NEW EVIDENCE AND NOVEL THERAPIES FOR SEVERE ASTHMA MANAGEMENT

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ABSTRACT

The 2014 European Respiratory Society International Congress, held last month from 6th-10th September in Munich, Germany, provided a platform for key opinion leaders in the field of asthma management to disseminate new clinical data and recent developments. Despite the use of high-dose inhaled corticosteroids and long-acting β_2 agonists, a proportion of patients still have uncontrolled disease and are at risk of exacerbation and hospitalisations, thus requiring the use of intermittent or continuous oral corticosteroid therapy. In severe uncontrolled asthma, exacerbations can be potentially life-threatening, and are the main cause for morbidity and mortality in asthma patients, necessitating considerable healthcare resource utilisation. Consequently, there remains an unmet need for newer therapies to manage asthma in several patient subsets, for which current therapeutic options do not yield adequate benefits and outcomes.

Keywords: Asthma, omalizumab, QGE031, ligelizumab, reslizumab, mepolizumab, QAV680, QMF149, QAW039, fevipiprant.

INTRODUCTION

The 2014 European Respiratory Society International Congress, held last month from 6th-10th September in Munich, Germany, provided a platform for key opinion leaders in the field of asthma management to disseminate new clinical data and recent developments. Asthma is a common chronic inflammatory disease affecting >300 million people worldwide,[1] and is associated with a considerable economic burden and impaired quality of life (QoL).[2] The most prevalent form of asthma is allergic asthma, accounting for two-thirds of the patient population.[3-5] Despite the use of high-dose inhaled corticosteroids (ICS) and long-acting β_2 agonists (LABAs), a proportion of patients still have uncontrolled disease, and are at risk of exacerbation and hospitalisations,[6-8] thus requiring the use of intermittent or continuous oral corticosteroid (OCS) therapy. In severe uncontrolled asthma, exacerbations can be potentially life-threatening and are the main cause for morbidity and mortality, necessitating considerable healthcare resources utilisation (HCRU).[9-11] Consequently, there remains an unmet need for newer therapies to manage asthma in several patient subsets, for which current therapeutic options do not yield adequate benefits and outcomes.[12] This review will summarise newly presented preclinical and clinical data at ERS 2014, providing further information on the efficacy and safety of new and emerging therapies for asthma.

NEW EVIDENCE ON QMF149 (INDACATEROL ACETATE/ MOMETASONE FUROATE)

QMF149 is an investigational once-daily (OD) inhaled bronchodilator (BD) fixed-dose combination (FDC) of indacaterol acetate (IND), a LABA, and mometasone furoate (MOM), an ICS, for the maintenance and treatment of asthma and chronic obstructive pulmonary disease (both compounds are already approved as monotherapeutic modalities). The FDC is delivered via the low-resistance Breezhaler® device.

New Clinical Data on the Efficacy and Safety of Indacaterol

In a 12-week multicentre, randomised, double-blind, placebo-controlled, parallel-group study[13] aiming to support the dose selection of IND for QMF149 in asthma, Beier et al.[13] assessed the effects of OD IND 150 µg and 75 µg compared with placebo in a cohort of 335 patients with persistent asthma, randomised (1:1:1) to one of these three treatment arms. The main endpoint was trough forced expiratory volume in 1 second ($tFEV_1$) at 12 weeks. The IND 150 µg OD and IND 75 µg OD treatment arms demonstrated statistically significant (106 ml, $p<0.002$ and 80ml, $p<0.019$) improvements in $tFEV_1$ compared with placebo after 12 weeks of therapy. From day 2 and onwards, for all time points, IND 150 µg OD was statistically superior to IND 75 µg OD (67 ml, $p=0.018$). However, the statistical power of the study was not sufficient to establish a statistically significant difference between both doses. Other endpoints demonstrated a clinically meaningful superiority of both IND doses over placebo, namely peak expiratory flow rate, asthma control questionnaire (ACQ)-5, and rescue medication use. Overall, a low incidence of adverse events (AEs) was observed in all treatment arms.

New Preclinical Data on the Pharmacokinetics of QMF149

In a randomised, open-label, four-way crossover study,[14] the pharmacokinetics of the components of QMF149, IND, and MOM were assessed, in order to determine the possibility of a pharmacokinetic or a biopharmaceutical interaction between both compounds. Their steady-state pharmacokinetics, as well as safety and tolerability, were evaluated in 64 healthy subjects receiving IND 150 µg, MOM 320 µg, a free combination (IND 150 µg + MOM 320 µg), or a FDC of QMF149 150/320 µg (IND/MOM) OD for 14 days. The results regarding systemic exposure did not reveal any pharmacokinetic interaction between IND and MOM, or any clinically relevant differences, as demonstrated by similar geometric mean ratios between QMF149 and the free combinations or IND and MOM as monotherapy. Likewise, all modalities were well tolerated, which supports the development of QMF149 as an FDC without any need for dose adjustment.

NEW CLINICAL EVIDENCE ON MONOCLONAL ANTIBODY THERAPY FOR ALLERGIC ASTHMA

New Clinical Evidence on Omalizumab

Omalizumab (Xolair®, Roche/Genentech, and Novartis) is a humanised monoclonal antibody that is already approved for the treatment of moderate-to-severe persistent allergic asthma that is not responding to high-dose ICS + LABA therapy. It has demonstrated clinical activity in reducing asthma exacerbations and use of ICS in patients with allergic asthma.[15-19]

New clinical evidence on predictive tools to treatment response

The global evaluation of treatment effectiveness (GETE) at 16 weeks is a tool used in clinical practice to evaluate the clinical response to omalizumab with regards to the control rate of asthma exacerbations in patients with uncontrolled severe asthma.[20] Bousquet et al.[21] presented the results of a study aiming to explore the GETE as a predictive tool and as an accurate predictor of response to omalizumab therapy. In a post-hoc analysis, the authors pooled the data (omalizumab arms, n=947; placebo arms, n=660) from three pivotal clinical trials: INNOVATE,[7] EXALT,[20] and EXTRA,[6] which explored the use of omalizumab in severe allergic asthma patients. In the negative binomial regression model, investigator GETE response was an accurate predictor of asthma exacerbations as well as response to omalizumab versus placebo ($p<0.001$). Annualised exacerbation rates (0.29) were significantly lower in patients responding to the GETE (defined as 'good' or 'excellent' score) and who received omalizumab, as compared with non-responding patients in the omalizumab group (0.67) and patients in the placebo group (responders, 0.46; non-responders, 0.78). In conclusion, these results are consistent with the results presented by Kasujee et al.;[22] GETE assessment at 16 weeks may be an effective predictive tool of response to omalizumab therapy, but further studies are required to confirm these findings.

New clinical evidence on the risk of asthma exacerbations

In a post-hoc analysis,[22] the treatment effects of omalizumab, as evaluated by the GETE, were assessed in moderate-to-severe persistent allergic

asthma, and comprised data (omalizumab arms, n=858; placebo arms, n=901) from five randomised, double-blind, pivotal registration trials, including the INNOVATE and SOLAR studies.[7,16-18,23] The results of this analysis established the role of omalizumab in reducing exacerbation rates for GETE-responders. Omalizumab GETE-responders had significantly lower (-51%) annualised exacerbation rates than placebo responders. These results further support the use of GETE assessment as a predictive tool for response to omalizumab therapy, and may help to select patients who would most benefit from this therapeutic option.

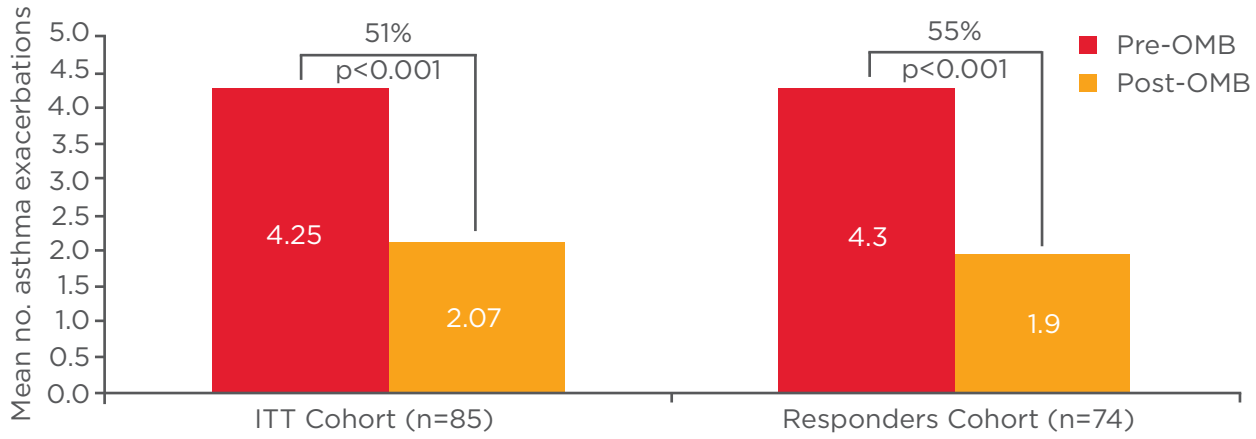

Figure 1: Mean number of asthma exacerbations per patient in the 12 months before and after starting omalizumab (OMB) in the intent-to-treat (ITT) (n=85) and responder (n=74) cohorts.[24]

ITT cohort: patients with 12 months of assessment at interim analysis; Responder cohort: patients classified as responders to treatment by their clinician at 16-week assessment.

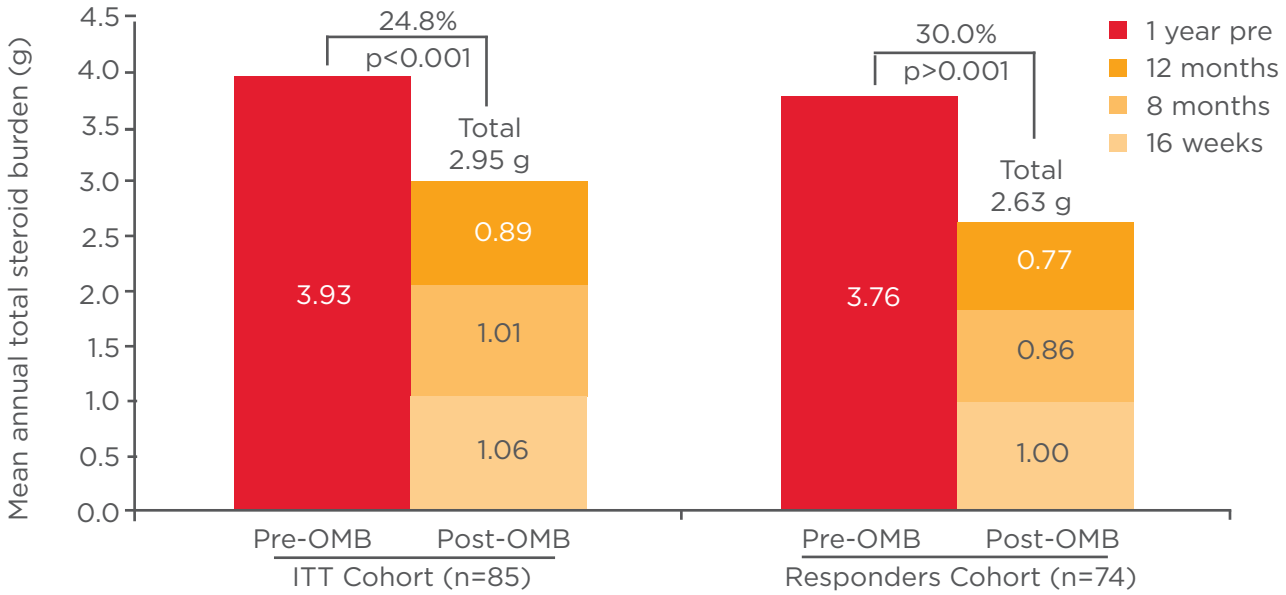

Figure 2: Total per-patient use of oral corticosteroids (OCS) in the 12 months pre and post-omalizumab (OMB) initiation in the intent-to-treat (ITT) (n=85) and responder (n=74) cohorts.[26]

ITT cohort: patients with 12 months of assessment at interim analysis; Responder cohort: patients classified as responders to treatment by their clinician at 16-week assessment.

The APEX study: clinical evidence on exacerbations, lung function, and OCS use

The APEX II study was a multicentre observational study evaluating the role of omalizumab in asthma control, OCS burden, HCRU, and patient-reported outcomes in 235 UK patients, across 22 centres, suffering from severe allergic asthma. This study is particularly interesting because it provides real-world data on the impact of omalizumab therapy in daily clinical practice. Interim analysis results at 12 months (n=85) were presented at ERS 2014; data were reported on exacerbation rates, lung function, and OCS use following omalizumab therapy.

The mean number of exacerbations was significantly reduced in the first 12 months post-omalizumab, as compared with the 12-month period prior to therapy (2.07±2.01 versus 4.25±2.73, -51%, p<0.001; Figure 1).[24] Similar and statistically significant decreases were also observed in terms of hospitalised asthma exacerbations and healthcare utilisation. Lung function, as assessed by FEV_1, was overall (average on the 12-month period) significantly improved in both the intent-to-treat (ITT) population (+7.78% predicted, p<0.001) and patients who responded to omalizumab therapy (n=75; +8.86% predicted, p<0.001; Table 1).[25] In the ITT and responders populations, isolated assessment analyses at 16 weeks (+14.14% and +9.68%, respectively; p<0.001 for both groups) and 8 months (+13.84% and +11.07%, respectively; p<0.001 for both groups), post-omalizumab initiation, yielded similar results. However, 12-month data differences were not significant (+4.41% and +5.32%, respectively; p>0.1 for both groups). The annual OCS use in the first 12 months following omalizumab therapy was significantly decreased in comparison to OCS use prior to omalizumab treatment (-0.97g [-24.8%] of prescribed OCS daily dose, p<0.001; Figure 2). In the responder cohort, this difference is even more pronounced (-1.13g [-30.0%] of prescribed OCS daily dose, p<0.001).[26] During the first 12 months after treatment initiation, 54.8% of patients stopped OCS therapy, while 57.7% of patients reduced their OCS dose by 20% or more.

The XPORT study: clinical evidence regarding long-term therapy and outcomes

While there are a lot of available clinical or real-life data on the efficacy and safety of omalizumab in the short term (up to 12 months),[7,16,17,27] there are limited data on the long-term use of omalizumab and the persistency of response to this treatment modality. XPORT was a Phase IV, multicentre, randomised, double-blind, placebo-controlled study aiming to evaluate the persistency of response to omalizumab (n=88) versus placebo (n=88) in patients with moderate-to-severe persistent allergic asthma, who continued (omalizumab arm) or who discontinued omalizumab (placebo arm) after long-term treatment (5 years and over).[28] Key results demonstrated that continuation of therapy after 5 years allowed for additional benefits in terms of exacerbation and symptom control, as compared with the placebo group. 67.0% of patients in the omalizumab group had a persistency of response, as compared with 47.7% in the placebo arm. The occurrence of AEs or serious AEs was similar between both arms, and the safety profile of omalizumab was consistent with regards to the approved label.

Table 1: Suggestions for reversal of target-specific oral anticoagulants.

Parameter	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
3-factor PCC	Unclear	Unclear	Unclear	Unclear
4-factor PCC	Possible (activated)	Possible	Possible	Possible
Activated factor VIIa	No	No	No	No
FFP	No	No	No	No
Haemodialysis	Yes	No	No	No
Hemoperfusion with activated charcoal	Yes	Possible	Possible	N/A
Oral activated charcoal	Yes	Yes	Yes	N/A

FFP: fresh frozen plasma; PCC: prothrombin complex concentrate.
Updated after Kaatz et al.[24]

New Clinical Evidence on QGE031 (Ligelizumab) versus Omalizumab

In a Phase IIa, exploratory parallel group, double-blind, placebo-controlled study, the relative efficacy and safety of QGE031 (3 subcutaneous [SC] dose groups) was compared to those of omalizumab or placebo, in 37 patients with mild atopic asthma. At 12 weeks, bronchial provocation testing revealed an increased tolerance (by approximately 3-fold) towards inhaled allergen in bronchial provocation testing (change from baseline in the concentration of inhaled allergen leading to a 15% decline in FEV_1) for the two higher QGE031 doses tested (72 mg and 240 mg dosed every 2 weeks), as compared with omalizumab; due to the small sample size of this exploratory trial, the results were only statistically significant for the comparison with the placebo arm.

New Clinical Evidence on Reslizumab and its Relative Efficacy in Relation to Eosinophilia

Corren et al.[29] presented very interesting findings of a double-blind, 16-week, placebo-controlled, Phase III study evaluating the efficacy and safety parameters of reslizumab (Cinquil®, Teva, Petah Tikva, Israel), an investigative anti-interleukin (IL)-5 antibody, in subjects aged 18-65 years with uncontrolled asthma. The findings revealed significant improvements in lung function (FEV_1) over placebo (+68 ml from baseline between both treatment arms). When stratified according to eosinophilia, patients with higher eosinophil blood counts and who were treated with reslizumab presented the highest improvements. The safety profile of reslizumab was mild-to-moderate in severity and was consistent with that reported for the placebo group.

New Clinical Evidence on Mepolizumab

The SIRIUS study

In the SIRIUS study,[30] a randomised, double-blind, placebo-controlled trial, the investigative monoclonal antibody mepolizumab (n=69) was administered as monthly 100 mg SC injections for 6 months and evaluated, versus placebo (n=66), in patients with severe, OCS-dependent asthma. In the active treatment arm, the steroid-sparing effect of mepolizumab was greater than the placebo: 54% versus 33% of patients achieved a dose reduction of 50%. The median OCS dose reduction from baseline was 50% in the mepolizumab group and 0% in the placebo group (p=0.007), while patients receiving mepolizumab experienced a 32% decrease in the rate of exacerbations, despite OCS dose reduction. These findings suggest that in patients with severe eosinophilic asthma, OCS dose could be reduced with concurrent mepolizumab administration while maintaining exacerbation management, which could improve the benefit-to-risk ratio experienced by these patients who often present with AEs due to long-term OCS.[31]

The MENSA study

In a 32-week randomised, double-blind, double-dummy study, mepolizumab therapy (intravenous [IV] or SC injection) was evaluated for efficacy and safety parameters against placebo.[32] 576 patients with severe eosinophilic asthma were randomised to three treatment arms: mepolizumab IV or SC, and placebo. The rate of reduction in exacerbations was statistically significant and greater in the mepolizumab arms (53% and 47%, respectively; p<0.001 for both arms) when compared with the placebo arm. Similar results were observed with respect to lung function (FEV_1) and QoL (St. George's Respiratory Questionnaire). The safety profile of mepolizumab was comparable to that of the placebo.

New clinical evidence on benralizumab therapy for uncontrolled eosinophilic asthma

Benralizumab (n=80) was evaluated against placebo (n=82) in a double-blind Phase II study conducted in patients, stratified by eosinophil blood count, with uncontrolled asthma and receiving ICS therapy.[33] The findings revealed that benralizumab therapy reduced the annual asthma exacerbation rate while improving (statistically significant differences) lung function (FEV_1) and asthma control (ACQ-6), when compared to placebo.

The pharmacoeconomics of allergic asthma

As stated earlier, asthma is associated with a high economic burden, particularly in allergic asthma. Available literature has already explored omalizumab's impact on resource utilisation;[34,35] few data are available on the HCRU of patients at initiation of therapy with omalizumab. In a retrospective study, Baldwin et al.[36] explored the demographic, clinical, and HCRU characteristics of allergic asthma patients. Increasing HCRU (emergency room visits, urgent care, or hospitalisations) in the year before omalizumab

therapy was detected, in comparison with the 13-24 months prior to therapy initiation. The patients with moderate asthma presented larger proportional increases in HCRU than patients with severe asthma.

NOVEL AND EMERGING THERAPIES TARGETING THE CRTH2 RECEPTOR FOR UNCONTROLLED ASTHMA MANAGEMENT

QAV680 and QAW039 (fevipiprant) are selective, competitive, and reversible oral CRTh2 receptor antagonists; the former has been investigated in allergic diseases, particularly in allergic rhinitis,[37] and the latter is currently being investigated in Phase II studies for uncontrolled asthma.

New Preclinical Data on QAV680 and QAW039

Pharmacological characterisation of QAV680 and QAW039

At ERS 2014, Willard et al.[38] presented the detailed *in vitro* and *in vivo* pharmacological characterisation and the evaluation of *in vivo* pharmacokinetic profiles of QAW039 and QAV680. Both compounds possess a high selectivity for the CRTh2 receptor, and inhibit eosinophil shape change (i.e. their activation) and IL-5 and 13 production by Th2 cells. The data suggest that QAW039 is much more potent than QAV680 with regards to these assays.

Pharmacokinetics and safety of QAW039 in healthy subjects

Sykes et al.[39] described the receptor binding kinetics of QAW039 and compared them to other CRTh2 antagonists, including QAV680. The authors observed an improved duration of action for QAW039 due to a very slow off-rate from the CRTh2 receptor, and a prolonged occupancy is expected to have an impact on its clinical efficacy.

Safety, tolerability, and pharmacokinetics of QAW039

Erpenbeck et al.[40] presented the results of two randomised, single-centre, double-blind, placebo-controlled studies aiming to evaluate the safety, tolerability, and pharmacokinetics of QAW039 in healthy subjects. The first study (n=16) was a single ascending dose study with an alternating cohort design in which subjects were randomised to QAW039 at different doses (10-100 mg or 30-300 mg) or to placebo. The second study (n=32) was a multiple ascending dose study in which subjects were randomised to QAW039 or placebo within four cohorts of various doses and schedules. Overall, QAW039 was safe and well tolerated across all cohorts for all doses (range: 10-500mg), both for single and multiple dosing in these two studies. The pharmacokinetic parameters showed rapid absorption, limited accumulation, and limited impact of food on exposure.

Safety, tolerability, and pharmacokinetics of QAV680

Safety, tolerability, and pharmacokinetics of QAV680 were assessed in two double-blind, placebo-controlled Phase I studies, a single-ascending dose study (n=19) and a multiple-ascending dose study (n=40) in healthy subjects.[41] The pharmacokinetic parameters of QAV680 were assessed, and demonstrated approximate dose-proportionate area under curves and C_{max}, a rapid absorption following oral administration of either single or multiple doses with a T_{max} of 0.5-3 hours and a $T_{1/2}$ of 11.5-20.4 hours. Single and multiple doses of QAV680, up to 1,000 mg twice-daily, were safe and well tolerated. No systemic accumulation was observed, nor food impact on exposure.

Clinical Evidence on QAW039 Therapy in Eosinophilic Asthma

QAW039 was evaluated in a Phase IIa, single-centre, double-blind, randomised controlled study in which 61 patients with eosinophilic severe (GINA IV and V) asthma were randomly assigned to a 12-week regimen of either QAW039 225 mg twice-daily or placebo.[42] Eosinophilic inflammation is common in asthma, and attenuation of sputum eosinophilia is strongly associated with reduced exacerbation frequency.[43] At 12 weeks, the primary endpoint, reduction of sputum eosinophils, was met: QAW039 reduced sputum eosinophils 3.5-fold over placebo (95% CI: 1.7-7.0, p=0.001). Asthma-related QoL improved in those treated with QAW039 compared to placebo (0.59 points; p=0.008) with non-significant improvements in ACQ-7 in the group as a whole (0.40 points; p=0.084), which was greater in those with poor asthma control (ACQ≥1.5) at baseline (0.56 points; p=0.046). FEV_1 improved in those receiving QAW039 versus placebo (0.074L; p=0.408; pre-BD, 0.163L; p=0.022; post-BD).

Overall, QAW039 was associated with a favourable safety profile, consistent with the placebo group, with no reported serious AEs or deaths.

CONCLUSION

Asthma, and particularly severe asthma, is a chronic disease associated with a significant impact on QoL and HCRU, and for which some unmet needs remain unaddressed. Omalizumab has been on the market for >10 years for severe allergic asthma, but emerging therapies, such as monoclonal antibodies - the new high-affinity anti-IgE QGE031, mepolizumab, benralizumab, reslizumab - or the CRTh2 antagonists QAV680 and QAW039, may have the potential to provide additional clinical outcomes to patients, within acceptable safety profiles and pharmacoeconomics. Moreover, the development of predictive tools to evaluate treatment response and data collection on real-world populations will help refine the guidelines for optimal management of these diseases and help select the right drug for the right patient, which is of crucial importance in the era of 'personalised medicine'.

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