**Online Data Supplement**

# Omalizumab for Aspirin-Hypersensitivity and Leukotriene Overproduction in Aspirin-Exacerbated Respiratory Disease: A Randomized Trial

Hiroaki Hayashi, Yuma Fukutomi, Chihiro Mitsui, Keiichi Kajiwara, Kentaro Watai, Yosuke Kamide, Yuto Nakamura, Yuto Hamada, Yasuhiro Tomita, Kiyoshi Sekiya, Takahiro Tsuburai, Kenji Izuhara, Keiko Wakahara, Naozumi Hashimoto, Yoshinori Hasegawa, Masami Taniguchi

## Methods

### Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) aged 20 to 79 years; 2) asthma diagnosed according to criteria of the American Thoracic Society (E1); 3) AERD confirmed using the modified oral challenge protocol outlined by Stevenson et al. (E2, E3) within the last two years of enrolment; 4) at least one positive result in by skin test or serum-specific immunoglobulin E test for common environmental allergens; and 5) no previous treatment with omalizumab. Patients were also required to be clinically stable with no recent exacerbations, infections, non-steroidal anti-inflammatory drug ingestion, or changes in maintenance medication for at least 4 weeks before study entry.

The exclusion criteria were as follows: 1) at risk of sinusitis and/or nasal polyp surgery during the study period; 2) comorbidities including autoimmune diseases, renal, hepatic, heart diseases, unstable diabetes mellitus, mental disorders, alcoholism, and malignancy that require treatment; 3) pregnancy, breast-feeding, or potential pregnancy; and 4) patients considered unsuitable by the attending physician. Mepolizumab and immunotherapy or other immunomodulatory drugs were prohibited throughout the study.

**Randomisation and masking**

Patients individually randomised at a 1:1 ratio in block sizes of four received omalizumab or placebo (saline) at treatment phase 1 at the Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital. Treatment assignments linked to a pre-specified unique participant ID number were randomly generated by staff in the research centre using Excel (Microsoft Corporation, Tokyo, Japan). The treatment assignments were sealed in opaque envelopes labelled with the participant ID number by centre staff. Hospital nurses opened the envelopes and provided treatment independent of the investigators. Thus, investigators and/or staff involved in assessing laboratory outcomes were masked to the study assignments.

**Anti-immunoglobulin E therapy and placebo**

The doses of omalizumab were individualized on the basis of individual body weight and serum immunoglobulin E level. Omalizumab administered every 2 or 4 weeks by subcutaneous injection provided a dose of at least 0.016 mg/kg per IU of immunoglobulin E (E4). Subjects in the placebo group received a physiologic salt solution administered as for omalizumab with the same dosing frequency and injection volume. Furthermore, nurses reconstituted and injected the study drug or placebo independent of investigators because the time for reconstitution and viscosities were different. Patients were observed for 2 h after injection.

**Washout period**

The drug-washout period was set to be over 126 days (over 18 weeks) in this study, which was 5-times longer than the half-life of omalizumab (21.0 ± 3.5 days) (E5) based on the following calculation: 24.5 days × 5 = 122.5 days. This calculation was also based on previous clinical studies for molecular target drugs against asthma: mepolizumab (E6-E9), benralizumab (E10, E11), and dupilumab (E12, E13).

**Aspirin challenge**

Single-blind aspirin challenges were performed using the modified oral challenge protocol (E2, E3). The initial dosage of aspirin was 30 mg, and this was doubled (30, 60, 120, 240, and 480 mg; total dose = 930 mg) at 3 h intervals until a positive reaction was observed. All patients were clinically stable at time of testing. Except for daily oral corticosteroids, all medications were stopped for at least 24 h prior to the test. Forced expiratory volume in 1 s was assessed by spirometry (Minato Autospiro AS-303; Minato Medical Science Co., Ltd., Osaka, Japan), three times at each timepoint, and the highest value was used.

Positive reactions were defined as meeting any of following three criteria: 1) decrease in forced expiratory volume in 1 s by 20% or greater compared with baseline value; 2) decrease in forced expiratory volume in 1 s by 10% to 20% with the presence of nasal congestion, rhinorrhoea, sneezing, nasal/eye itching, or eye redness/tearing; and 3) appearance of

additional extra-pulmonary symptoms including unbearable nasal symptoms, chest pain, abdominal pain, nausea, diarrhoea, and/or cutaneous symptoms such as flushing or a pruritic macular eruption on the distal extremities, irrespective of a change in forced expiratory volume in 1 s. Challenges were stopped when a positive reaction was noted or when the highest dose of aspirin had been administered.

**Assessments**

**Baseline characteristics**

Baseline characteristics of studied patients were recorded at study entry (at visit 0).

**Quantification of urinary leukotriene $E_4$ ($LTE_4$) and 11,15-dioxo-9α-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid (tetranor-PGDM)**

Spot urine samples were collected and stored (−80°C) at every visit and during oral aspirin challenge (at Before [0] to 3, 3 to 6, 6 to 9, and 9 to 24 h after ingestion of the last dose). Urinary eicosanoid concentrations were expressed as pg/mg of creatinine.

Polypropylene bottles containing 4-hydroxy-TEMPO (Sigma-Aldrich, St. Louis, MO) at a final concentration of 1 mmol/L were used to collect urine. An Empore C18 disk cartridge (3M, St. Paul, MN) and a high-performance liquid chromatography system (Shimadzu LC-$10AD_{VP}$) equipped with a NOVA-PACK C18 column (Waters, Milford, MA) were used to

purify 2 mL urine $LTE_4$, which was then quantified using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Cayman, Ann Arbor, MI) (E14).

To quantify tetranor-PGDM (E15), 1 mL urine was acidified using 0.05 mL 1 N HCl and then added to an Empore C18 SD cartridge. Then, tetranor-PGDM was eluted by ethyl acetate (1 mL) and purified by high-performance liquid chromatography using a NOVA-PAK C18 column and a solvent mixture of acetonitrile-distilled water-phosphoric acid (15:85:0.1 *vol/vol/vol*) at a flow rate of 1.0 mL/min at 35°C. The column effluent that corresponded with the retention time of authentic tetranor-PGDM (approximately 7.0 minutes) was collected. Following the purification of urine by high-performance liquid chromatography, tetranor-PGDM was extracted using the Empore C18 disk cartridge. The methanol extract was stored at −80°C until quantified by ELISA within 1 week of storage.

**Blood sample analysis**

Peripheral blood eosinophil counts and the serum levels of periostin, tryptase, and eosinophilic cationic protein were measured at every visit. The peripheral eosinophil counts of all patients were determined in the morning (from 9 AM to 11 AM). The serum total immunoglobulin E was assayed before and after each treatment phase (at visits 1, 6, 7, and 12). Blood samples were collected prior to placebo or omalizumab injection and immediately stored at −80°C until further use. Serum periostin (E16) levels were determined by ELISA (Shino-test, Kanagawa,

Japan) (E17). The total concentrations of immunoglobulin E, tryptase, and eosinophilic cationic protein were quantified with Immuno CAP (Thermo Fisher Scientific, Tokyo, Japan).

**Platelet activation markers.**

Data were collected before and after each treatment phase (at visits 1, 6, 7, and 12). Levels of surface markers (CD62P and CD63) expressed on platelets were analysed by flow cytometry. Plasma soluble P-selectin levels were measured by ELISA.

Fluorescence-activated cell sorting was performed as described previously (E18). Fluorescein isothiocyanate-conjugated anti-CD61 (GPIIIa) and phycoerythrin-conjugated anti-CD63 were purchased from Beckman Coulter (Fullerton, CA). PE-conjugated anti-CD62P was obtained from BD Biosciences (San Jose, CA). The corresponding isotypes (Beckman Coulter) were used as controls. A FACSCalibur flow cytometer with CellQuest software (Becton Dickinson, San Jose, CA) was used to analyse samples. A 21 G needle was used to collect whole peripheral blood, which was then added into a 3.2% sodium citrate tube. Blood cells were then stained within 10 minutes after collection. Directly-conjugated specific antibodies to CD61 and CD62P, or CD63 were used to stain 10 μL of unstimulated whole blood for 15 minutes. Cells were then fixed by 1% paraformaldehyde. The detection of platelets was performed using the forward/side scatter characteristics of cells and their expression of CD61. At least 20,000 $CD61^+$ platelet events were collected per sample. Platelet activation was

quantified as the percentage of cells positive for each surface marker and the mean fluorescence intensity of cells in the platelet gate, which was drawn based on $CD61^+$ staining.

For the quantification of plasma soluble P-selectin (E18), tubes with 1.5 mg/mL EDTA anticoagulant solution were used to collect blood, which was centrifuged for 10 minutes at room temperature at 1600 × g. The final supernatant was stored in aliquots at −80°C until measurement. The concentrations of sP-selectin were measured by ELISA (R&D Systems, Minneapolis, MN). Samples were diluted with ELISA buffer to a final dilution of 1:20 for sP-selectin analysis. The absorbance of the coloured product was measured at 450 nm using a microplate reader (iMark, Bio-Rad Laboratories, Hercules, CA). Each dilution was run in duplicate. The detection limit of the soluble P-selectin assay was 0.5 ng/mL.

**Cytokines and chemokines.**

The serum levels of 58 cytokines and chemokines (CC chemokine ligand [CCL]1/I-309, CCL2/monocyte chemotactic protein [MCP]-1, CCL3/macrophage inflammatory protein [MIP]-1α, CCL4/MIP-1β, CCL5/regulated on activation, normal T cell expressed and secreted [RANTES], CCL7/MCP-3, CCL8/MCP-2, CCL11/eotaxin, CCL13/MCP-4, CCL17/thymus and activation-regulated chemokine [TARC], CCL24/eotaxin-2, CCL26/eotaxin-3, C-X-C motif ligand [CXCL]1/growth related oncogene [GRO]α, CX3CL1/fractalkine, CXCL5/epithelial neutrophil-activating peptide [ENA]-78, CXCL8/interleukin [IL]-8,

CXCL9/monokine induced by γ interferon [MIG], CXCL10/interferon γ-induced protein [IP]-10, CXCL12/stromal cell-derived factor [SDF]-1α, CXCL13/B-lymphocyte chemoattractant [BLC]/B cell-attracting chemokine [BCA]-1, CD23/FcεRII, CD40 ligand, granulocyte colony-stimulating factor [G-CSF], granulocyte/macrophage colony-stimulating factor [GM-CSF], IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-11, IL-12 [p70], IL-13, IL-16, IL-17A, IL-17E/IL-25, IL-18, IL-21, IL-22, IL-23, IL-27, IL-31, IL-33, interferon [IFN]-γ, transforming growth factor [TGF]-α, tumor necrosis factor [TNF]-α, stem cell factor [SCF], intercellular adhesion molecule [ICAM]-1, vascular cell adhesion molecule [VCAM]-1, thymic stromal lymphopoietin [TSLP], a proliferation-inducing ligand [APRIL], B-cell activating factor of the TNF family [BAFF]/B-lymphocyte stimulator [BLyS], E-Selectin, P-Selectin, vascular endothelial growth factor [VEGF]-A, and platelet-derived growth factor [PDGF]-BB) were assayed using multiplex assays (Magnetic Luminex® Assay, Human Premixed Multi-Analyte Kit from R&D Systems, Minneapolis, MN) on a ‘‘Bio-Plex 200” system (Bio-Rad Laboratories) at Filgen (Nagoya, Japan), following the manufacturer’s instructions.

**Questionnaires**

The patient-reported scores were assessed using Asthma Control Test (at visits 1, 4-6, 7, and 10-12), Asthma Control Questionnaire-6 (at visits 1, 3-6, 7, and 9-12), and Sino-nasal Outcome Test-22 (at visits 1, 4-6, 7, and 10-12) at baseline and during the omalizumab or placebo phase.

At every visit, the asthma- and nasal-related symptoms were assessed by a validated 10 cm visual analogue scale at every visit and during oral aspirin challenge (at Before [0], 3, 6, 9, and 24 h after ingestion of the last dose). Global Evaluation of Treatment Effectiveness was used to assess the effectiveness of omalizumab treatment at every visit.

The Asthma Control Test was used to assess the interference of asthma related to shortness of breath, nocturnal symptoms, rescue medication use, and self-rating of asthma control, when undertaking various activities (E19). Overall scores for an individual patient were determined by the total of responses to five questions, and ranged from 5 (poorly controlled asthma) to 25 (well-controlled asthma). The minimum important difference for the Asthma Control Test was defined as ≥ 3 points (E20).

The overall Asthma Control Questionnaire-6 score (E21) is a six-item questionnaire that assesses daytime and night-time symptoms and rescue agonist use, on a scale from 0 (completely controlled) to 6 (extremely poorly controlled). The total score was divided by six and the mean value was calculated. A decrease in Asthma Control Questionnaire-6 score of ≥ 0.5 points is considered the minimal clinically important improvement (E22).

The Sino-nasal Outcome Test-22 questionnaire was completed by patients based on the severity of their nasal condition (E23). It consists of 22 questions and each item is scored using a 6-point scale (0 to 5). The maximum possible score is 110. A high score indicates severe

symptoms. A change of 8.9 or more points represents a minimally important difference (E24).

The asthma- and nasal-symptom visual analogue scale includes three asthma symptoms (dyspnea, wheezing, and cough) and three nasal symptoms (congestion, anterior rhinorrhoea, and anosmia). Patients were asked to indicate the severity of their symptoms on a validated 10 cm visual analogue scale (0-10 cm). A high score indicates troublesome symptoms (0 cm, none; 10 cm, the most severe).

Global Evaluation of Treatment Effectiveness was used to assess the effectiveness of omalizumab treatment as excellent (complete control), good (marked improvement), moderate (discernible, but limited improvement), poor (no appreciable change), or worsening. Patients with an 'excellent' or 'good' response were classified as responders, while those with 'moderate', 'poor', or 'worsening' were classified as non-responders (E25).

**Lung function testing**

Fractional exhaled nitric oxide (NO chemiluminescence analyzer; NOA model 280A, Sievers Instrument) was measured according to the American Thoracic Society guidelines as previously described (E26). The forced oscillation technique was performed with a commercially available device (MostGraph®; Chest M.I., Tokyo, Japan) to measure the respiratory impedance (E27). After the measurement of fractional exhaled nitric oxide and forced oscillation technique, spirometric measurements (forced expiratory volume in 1 s [%

predicted], forced vital capacity [% predicted], and forced expired flow between 25% and 75% of the volume expired) were taken with the spirometer (Minato Autospiro AS-303; Minato Medical Science Co., Ltd.) at visits 1, 6, 7, and 12.

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## Figure legends

**Figure E1. Difference in VAS for asthma and nasal symptoms during oral aspirin challenge between the placebo and omalizumab phases.**

**A)** Dyspnea, **B)** wheezing, **C)** cough, **D)** nasal congestion, **E)** anterior rhinorrhoea, and **F)** anosmia. Wilcoxon signed rank test. * $p < 0.05$ and ** $p < 0.01$. Closed circles (placebo phase) and squares (omalizumab phase) indicate median values and bars indicate interquartile ranges. Visual analogue scale (VAS) incorporates quantitative and objective measures to assess the severity of asthma and nasal symptoms as well as the efficacy of treatment. VAS scores ranged from 'not at all bothersome' (0 cm) to 'extremely bothersome' (10 cm). At Before [0], 3, 6, 9, and 24 h after ingestion of the dose that produced a positive reaction or after ingestion of the last dose of aspirin in patients with AERD who produced a negative reaction.

**Figure E2. Difference in the levels of blood biomarkers between placebo and omalizumab phases.**

**A)** Eosinophil count, **B)** eosinophil cationic protein, **C)** periostin, and **D)** tryptase. Wilcoxon signed rank test. * $p < 0.05$. Closed circles (placebo phase) and squares (omalizumab phase) indicate median values and bars indicate interquartile ranges.

**Figure E3. Difference in VAS for asthma and nasal symptoms between the placebo and omalizumab phases.**

**A)** Dyspnea, **B)** wheezing, **C)** cough, **D)** nasal congestion, **E)** anterior rhinorrhoea, and **F)** anosmia. Wilcoxon signed rank test. ***** $p < 0.05$. Closed circles (placebo phase) and squares (omalizumab phase) indicate median values and bars indicate interquartile ranges. Visual analogue scale (VAS) incorporates quantitative and objective measures to assess the severity of asthma and nasal symptoms as well as the efficacy of treatment. VAS scores ranged from 'not at all bothersome' (0 cm) to 'extremely bothersome' (10 cm).

**Table E1. Differences in VAS for respiratory symptoms between placebo and omalizumab phases during oral aspirin challenge.**

| VAS¶ scores * | Placebo n = 16 | Omalizumab n = 16 | P value |
|---|---|---|---|
| Dyspnea (cm) | | | |
| Before | 2.0 (1.5–4.8) | 1.2 (0.5–1.8) | <0.001 |
| 3 h | 4.0 (2.3–7.1) | 1.4 (0.5–2.2) | <0.001 |
| 6 h | 3.9 (2.2–6.4) | 1.0 (0.5–2.1) | <0.001 |
| 9 h | 2.7 (1.9–5.3) | 1.0 (0.4–1.8) | <0.001 |
| 24 h | 2.4 (1.6–4.6) | 1.2 (0.4–1.7) | <0.001 |
| Wheezing (cm) | | | |
| Before | 2.0 (1.4–4.8) | 1.1 (0.4–1.8) | 0.001 |
| 3 h | 3.5 (2.7–6.9) | 1.3 (0.5–2.5) | <0.001 |
| 6 h | 3.4 (2.4–6.3) | 1.3 (0.4–2.2) | <0.001 |
| 9 h | 2.9 (2.0–4.3) | 1.1 (0.4–2.1) | <0.001 |
| 24 h | 2.3 (1.7–3.9) | 1.1 (0.4–2.2) | <0.001 |
| Cough (cm) | | | |
| Before | 3.7 (1.9–6.0) | 1.5 (0.7–2.0) | <0.001 |
| 3 h | 4.3 (2.2–7.0) | 1.5 (0.4–2.2) | <0.001 |

| | | | |
|---|---|---|---|
| 6 h | 3.9 (2.0–6.4) | 1.5 (0.5–1.9) | <0.001 |
| 9 h | 3.0 (1.8–4.6) | 1.5 (0.6–1.6) | <0.001 |
| 24 h | 2.9 (1.4–4.7) | 1.5 (0.5–1.6) | <0.001 |
| Nasal congestion (cm) | | | |
| Before | 4.0 (2.2–6.5) | 2.8 (1.2–4.7) | 0.002 |
| 3 h | 6.1 (3.5–8.2) | 2.8 (1.3–5.3) | <0.001 |
| 6 h | 5.7 (3.6–9.2) | 2.0 (1.2–4.3) | <0.001 |
| 9 h | 4.7 (2.0–6.6) | 2.0 (0.9–4.3) | <0.001 |
| 24 h | 3.3 (2.2–4.7) | 2.0 (1.0–3.6) | 0.002 |
| Anterior rhinorrhoea (cm) | | | |
| Before | 5.3 (2.2–9.0) | 3.0 (1.3–5.1) | 0.018 |
| 3 h | 7.0 (4.8–8.5) | 3.8 (1.6–5.6) | <0.001 |
| 6 h | 6.1 (4.5–8.6) | 3.2 (1.4–4.8) | <0.001 |
| 9 h | 6.1 (2.8–8.0) | 1.5 (1.0–4.4) | <0.001 |
| 24 h | 3.8 (2.3–5.7) | 2.7 (1.2–4.2) | 0.006 |
| Anosmia (cm) | | | |
| Before | 8.9 (4.3–10.0) | 4.8 (1.4–7.1) | 0.034 |
| 3 h | 9.3 (1.9–10.0) | 4.7 (1.1–7.1) | <0.001 |
| 6 h | 9.5 (2.0–10.0) | 3.2 (0.9–7.2) | <0.001 |

| | | | |
|---|---|---|---|
| 9 h | 8.6 (1.6–9.8) | 2.7 (1.0–7.3) | <0.001 |
| 24 h | 6.2 (1.6–9.9) | 3.0 (1.0–7.4) | <0.001 |

Data are expressed as the median (interquartile range).

Significance testing was performed using the Wilcoxon signed rank test.

* At Before [0], 3, 6, 9, and 24 h after ingestion of the dose that produced a positive reaction or after ingestion of the last dose of aspirin in patients with AERD who produced a negative reaction.

¶VAS scores ranged from ‘not at all bothersome’ (0 cm) to ‘extremely bothersome’ (10 cm).

VAS, visual analogue scale.

**Table E2. Differences in the maximal decline in $FEV_1$ during oral aspirin challenge between placebo and omalizumab phases.**

| | Placebo<br>n = 16 | Omalizumab *<br>n = 16 | P value |
|---|---|---|---|
| Change in $FEV_1$ (%) | −10.0 (−14.6 to −3.6) | −4.7 (−7.5 to −0.5) | 0.039 |

Data are expressed as the median (interquartile range).

Significance testing was performed using the Wilcoxon signed rank test.

* Ten of 16 patients (62.5%) did not show a positive reaction, even after the highest cumulative dose (930 mg) was administered.

$FEV_1$, forced expiratory volume in 1 s.

**Table E3. Comparison of baseline characteristics between patients who did and did not develop aspirin tolerance.**

| Variable before initial treatment | Developed aspirin tolerance n = 10 | Not developed aspirin tolerance n = 6 | P value |
|---|---|---|---|
| Age (years) | 57.0 (53.0–63.8) | 46.5 (41.0–51.3) | 0.051 |
| Gender, no. (%) | | | 0.307 |
| Male | 5 (50.0) | 1 (16.7) | |
| Female | 5 (50.0) | 5 (83.3) | |
| Body weight (kg) | 50.9 (49.1–56.4) | 58.5 (57.2–59.7) | 0.313 |
| Body mass index (kg/m$^2$) | 20.8 (20.4–21.7) | 22.6 (21.7–23.1) | 0.220 |
| Smoking status (never/past/current), no. (%) | 6 (60.0)/4 (40.0)/0 (0.0) | 2 (33.3)/2 (33.3)/2 (33.3) | 0.275 |
| Pack-year (among smokers) | 28.0 (20.3–30.0) | 10.0 (5.0–16.9) | 0.146 |
| Asthma onset age | 53.0 (41.3–57.8) | 26.5 (13.5–38.8) | 0.023 |
| History of sinus surgery and polypectomy, no (%) | 3 (30.0) | 4 (66.7) | 0.307 |
| Cumulative provoking aspirin dose (mg) | 210.0 (90.0–270.0) | 90.0 (90.0–210.0) | 0.351 |

| | | | |
|---|---|---|---|
| (Placebo phase) | | | |
| Inhaled corticosteroid dose (μg/day) (Fluticasone equivalents) | 500.0 (357.5–1000.0) | 1000.0 (812.5–1000.0) | 0.079 |
| Systemic corticosteroids, no. (%) | 1 (10.0) | 2 (33.3) | 0.518 |
| Systemic corticosteroids (mg/day) (Prednisolone equivalents) | 3 | 3 / 7 | |
| Omalizumab dose (mg) | 300.0 (300.0–600.0) | 150.0 (150.0–262.5) | 0.112 |
| Washout phase (days) | 142.5 (132.3–145.8) | 135.0 (129.0–139.5) | 0.440 |
| Urine biomarkers (log-transformed) | | | |
| $LTE_4$ (pg/mg of creatinine) | 2.4 (2.0–2.7) | 2.6 (2.1–3.1) | 0.713 |
| Tetranor-PGDM (pg/mg of creatinine) | 2.4 (2.4–2.5) | 2.6 (2.5–2.8) | 0.147 |
| Blood biomarkers | | | |

| | | | |
|---|---|---|---|
| Total IgE (IU/mL) | 221.0 (118.8–1055.8) | 44.9 (34.4–214.8) | 0.093 |
| Eosinophil count (per μL) | 370.0 (287.5–495.0) | 335.0 (270.0–505.0) | 0.936 |
| Periostin (ng/mL) | 110.5 (98.8–134.3) | 136.5 (108.5–230.5) | 0.428 |
| Eosinophil cationic protein (μg/L) | 11.7 (4.7–13.1) | 11.8 (7.5–13.8) | 0.580 |
| Tryptase (μg/L) | 2.7 (2.4–4.7) | 3.0 (2.9–3.6) | 0.428 |
| Platelet count and activation markers | | | |
| Platelet count ($\times 10^4$ per μL) | 23.4 (20.5–26.0) | 30.2 (27.0–30.9) | 0.003 |
| Plasma soluble P-selectin level (ng/mL) | 111.1 (101.1–141.3) | 125.8 (118.0–132.1) | 0.635 |
| CD62P expression on platelets (%) | 3.3 (1.3–4.5) | 2.6 (2.0–3.8) | 1.000 |
| CD63 expression on platelets (%) | 4.3 (1.8–5.5) | 4.2 (2.9–4.8) | 0.958 |
| Symptom scores | | | |

| | | | |
|---|---|---|---|
| ACT | 20.5 (16.3–22.8) | 20.5 (15.3–24.3) | 0.936 |
| ACQ6 | 0.9 (0.8–2.2) | 0.8 (0.2–2.1) | 0.630 |
| SNOT-22 | 43.5 (33.8–54.5) | 40.5 (30.0–42.8) | 0.382 |
| VAS ¶ (cm) | | | |
| Dyspnea | 2.0 (1.7–3.0) | 3.3 (1.2–4.3) | 0.855 |
| Wheezing | 1.7 (1.1–3.1) | 2.7 (1.0–3.9) | 0.816 |
| Cough | 1.9 (1.6–4.7) | 3.5 (1.6–5.5) | 0.852 |
| Nasal congestion | 4.9 (2.1–7.4) | 3.2 (1.1–7.2) | 0.411 |
| Anterior rhinorrhoea | 4.5 (3.0–8.1) | 3.6 (1.7–7.0) | 0.618 |
| Anosmia | 7.0 (2.6–8.7) | 9.6 (5.7–10.0) | 0.248 |
| Respiratory function | | | |
| $FEV_1$ (% predicted) | 103.9 (94.0–112.6) | 102.2 (90.5–105.4) | 0.635 |
| $FEV_1$/FVC (%) | 76.9 (70.5–78.0) | 75.1 (66.5–81.2) | 0.958 |
| FVC (% predicted) | 116.8 (106.8–127.4) | 124.8 (115.3–127.2) | 0.635 |
| $FEF_{25–75\%}$ (%) | 63.5 (44.8–68.5) | 55.8 (37.8–73.7) | 1.000 |
| FeNO (ppb) | 27.3 (23.9–33.3) | 18.0 (12.6–29.4) | 0.181 |

Data are presented as medians and interquartile ranges.

Significance testing was performed using the Mann-Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables.

¶VAS scores ranged from 'not at all bothersome' (0 cm) to 'extremely bothersome' (10 cm).

ACT, Asthma Control Test; ACQ-6, Asthma Control Questionnaire-6; $FEF_{25–75}$, forced expired flow between 25% and 75% of the volume expired; FeNO, fraction of exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; $LTE_4$, leukotriene $E_4$; SNOT-22, Sino-Nasal Outcome Test-22; Tetranor-PGDM, 11,15-dioxo-9α-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid; VAS, visual analogue scale.

**Table E4. Comparison of baseline serum cytokine level between patients who did and did not develop aspirin tolerance.**

| Cytokines (pg/mL) | Developed aspirin tolerance n = 10 | Not developed aspirin tolerance n = 6 | P value |
|---|---|---|---|
| CCL1/I-309 | 7 BDL 10.2 (9.9–10.3) | 2 BDL 10.0 (9.9–10.2) | 0.971 |
| CCL2/MCP-1 | 305.5 (266.1–452.2) | 274.0 (265.3–304.8) | 0.793 |
| CCL3/MIP-1α | 5 BDL 231.3 (231.3–251.5) | 3 BDL 183.0 (183.0–207.1) | 0.125 |
| CCL4/MIP-1β | 1141.3 (1053.3–1245.5) | 1213.6 (1139.5–1281.6) | 0.211 |
| CCL5/RANTES | 46,303.7 (26,830.5–49,801.6) | 43,511.3 (40,189.2–48,412.3) | 0.958 |
| CCL7/MCP-3 | All BDL (–) | All BDL | NA |
| CCL8/MCP-2 | 1 BDL 83.2 (79.2–96.8) | 90.0 (68.4–96.9) | 0.930 |
| CCL11/eotaxin | 3 BDL 133.1 (129.2–181.3) | 5 BDL 148.1 (148.1–148.1) | 0.750 |
| CCL13/MCP-4 | 97.5 (80.1–144.4) | 115.6 (95.6–134.4) | 0.713 |
| CCL17/TARC | 714.3 (529.7–1006.2) | 821.8 (716.7–1112.5) | 0.368 |
| CCL24/eotaxin-2 | 1116.0 (771.6–1252.4) | 883.8 (804.6–1044.6) | 0.713 |
| CCL26/eotaxin-3 | All BDL | All BDL | NA |
| CXCL1/ GROα | 9 BDL 515.6 (515.6–515.6) | 5 BDL 564.5 (564.5–564.5) | 1.000 |
| CX3CL1/fractalkine | 6654.0 (5853.6–7094.1) | 6072.6 (5592.3–6982.4) | 0.543 |

| | | | |
|---|---|---|---|
| CXCL5/ENA-78 | 1298.2 (1077.9–1424.1) | 1338.8 (1025.5–2163.0) | 0.736 |
| CXCL8/IL-8 | 1 BDL 11.5 (11.2–13.8) | 1 BDL 11.5 (10.2–12.7) | 0.897 |
| CXCL9/MIG | 9 BDL 3648.2 (3648.2–3648.2) | All BDL | NA |
| CXCL10/IP-10 | 36.0 (25.7–42.4) | 35.3 (32.7–38.2) | 0.958 |
| CXCL12/SDF-1α | 851.8 (821.6–904.0) | 1004.6 (891.0–1104.7) | 0.077 |
| CXCL13/BLC)/BCA-1 | 64.5 (57.5–82.3) | 69.5 (53.8–79.8) | 0.980 |
| CD23/FcεRII | 2354.6 (1521.1–3012.6) | 2311.1 (1855.4–2811.6) | 1.000 |
| CD40 ligand | 5494.7 (5009.8–6450.1) | 8323.8 (6907.4–8674.9) | 0.099 |
| G-CSF | 9 BDL 68.1 (68.1–68.1) | All BDL | NA |
| GM-CSF | 9 BDL 25.6 (25.6–25.6) | All BDL | NA |
| IL-1β | 9 BDL 34.6 (34.6–34.6) | 5 BDL 36.5 (36.5–36.5) | 1.000 |
| IL-2 | 2 BDL 160.6 (125.5–269.0) | 1 BDL 152.5 (146.8–231.9) | 0.971 |
| IL-3 | All BDL | All BDL | NA |
| IL-4 | 8 BDL 86.0 (83.2–88.8) | All BDL | NA |
| IL-5 | All BDL | All BDL | NA |
| IL-6 | All BDL | All BDL | NA |
| IL-7 | 4 BDL 16.0 (13.6–20.0) | 14.5 (12.3–15.6) | 0.333 |
| IL-10 | 9 BDL 20.6 (20.6–20.6) | All BDL | NA |
| IL-11 | All BDL | All BDL | NA |

| | | | |
|---|---|---|---|
| IL-12 (p70) | 9 BDL 302.4 (302.4–302.4) | All BDL | NA |
| IL-13 | All BDL | All BDL | NA |
| IL-16 | 129.0 (120.1–163.5) | 130.9 (128.1–151.0) | 0.852 |
| IL-17A | All BDL | All BDL | NA |
| IL-17E/IL-25 | 9 BDL 1329.3 (1329.3–1329.3) | All BDL | NA |
| IL-18 | 189.7 (169.5–214.7) | 159.8 (139.8–189.7) | 0.118 |
| IL-21 | All BDL | All BDL | NA |
| IL-22 | 188.1 (179.4–196.9) | 206.7 (194.8–219.3) | 0.042 |
| IL-23 | 957.8 (803.8–1033.8) | 1025.7 (928.8–1122.3) | 0.580 |
| IL-27 | All BDL | All BDL | NA |
| IL-31 | All BDL | All BDL | NA |
| IL-33 | All BDL | 5 BDL 32.4 (32.4–32.4) | NA |
| IFN-γ | All BDL | All BDL | NA |
| TGF-α | All BDL | All BDL | NA |
| TNF-α | All BDL | All BDL | NA |
| SCF | 1 BDL 52.6 (43.0–67.3) | 52.3 (48.1–72.6) | 0.510 |
| ICAM-1 | 300,482.3 (282,840.7–340,813.5) | 256,993.4 (196,382.9–352,890.6) | 0.313 |
| VCAM-1 | 885,105.2 (772,516.0–963,921.1) | 860,086.5 (744,720.3–1,025,740.6) | 1.000 |

| TSLP | All BDL | All BDL | NA |
|---|---|---|---|
| APRIL | 2732.8 (2620.8–2962.3) | 3223.6 (3081.5–3247.1) | 0.073 |
| BAFF/BLyS | 818.9 (776.9–857.8) | 971.4 (916.4–1020.2) | 0.073 |
| E-Selectin | 19,011.4 (16,793.1–22,997.4) | 22,912.5 (14,228.5–27,716.0) | 0.793 |
| P-Selectin | 43,610.4 (33,110.2–50,395.1) | 51,785.5 (46,351.9–57,613.2) | 0.313 |
| VEGF-A | 104.0 (92.1–157.8) | 170.7 (117.5–223.7) | 0.264 |
| PDGF-BB | 7092.1 (6164.5–7753.1) | 8652.3 (6977.5–10125.3) | 0.252 |

Data are presented as medians and interquartile ranges.

Significance testing was performed using the Mann-Whitney *U*-test.

BDL, below detectable level; NA, not available.

**Table E5. Differences in platelet activation markers between placebo and omalizumab phases.**

| Variable | Placebo n = 16 | Omalizumab n = 16 | P value |
|---|---|---|---|
| Platelet cell ($\times 10^4/\mu L$) | | | |
| Day 0 | 25.2 (22.5–28.6) | 26.5 (22.5–27.5) | 0.831 |
| Day 1 | 25.3 (22.9–29.6) | 26.0 (22.5–27.4) | 0.411 |
| Day 7 | 25.5 (23.1–28.5) | 27.2 (23.7–29.2) | 0.368 |
| Month 1 | 25.8 (23.3–29.6) | 25.7 (24.1–28.0) | 0.463 |
| Month 2 | 26.0 (23.8–29.9) | 26.7 (24.5–28.4) | 0.678 |
| Month 3 | 27.0 (24.1–30.7) | 26.9 (25.5–28.6) | 0.734 |
| Platelet activation markers | | | |
| Plasma soluble P-selectin level (ng/mL) | | | |
| Day 0 | 108.7 (88.1–133.4) | 105.3 (94.2–134.7) | 0.669 |
| Month 3 | 117.6 (94.0–127.9) | 96.5 (86.7–106.9) | 0.298 |
| CD62P expression on platelets (%) | | | |
| Day 0 | 3.5 (2.0–5.1) | 3.5 (1.9–6.1) | 0.495 |
| Month 3 | 4.8 (3.7–7.6) | 5.0 (3.8–9.6) | 0.404 |

| | | | |
|---|---|---|---|
| CD63 expression on platelets (%) | | | |
| Day 0 | 4.0 (2.7–5.1) | 4.9 (3.0–6.1) | 0.821 |
| Month 3 | 5.0 (2.6–11.3) | 5.0 (3.4–8.8) | 0.669 |

Data are expressed as the median (interquartile range).

Significance testing was performed using the Wilcoxon signed rank test.

**Table E6. Differences in each serum cytokine level between placebo and omalizumab phases.**

| Cytokines (pg/mL) | Placebo n = 16 | Omalizumab n = 16 | P value |
|---|---|---|---|
| CCL1/I-309 | | | |
| Day 0 | 9 BDL 9.9 (9.8–11.2) | 10 BDL 1.0 (9.8–10.2) | 0.438 |
| Month 3 | 10 BDL 9.9 (9.5–10.5) | 11 BDL 9.7 (9.7–9.9) | 0.625 |
| CCL2/MCP-1 | | | |
| Day 0 | 299.0 (223.6–320.1) | 279.3 (235.0–356.5) | 0.376 |
| Month 3 | 277.7 (225.2–355.9) | 315.0 (228.8–360.1) | 0.274 |
| CCL3/MIP-1α | | | |
| Day 0 | 7 BDL 183.0 (183.0–208.8) | 9 BDL 220.4 (202.6–231.3) | 0.375 |
| Month 3 | 8 BDL 208.8 (183.0–231.3) | 5 BDL 208.8 (183.0–231.3) | 1.000 |
| CCL4/MIP-1β | | | |
| Day 0 | 1147.0 (1061.2–1244.0) | 1148.9 (1095.5–1267.7) | 0.940 |
| Month 3 | 1132.0 (1103.3–1234.4) | 1137.6 (1093.6–1221.9) | 0.890 |
| CCL5/RANTES | | | |
| Day 0 | 37,133.1 (28,032.1–46,262.0) | 36,151.8 (24,333.4–48,898.7) | 0.706 |
| Month 3 | 25,494.2 (20,070.6–31,598.0) | 21,850.9 (15,917.3–34,164.8) | 0.669 |

| | | | |
|---|---|---|---|
| CCL7/MCP-3 | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | 15 BDL 155.6 (155.6–155.6) | All BDL | NA |
| CCL8/MCP-2 | | | |
| Day 0 | 2 BDL 96.1 (77.5–98.3) | 1 BDL 84.5 (71.1–103.1) | 0.685 |
| Month 3 | 1 BDL 77.8 (72.3–89.7) | 1 BDL 85.8 (72.0–98.0) | 0.808 |
| CCL11/eotaxin | | | |
| Day 0 | 9 BDL 133.1 (129.2–150.0) | 11 BDL 152.9 (148.1–229.6) | 0.125 |
| Month 3 | 11 BDL 157.6 (143.2–178.1) | 10 BDL 140.7 (130.5–175.9) | 1.000 |
| CCL13/MCP-4 | | | |
| Day 0 | 107.9 (82.6–136.5) | 92.0 (76.6–146.7) | 0.900 |
| Month 3 | 94.1 (79.5–135.6) | 94.5 (77.2–123.4) | 0.528 |
| CCL17/TARC | | | |
| Day 0 | 710.7 (576.5–864.3) | 806.3 (554.6–862.6) | 0.747 |
| Month 3 | 1 BDL 656.2 (568.0–846.4) | 727.7 (621.5–844.7) | 0.946 |
| CCL24/eotaxin-2 | | | |
| Day 0 | 872.0 (723.0–1073.8) | 889.3 (765.8–1173.8) | 0.376 |
| Month 3 | 875.4 (696.2–970.7) | 917.7 (699.8–1079.5) | 0.376 |
| CCL26/eotaxin-3 | | | |

| | | | |
|---|---|---|---|
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| CXCL1/GROα | | | |
| Day 0 | 13 BDL 422.1 (380.7–493.3) | 14 BDL 515.6 (515.6–515.6) | 1.000 |
| Month 3 | 14 BDL 443.4 (402.3–484.5) | 14 BDL 475.2 (446.8–503.7) | 1.000 |
| CX3CL1/fractalkine | | | |
| Day 0 | 6320.8 (5653.0–7171.7) | 6320.3 (5570.6–7130.8) | 0.821 |
| Month 3 | 6176.2 (5790.7–6876.9) | 6337.3 (5777.9–6537.9) | 0.761 |
| CXCL5/ENA-78 | | | |
| Day 0 | 1288.1 (885.0–1472.7) | 1213.6 (1069.9–1297.4) | 0.720 |
| Month 3 | 1081.1 (877.5–1312.5) | 1051.2 (931.9–1287.1) | 0.706 |
| CXCL8/IL-8 | | | |
| Day 0 | 4 BDL 11.5 (10.1–12.8) | 4 BDL 11.3 (10.0–12.5) | 0.645 |
| Month 3 | 13 BDL 11.0 (10.0–11.5) | 4 BDL 10.3 (9.3–11.9) | 1.000 |
| CXCL9/MIG | | | |
| Day 0 | All BDL | 15 BDL 3648.2 (3648.2–3648.2) | NA |
| Month 3 | All BDL | All BDL | NA |
| CXCL10/IP-10 | | | |
| Day 0 | 32.3 (29.0–40.9) | 32.8 (28.2–45.0) | 0.980 |

| | | | |
|---|---|---|---|
| Month 3 | 32.6 (26.5–41.5) | 35.8 (29.1–45.8) | 0.433 |
| CXCL12/SDF-1α | | | |
| Day 0 | 861.1 (808.5–1031.3) | 879.3 (823.9–998.8) | 0.855 |
| Month 3 | 879.3 (849.5–1015.4) | 915.0 (826.3–994.5) | 0.744 |
| CXCL13/BLC/BCA-1 | | | |
| Day 0 | 63.7 (51.7–78.3) | 66.1 (57.9–81.5) | 0.685 |
| Month 3 | 59.3 (48.7–74.6) | 60.9 (56.4–75.4) | 0.463 |
| CD23/FcεRII | | | |
| Day 0 | 2368.0 (1642.7–3081.1) | 2293.7 (1363.5–2989.6) | 0.433 |
| Month 3 | 2292.6 (1519.7–2827.7) | 2541.0 (1517.9–2926.5) | 0.489 |
| CD40 ligand | | | |
| Day 0 | 5729.4 (4845.1–8185.0) | 6281.0 (5616.6–7021.5) | 0.597 |
| Month 3 | 5985.4 (4906.2–7902.7) | 6738.1 (5522.1–7428.5) | 0.083 |
| G-CSF | | | |
| Day 0 | All BDL | 15 BDL 68.1 (68.1–68.1) | NA |
| Month 3 | All BDL | All BDL | NA |
| GM-CSF | | | |
| Day 0 | All BDL | 15 BDL 25.6 (25.6–25.6) | NA |
| Month 3 | All BDL | All BDL | NA |

| | | | |
|---|---|---|---|
| IL-1β | | | |
| Day 0 | 14 BDL 36.5 (36.5–36.5) | 14 BDL 33.6 (33.1–34.1) | 1.000 |
| Month 3 | All BDL | 14 BDL 32.7 (32.7–32.7) | NA |
| IL-2 | | | |
| Day 0 | 4 BDL 148.2 (101.8–204.0) | 6 BDL 160.6 (111.4–257.9) | 0.910 |
| Month 3 | 5 BDL 171.8 (112.9–184.9) | 7 BDL 158.1 (129.0–263.9) | 0.719 |
| IL-3 | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| IL-4 | | | |
| Day 0 | 15 BDL 80.5 (80.5–80.5) | 14 BDL 80.0 (74.3–85.8) | 1.000 |
| Month 3 | 14 BDL 65.7 (52.8–78.6) | 15 BDL 91.6 (91.6–91.6) | 1.000 |
| IL-5 | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| IL-6 | | | |
| Day 0 | All BDL | 15 BDL 17.6 (17.6–17.6) | NA |
| Month 3 | 15 BDL 9.9 (9.9–9.8) | All BDL | NA |
| IL-7 | | | |

| | | | |
|---|---|---|---|
| Day 0 | 4 BDL 13.4 (11.7–16.2) | 4 BDL 15.6 (13.0–20.1) | 0.037 |
| Month 3 | 4 BDL 12.7 (11.2–14.3) | 6 BDL 14.5 (10.7–17.8) | 0.625 |
| IL-10 | | | |
| Day 0 | All BDL | 15 BDL 20.6 (20.6–20.6) | NA |
| Month 3 | 15 BDL 7.3 (7.3–7.3) | All BDL | NA |
| IL-11 | | | |
| Day 0 | 15 BDL 1054.6 (1054.6–1054.6) | All BDL | NA |
| Month 3 | 15 BDL 1112.0 (1112.0–1112.0) | All BDL | NA |
| IL-12 (p70) | | | |
| Day 0 | All BDL | 15 BDL 302.4 (302.4–302.4) | NA |
| Month 3 | All BDL | All BDL | NA |
| IL-13 | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| IL-16 | | | |
| Day 0 | 1 BDL 166.3 (128.1–180.2) | 128.1 (102.1–160.6) | 0.048 |
| Month 3 | 144.4 (131.2–163.9) | 130.0 (113.2–153.2) | 0.083 |
| IL-17A | | | |
| Day 0 | All BDL | All BDL | NA |

| | | | |
|---|---|---|---|
| Month 3 | All BDL | All BDL | NA |
| IL-17E/IL-25 | | | |
| Day 0 | All BDL | 15 BDL 1329.3 (1329.3–1329.3) | NA |
| Month 3 | All BDL | All BDL | NA |
| IL-18 | | | |
| Day 0 | 165.8 (154.2–197.0) | 195.7 (156.9–227.3) | 0.144 |
| Month 3 | 167.8 (156.5–203.0) | 190.4 (146.3–252.7) | 0.193 |
| IL-21 | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| IL-22 | | | |
| Day 0 | 179.3 (168.9–213.3) | 191.4 (178.2–200.6) | 0.744 |
| Month 3 | 187.5 (174.7–201.0) | 189.9 (177.7–201.3) | 0.404 |
| IL-23 | | | |
| Day 0 | 973.5 (905.1–1122.3) | 984.0 (936.7–1015.5) | 0.855 |
| Month 3 | 1057.3 (931.5–1078.1) | 1025.9 (860.0–1059.9) | 0.421 |
| IL-27 | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |

| | | | |
|---|---|---|---|
| IL-31 | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| IL-33 | | | |
| Day 0 | 15 BDL 32.4 (32.4–32.4) | All BDL | NA |
| Month 3 | 15 BDL 32.4 (32.4–32.4) | All BDL | NA |
| IFN-γ | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | 15 BDL 99.6 (99.6–99.6) | All BDL | NA |
| TGF-α | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| TNF-α | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| SCF | | | |
| Day 0 | 1 BDL 48.1 (44.7–63.0) | 1 BDL 48.1 (41.3–67.3) | 0.762 |
| Month 3 | 2 BDL 54.0 (47.9–67.0) | 2 BDL 54.3 (45.8–66.1) | 0.966 |
| ICAM-1 | | | |

| | | | |
|---|---|---|---|
| Day 0 | 285,661.3 (255,347.5–332,163.6) | 295,542.8 (251,607.6–350,148.9) | 0.940 |
| Month 3 | 299,279.5 (259,386.3–336,682.6) | 294,381.6 (249,565.1–352,364.3) | 0.900 |
| VCAM-1 | | | |
| Day 0 | 885,105.2 (756,313.8–987,991.4) | 965,757.9 (760,943.9–1,103,350.0) | 0.348 |
| Month 3 | 926,067.1 (819,052.4–1,015,725.0) | 951,435.7 (776,413.6–1,043,275.0) | 0.744 |
| TSLP | | | |
| Day 0 | All BDL | All BDL | NA |
| Month 3 | All BDL | All BDL | NA |
| APRIL | | | |
| Day 0 | 2732.8 (2540.6–3029.9) | 2837.4 (2599.2–3192.1) | 0.821 |
| Month 3 | 2775.8 (2568.6–3032.8) | 2774.3 (2554.9–2956.0) | 0.706 |
| BAFF/BLyS | | | |
| Day 0 | 840.4 (766.5–961.1) | 847.6 (761.3–958.1) | 0.934 |
| Month 3 | 869.0 (731.9–888.5) | 885.4 (815.1–947.8) | 0.025 |
| E-selectin | | | |

| | | | |
|---|---|---|---|
| Day 0 | 18,862.1 (15,686.9–27,509.0) | 18,233.0 (13,222.0–26,846.5) | 0.117 |
| Month 3 | 20,640.8 (12,918.7–24,752.5) | 18,601.2 (13,636.0–23,789.8) | 0.323 |
| P-selectin | | | |
| Day 0 | 1 BDL 46,140.8 (32,903.9–51,661.5) | 46,725.9 (36,761.3–53,918.7) | 0.277 |
| Month 3 | 45,397.4 (36,660.8–53,497.1) | 45,956.0 (39,041.0–52,513.1) | 0.323 |
| VEGF-A | | | |
| Day 0 | 119.5 (91.8–198.6) | 124.0 (99.9–219.7) | 0.175 |
| Month 3 | 112.0 (88.1–196.8) | 112.3 (93.3–169.1) | 1.000 |
| PDGF-BB | | | |
| Day 0 | 7458.2 (6139.3–8408.5) | 7005.8 (6669.4–7904.4) | 1.000 |
| Month 3 | 6821.2 (5833.1–7574.0) | 6821.1 (4945.9–8137.5) | 0.706 |

Data are expressed as the median (interquartile range).

Significance testing was performed using the Wilcoxon signed rank test.

BDL, below detectable level; NA, not available

**Table E7. Differences in symptom scores between placebo and omalizumab phases.**

| Variable | Placebo n = 16 | Omalizumab n = 16 | P value |
|---|---|---|---|
| Symptom scores | | | |
| ACT | | | |
| Day 0 | 20.0 (17.8–25.0) | 20.5 (14.0–22.5) | 0.253 |
| Day 1 | NA | NA | |
| Day 7 | NA | NA | |
| Month 1 | 20.5 (17.8–24.0) | 22.0 (20.0–25.0) | 0.054 |
| Month 2 | 20.0 (15.0–22.5) | 23.0 (21.0–25.0) | 0.002 |
| Month 3 | 20.5 (17.8–24.0) | 23.0 (21.0–24.3) | 0.003 |
| ACQ-6 | | | |
| Day 0 | 0.9 (0.7–1.7) | 1.0 (0.8–2.3) | 0.556 |
| Day 1 | NA | NA | |
| Day 7 | 1.1 (0.7–1.7) | 0.8 (0.4–1.2) | 0.123 |
| Month 1 | 1.0 (0.7–1.8) | 0.8 (0–1.1) | 0.026 |
| Month 2 | 1.4 (0.8–2.4) | 0.8 (0–1.0) | 0.002 |
| Month 3 | 1.1 (0.8–2.0) | 0.8 (0.2–0.8) | 0.002 |
| SNOT-22 | | | |

| | | | |
|---|---|---|---|
| Day 0 | 29.5 (25.3–47.0) | 43.0 (33.8–56.8) | 0.074 |
| Day 1 | NA | NA | |
| Day 7 | NA | NA | |
| Month 1 | 44.0 (22.8–54.3) | 31.0 (19.8–44.5) | 0.049 |
| Month 2 | 43.5 (29.8–54.5) | 28.0 (17.3–36.0) | 0.006 |
| Month 3 | 40.5 (30.5–50.8) | 27.0 (16.3–35.5) | 0.004 |
| VAS¶ | | | |
| Dyspnea (cm) | | | |
| Day 0 | 2.5 (1.7–3.8) | 2.0 (1.5–6.5) | 0.504 |
| Day 1 | 2.3 (1.8–3.6) | 2.3 (1.5–3.5) | 0.572 |
| Day 7 | 2.0 (1.6–3.5) | 1.7 (1.0–2.8) | 0.058 |
| Month 1 | 2.0 (1.7–3.2) | 1.6 (0.6–2.5) | 0.011 |
| Month 2 | 2.1 (1.5–4.8) | 1.4 (0.4–2.2) | <0.001 |
| Month 3 | 2.0 (1.5–4.8) | 1.2 (0.5–1.8) | <0.001 |
| Wheezing (cm) | | | |
| Day 0 | 1.9 (1.2–3.5) | 2.1 (1.3–6.4) | 0.266 |
| Day 1 | 1.9 (1.2–3.3) | 1.9 (1.5–3.5) | 0.812 |
| Day 7 | 1.9 (1.3–3.9) | 1.7 (0.9–2.5) | 0.052 |
| Month 1 | 2.0 (1.4–3.6) | 1.6 (0.6–2.3) | 0.014 |

| | | | |
|---|---|---|---|
| Month 2 | 2.8 (1.8–4.9) | 1.5 (0.4–2.1) | <0.001 |
| Month 3 | 2.0 (1.4–4.8) | 1.1 (0.4–1.8) | 0.001 |
| Cough (cm) | | | |
| Day 0 | 2.8 (1.8–4.0) | 2.6 (1.6–6.3) | 0.163 |
| Day 1 | 2.9 (1.7–4.1) | 2.6 (1.6–4.7) | 0.946 |
| Day 7 | 2.5 (1.5–4.3) | 1.8 (1.5–2.8) | 0.310 |
| Month 1 | 2.4 (1.5–5.3) | 1.6 (1.3–2.2) | 0.046 |
| Month 2 | 3.0 (2.0–7.6) | 1.4 (0.6–1.9) | <0.001 |
| Month 3 | 3.7 (1.9–6.0) | 1.5 (0.7–2.0) | 0.001 |
| Nasal congestion (cm) | | | |
| Day 0 | 4.9 (2.5–7.2) | 5.6 (1.8–7.9) | 1.000 |
| Day 1 | 4.7 (1.9–6.6) | 5.0 (1.5–6.8) | 0.524 |
| Day 7 | 4.7 (1.5–7.0) | 4.3 (1.4–6.4) | 0.382 |
| Month 1 | 5.6 (1.5–7.1) | 3.1 (1.6–5.6) | 0.135 |
| Month 2 | 5.5 (2.3–8.2) | 3.3 (1.2–5.6) | 0.007 |
| Month 3 | 4.0 (2.2–6.5) | 2.8 (1.2–4.7) | 0.002 |
| Anterior rhinorrhoea (cm) | | | |
| Day 0 | 5.3 (3.1–8.3) | 4.5 (2.1–8.3) | 0.326 |
| Day 1 | 5.5 (2.7–8.1) | 3.4 (1.2–7.9) | 0.189 |

| | | | |
|---|---|---|---|
| Day 7 | 5.3 (2.5–8.6) | 2.2 (1.5–6.3) | 0.130 |
| Month 1 | 5.6 (2.3–8.6) | 3.7 (1.4–6.3) | 0.066 |
| Month 2 | 6.3 (2.5–8.6) | 3.6 (1.3–5.9) | 0.004 |
| Month 3 | 5.3 (2.2–9.0) | 3.0 (1.3–5.1) | 0.018 |
| Anosmia (cm) | | | |
| Day 0 | 8.4 (3.7–10.0) | 9.1 (4.0–9.8) | 1.000 |
| Day 1 | 8.5 (3.6–9.7) | 7.4 (3.7–9.1) | 0.678 |
| Day 7 | 8.7 (3.9–10.0) | 5.3 (1.9–8.4) | 0.208 |
| Month 1 | 9.0 (5.0–9.8) | 5.0 (1.6–7.0) | 0.079 |
| Month 2 | 9.3 (4.3–10.0) | 4.8 (1.5–7.5) | 0.027 |
| Month 3 | 8.9 (4.3–10.0) | 4.8 (1.4–7.1) | 0.034 |

Data are expressed as the median (interquartile range).

Significance testing was performed using the Wilcoxon signed rank test.

¶VAS scores ranged from ‘not at all bothersome’ (0 cm) to ‘extremely bothersome’ (10 cm).

ACT, Asthma Control Test; ACQ-6, Asthma Control Questionnaire-6; NA, not applicable;

SNOT-22, Sino-Nasal Outcome Test; VAS, visual analogue scale.

**Table E8. Differences in each variable for respiratory function between placebo and omalizumab phases.**

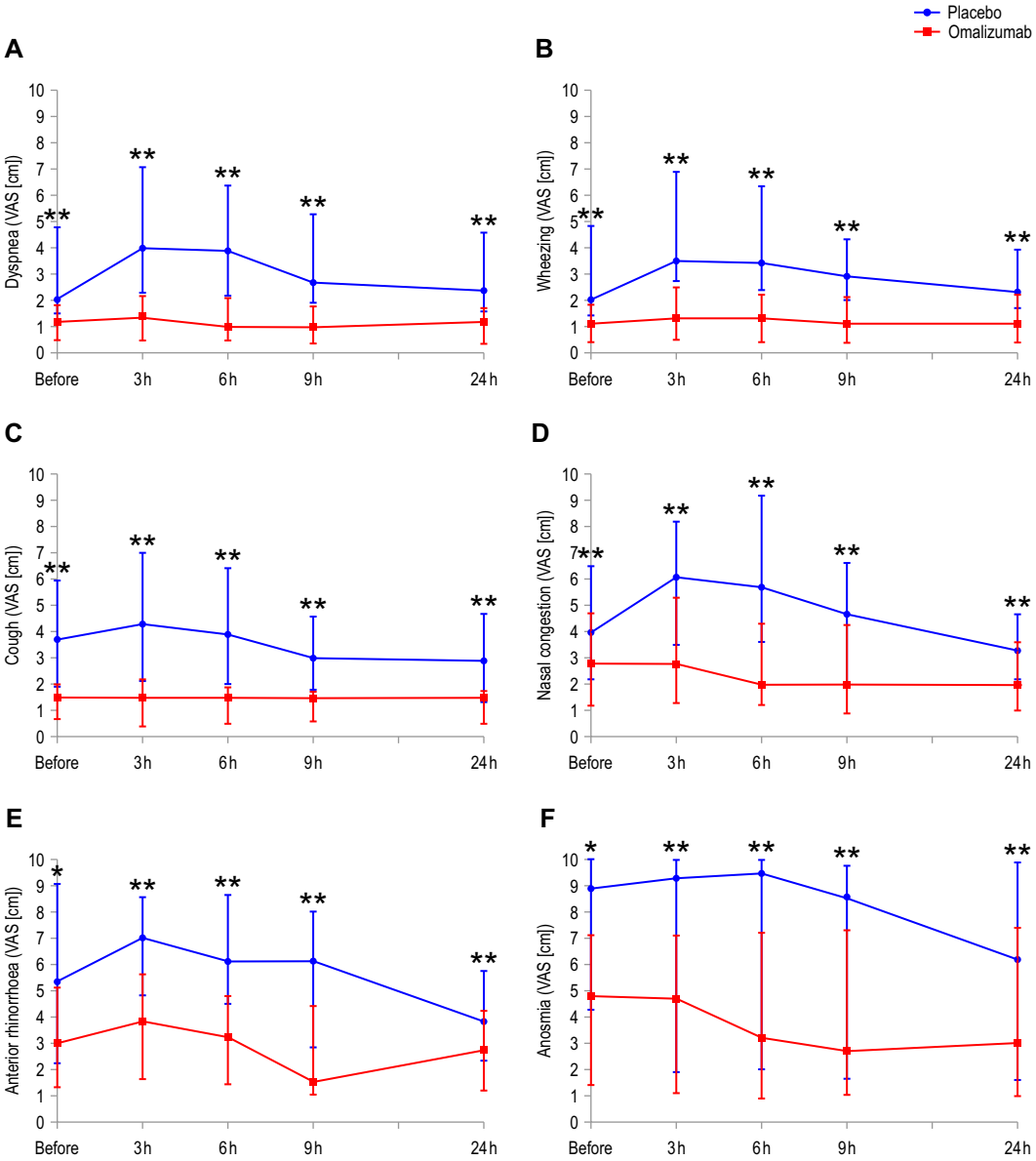
| Variable | Placebo<br>n = 16 | Omalizumab<br>n = 16 | P value |
|---|---|---|---|
| Spirometry | | | |
| $FEV_1$ (% predicted) | | | |
| Day 0 | 105.2 (94.5–112.0) | 103.8 (89.1–110.8) | 0.348 |
| Month 3 | 99.1 (92.4–108.5) | 106.7 (99.1–114.7) | 0.003 |
| $FEV_1$/FVC (%) | | | |
| Day 0 | 75.2 (68.7–79.6) | 75.2 (71.9–77.7) | 1.000 |
| Month 3 | 73.3 (68.5–75.5) | 75.6 (70.7–81.4) | 0.004 |
| FVC (% predicted) | | | |
| Day 0 | 121.7 (111.2–129.7) | 117.7 (113.4–126.0) | 0.277 |
| Month 3 | 121.6 (108.9–127.3) | 123.3 (116.4–130.8) | 0.159 |
| $FEF_{25–75\%}$ (%) | | | |
| Day 0 | 61.7 (43.7–70.8) | 53.2 (43.5–70.0) | 0.782 |
| Month 3 | 50.9 (42.2–60.4) | 61.8 (46.2–70.6) | 0.006 |
| FeNO (ppb) | | | |

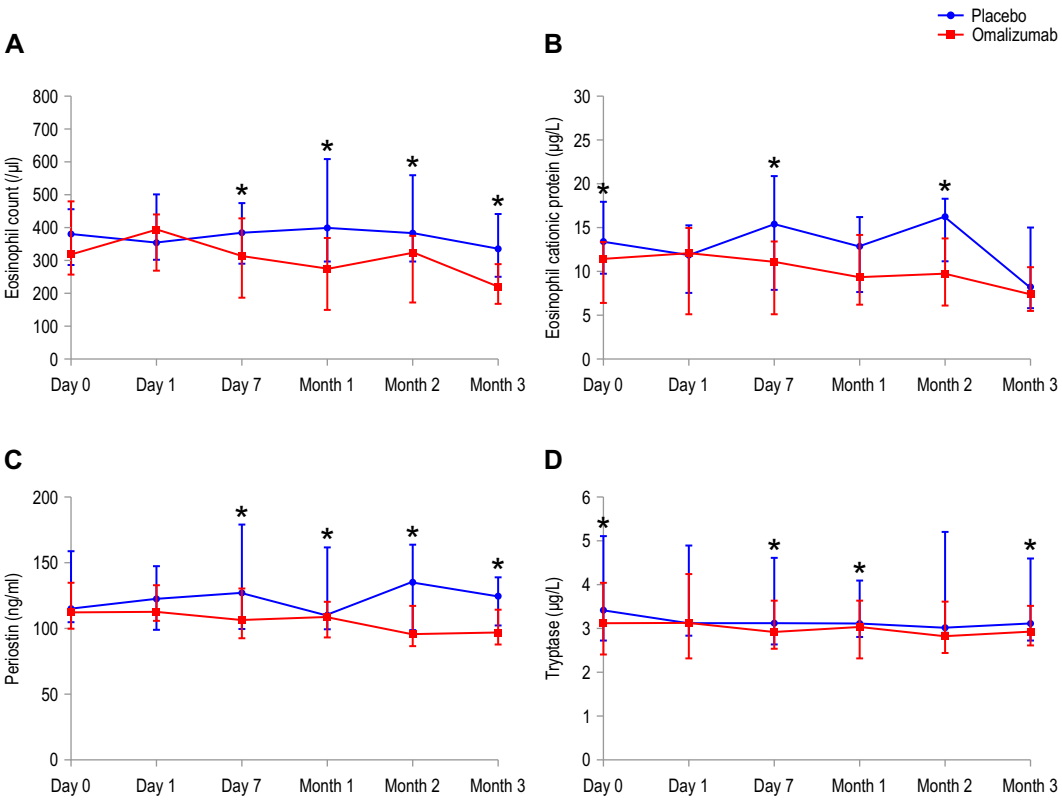
| | | | |
|---|---|---|---|
| Day 0 | 23.1 (18.9–30.9) | 19.9 (12.9–29.4) | 0.348 |
| Month 3 | 24.3 (15.6–39.7) | 20.2 (15.5–37.0) | 0.323 |

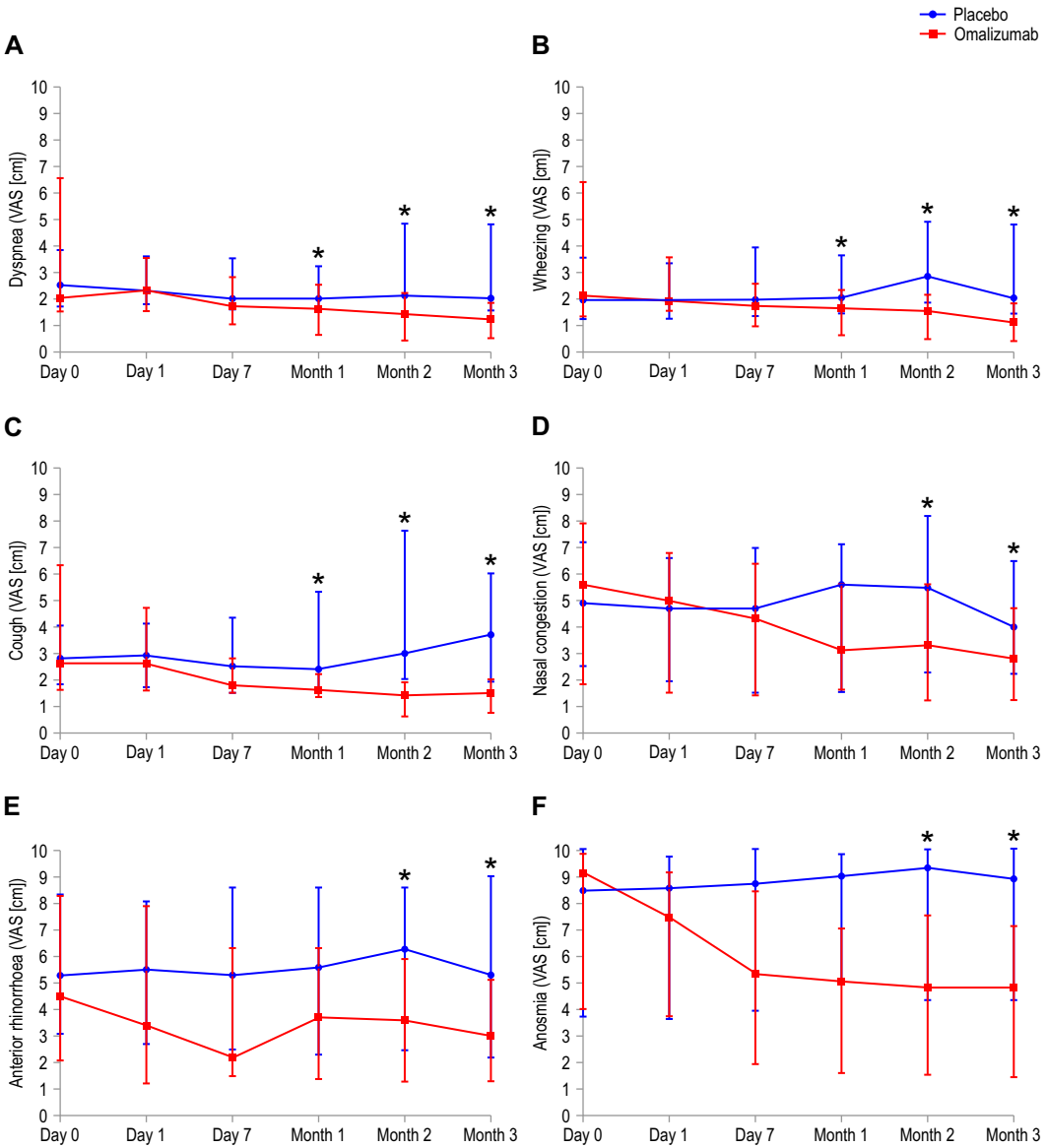
Data are expressed as the median (interquartile range).

Significance testing was performed using the Wilcoxon signed rank test.

$FEF_{25–75}$, forced expired flow between 25% and 75% of the volume expired; FeNO, fraction of exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity.


Placebo
Omalizumab
A
Dyspnea (VAS [cm])
B
Wheezing (VAS [cm])
C
Cough (VAS [cm])
D
Nasal congestion (VAS [cm])
E
Anterior rhinorrhoea (VAS [cm])
F
Anosmia (VAS [cm])
Before
3h
6h
9h
24h


Placebo
Omalizumab
A
Eosinophil count (/µl)
800
700
600
500
400
300
200
100
0
Day 0
Day 1
Day 7
Month 1
Month 2
Month 3
B
Eosinophil cationic protein (µg/L)
30
25
20
15
10
5
0
C
Periostin (ng/ml)
200
150
100
50
0
D
Tryptase (µg/L)
6
5
4
3
2
1
0


Placebo
Omalizumab
A
Dyspnea (VAS [cm])
B
Wheezing (VAS [cm])
C
Cough (VAS [cm])
D
Nasal congestion (VAS [cm])
E
Anterior rhinorrhoea (VAS [cm])
F
Anosmia (VAS [cm])
Day 0
Day 1
Day 7
Month 1
Month 2
Month 3
*