderate to severe COPD	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Infliximab 24 wk	1° CRQ 2° FEV ₁ , 6MWD, SF-36, TDI, exacerbations	No change in CRQ, FEV ₁ , 6MWD, SF-36, TDI, exacerbations
Dentener et al. [101]	16 patients with moderate to severe COPD	Randomized, double-blind placebo-controlled	Infliximab 6 wk	Levels of inflammatory mediators in EBC and in blood	No effect in local inflammation and minor effects on systemic inflammation.
Suissa et al. [102]	15,771 subjects with both rheumatoid arthritis and COPD	Observational study	Infliximab Etanercept	First occurrence of a hospitalisation for COPD during follow-up	Reduction in the rate of COPD hospitalisation with etanercept but not with infliximab

BHR, bronchial hyperresponsiveness; CCQ, Clinical COPD Questionnaire; CRQ, Chronic Respiratory Questionnaire; EBC, exhaled breath condensate; eNO, exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; REE, resting energy expenditure; SGRQ, St. George Respiratory Questionnaire; SF-36, Short Form-36; TDI, transition dyspnea index; 6MWD, 6-minute-walk distance

