

Expert Opinion

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Golimumab for severe asthma

Evaluation: 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(7):549-58

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Background: In severe asthma anti-TNF- α therapies might be effective in improving disease control based on preclinical results and on clinical short-term data. However, the long-term efficacy and safety is not known. **Objective:** To discuss the data on golimumab, an anti-TNF- α monoclonal antibody currently used in various forms of arthritis, evaluated as an add-on anti-inflammatory therapy in severe asthma. **Methods/results:** Critical appraisal of the efficacy and safety clinical data. Golimumab was not found to be generally efficacious and demonstrated an unfavourable risk-benefit ratio, but in some asthma subsets its better therapeutic effects might support its use provided the long-term safety is acceptable. **Conclusions:** Although at first sight the safety and efficacy data of long-term use of golimumab in severe asthma might be unsupportive, in some disease subsets it might be really effective.

Keywords: asthma, efficacy, golimumab, safety, TNF- α

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1. Introduction

Asthma is a disease of the airways that is closely linked to allergy and is increasing in prevalence. Airway inflammation renders them sensitive to various bronchoconstrictive triggers, bronchial hyperresponsiveness (BHR) being a hallmark of the disease and resulting in reversibility of lung function on bronchodilator testing or in variability of lung function. Rescue therapy represented by short-acting bronchodilators is used to relieve bronchospasm whereas inhaled corticosteroids (ICSs) and leukotriene modifiers are usually used as anti-inflammatory therapies, aimed at reducing BHR. These latter therapies alone or in combination are usually effective but sometimes asthma cannot be controlled adequately even if ICSs are replaced with continuous oral corticotherapy. In such patients, other therapies are required in addition or as stand-alone anti-inflammatory treatments based on their potential for blocking various inflammation pathways.

Currently, there are several compounds under investigation for such asthma subsets. One such class is represented by anti-TNF- α therapies, which are widely used currently to treat chronically debilitating diseases such as rheumatoid arthritis or psoriasis.

In asthma the pathogenic role of TNF- α is not well documented but the existing data demonstrate its increased activity in severe asthma in which inflammation of the airways does not show the common pattern for asthma and is less sensitive to corticosteroids [1,2].

Anti-TNF- α therapies such as etanercept (TNF- α receptor blocker) or infliximab (monoclonal antibody against TNF- α) were assessed previously in preclinical models and in small sample clinical trials in severe asthma [1,3,4]. The data derived from such studies supported the further evaluation of these therapies in the clinical setting of refractory asthma to usual maximal maintenance therapy, given the long-term efficacy and safety were not known [5].

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This randomised placebo-controlled study discussed hereby evaluated golimumab, another anti-TNF- α monoclonal antibody already approved as once monthly therapy in various forms of arthritis in subjects with severe asthma suboptimally controlled despite maximal maintenance therapy [6].

2. Methods and results

Included were adult patients with severe asthma of ≥ 1 year labelled as uncontrolled if having asthma symptoms on at least one-third of the days for ≥ 3 months before study screening, despite continuous therapy with high-dose ICSs (fluticasone $\geq 1,000$ μ g or equivalent) and long-acting beta-2 agonists (LABA) or oral corticosteroids, or if showing two or more asthma exacerbations within the previous year. The eligible patients were supposed to have quit smoking for ≥ 1 year and to have smoked < 10 pack-years. After a 2-week run-in phase in which ICS and LABA were standardised, patients were randomised to receive matching placebo, or golimumab 50, 100, 150 or 200 mg s.c. every 4 weeks for 52 weeks. During the first 25 weeks patients were maintained on their doses of inhaled or oral corticosteroids set up during the run-in period and thereafter these were attempted to be tapered according to a pre-specified protocol. Co-primary endpoints were change in prebronchodilator FEV1% predicted (forced expiratory volume in 1 sec % of predicted value), assessed every 4 weeks from baseline through week 64 and finally at week 76, and the number of asthma exacerbations by week 24. Secondary endpoints included: change from baseline in health-related quality of life (HRQoL) scores, rescue medication use and domiciliary morning peak expiratory flow rate (PEFR). Patients were followed up for 76 weeks. Safety was evaluated during each study visit. A total of 309 patients (78 to placebo, 77 – 50 mg arm, 76 – 100 mg arm, 78 – 200 mg arm) were randomised and efficacy and safety data were analysed preliminarily at 24 weeks. In terms of efficacy there were no significant improvements in all-golimumab versus placebo or in terms of mean number of severe asthma exacerbations, but in the combined 100 and 200 mg arms there was a trend of increased exacerbation free time (hazard ration, HR, 0.63, confidence interval, CI, 0.377 – 1.060, $p = 0.08$). Health-related quality of life scores demonstrated a clinically significant improvement in all study arms and no significant therapeutic effect was detected. No significant therapeutic effect was demonstrated with other endpoints.

Safety data reviewed at week 24 yielded an unfavourable risk–benefit profile for golimumab and prompted its discontinuation. This occurred when $\sim 50\%$ of subjects remaining in the study had completed the week 52 visit. The most commonly reported adverse events were asthma exacerbation, 91% in placebo and 89.2% in the golimumab group, infections occurred at a similar rate, with respiratory tract infections being the most common. The rate of serious adverse events was similar between groups as well, with asthma exacerbation

and pneumonia being reported most frequently. Increased incidence of infections and malignancies was reported in golimumab groups.

Pre-specified subgroup analysis demonstrated a trend towards a more significant therapeutic effect on exacerbations in golimumab groups if the median age was ≥ 49 years, or if patients had no more than a hospitalisation or an emergency room visit within 1 year before screening or the baseline median FEV1%pred was lower or age of disease onset was ≥ 12 years. *Post-hoc* analysis showed that patients with greater FEV1%pred reversibility and who had been treated with higher doses of golimumab were significantly less likely to experience disease exacerbations through week 24 (odds ratio 20.5 versus 4.4, $p = 0.014$), and these combined treatment subsets had a significantly lower risk of asthma exacerbations ($p = 0.005$). FEV1 reversibility was an independent predictor for golimumab therapeutic effect on asthma exacerbations.

3. Discussion

This study shows that apparently long-term treatment with golimumab added to usual maintenance therapy in patients with severe asthma uncontrolled with high doses of ICS or with permanent oral corticosteroids (OC) has no significant efficacy irrespective of the dose used: golimumab did not improve lung function, asthma exacerbations and only clinically improved the HRQoL. Furthermore, the preliminary safety analysis at 24 weeks yielded an unfavourable risk–benefit profile for golimumab, with higher rates of serious adverse events (including serious infections) occurring in patients receiving it and prompting its discontinuation for the remaining follow-up period.

Subset analyses, however, demonstrated that certain subsets would really benefit from long-term therapy with anti-TNF- α therapies: the most interesting and practical results are represented by the higher efficacy in subjects in whom lung function shows higher reversibility, in whom asthma had a later onset (with higher risk of non-atopic asthma) and in those with (probably chronic) sinusitis.

An increased incidence of malignancies was also reported in patients taking golimumab; however, a closer analysis of them does not support the use of golimumab as a causal factor but rather as a risk factor of increased tumoral aggressivity in elderly subjects.

The main limitation of this study is the fact that systemic and/or airway-related TNF- α activity was not considered as an outcome measure. This would have further helped with identification of asthma subsets who would benefit maximally from such a therapy.

4. Expert opinion and conclusions

This study shows that long-term therapy with golimumab, an anti-TNF α monoclonal antibody in severe asthma partially responsive/unresponsive to inhaled or oral corticosteroids, is

not universally effective and might be associated with an increased risk of infections. However, the clinical picture is not as dramatic as it might seem if only these data are taken into account: despite the unfavourable risk–benefit ratio including the increased incidence of malignancies in the elderly subjects, golimumab might be a potential therapy in some asthma subsets such as those in which oral and/or inhaled corticosteroids are not effective enough in achieving an optimal disease control. Given such results it might be assumed that golimumab as well as other anti-TNF- α therapies might be effective in specific asthma subsets in which the targeted mediator plays a more prominent role. However such ‘TNF- α ’ asthma phenotypes are not well-known and characterised, as the pathogenic role of TNF- α itself is not documented in detail. The identification of such disease phenotypes is very complex and difficult and the first step can be represented as in the case of the discussed study by the detection of subjects with uncontrolled asthma despite maximal anti-inflammatory and bronchodilator maintenance therapy being correctly administered. Interestingly enough and unlike in other cases where the pathogenesis is first deciphered and then targeted therapeutically, in this study, apart from general results that are not encouraging at all in terms of efficacy and, more importantly, safety, it is the therapy itself that helps *per primam* with the identification of these disease subsets in which anti-TNF- α would be potentially effective on a long-term

basis: corticosteroid-resistant airways inflammation, asthma with upper airways inflammation (perhaps even aspirin sensitive asthma) and non-atopic asthma.

In such subsets future attempts to document the inflammation pattern of airways, and the pathogenic role of TNF- α would provide a sounder scientific rationale for the use of anti-TNF- α therapies more appropriately in the asthma setting.

Anti-TNF- α therapies are traditionally associated with higher risks of malignancies and serious infections in other diseases such as rheumatoid arthritis or psoriasis. The same safety concerns seem to be the case with asthma too. However, the airway inflammation in asthma is not always as aggressive as in the other two diseases and, consequently, the drug dosage in terms of dose and rhythm of administration might have to be re-evaluated. This might result in a more acceptable risk-benefit profile and it might make the use of such therapies in asthma less challenging.

Therefore, the consideration of anti-TNF- α therapies in asthma must not be abandoned only based on the existing efficacy and safety data and efforts to identify the most appropriate population and dosages would be most helpful.

Declaration of interest

SA Antoniu received lecture fees and congress attendance sponsorship from Merck Sharp & Dohme, the company that manufactures singulair, which is used to treat asthma.

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