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Are Serum immunoglobulin Concentrations a Predictive Biomarker of Response to Anti-IL5/IL5R α Therapies?

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32 Abbreviations: Asthma control test: ACT, forced expiratory volume in one second: FEV1, forced
33 vital capacity: FVC, global evaluation of treatment effectiveness: GETE, interleukin 5: IL5,
34 interleukin 5 receptor: IL5R, ROC: receiver operating characteristic

35

36 Abstract:

37

38 Background: Approval of biologics has recently revolutionized T2 severe asthma management.

39 However, predictive biomarkers remain highly needed to improve patient's selection.

40 Objective: This study aims to determine whether serum immunoglobulins (Igs) levels might be
41 predictive biomarkers of response to anti-interleukin-5 (IL5)/IL5R α therapies.

42 Methods: Severe asthma patients eligible for mepolizumab or benralizumab were included
43 herein. Serum immunoglobulin quantification was performed at baseline before mepolizumab or
44 benralizumab initiation. After a 6-month treatment of mepolizumab or benralizumab, patients
45 presented a second serum immunoglobulin quantification. The treatment response was evaluated
46 by the GETE (Global Evaluation of Treatment Effectiveness) score at 6 months.

47 Results: A total of 50 patients were included. Median age was 56 [IQR 48.8-65.3] and 50% were
48 females. Compared to baseline, a significant increase in IgG was observed at 6 months (9.2 [7.8-
49 10.2] g/l vs 10.1 [8.8-11.1] g/l, $p=0.04$). The area under the ROC curve was 0.58 [95%IC 0.40-
50 0.77] for blood eosinophil count ($p=0.37$), 0.75 [95%IC: 0.58-0.92] for serum IgG concentration
51 ($p=0.009$) for predicting the treatment response. According to the Youden index, serum IgG
52 concentration ≥ 9.2 g/l predicts the response to anti-IL5 therapies with a sensitivity of 76.9% and
53 a specificity of 75.7%.

54 Conclusion: Baseline serum IgG concentrations may be a useful tool to predict the response to
55 anti-IL5/IL5R α therapies but should be confirmed in larger clinical trials. Interestingly, anti-
56 IL5/IL5R α therapies are associated with a significant increase in serum IgG concentrations at 6
57 months.

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59 Key words: asthma; mepolizumab; benralizumab; IgG; biomarkers

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61

62 **Introduction**

63 Severe asthma is a global health problem that affects approximatively 3.6% of all asthma
64 patients [1]. Severe asthma is defined as asthma requiring a high level of treatment [2]. Despite
65 this treatment, some patients with severe asthma experience frequent exacerbations and
66 hospitalizations[3, 4]. Severe asthma is also associated with a high economic burden and gathers
67 the major part of healthcare costs among these patients [5].

68 Severe asthma is a heterogeneous condition including many different phenotypes [6]. A severe
69 eosinophilic asthma phenotype has been previously identified in several cluster-based studies [7,
70 8] and it is characterized by severe asthma with type 2-high inflammation [9]. Recently,
71 biological therapies targeting eosinophils being the main components of T2 inflammation have
72 been approved [10, 11]. Mepolizumab, an anti-interleukin-5 monoclonal antibody (anti-IL5), and
73 benralizumab, an anti-IL5 receptor- α (IL5R α) antibody, are used as add-on therapies for patients
74 with severe uncontrolled eosinophilic asthma (blood eosinophils count ≥ 0.3 G/l). Mepolizumab
75 and benralizumab are associated with oral corticosteroid sparing as well as a significant
76 reduction in the rate of exacerbations [12, 13]. Although the response rate of those therapies is
77 very high, some patients show no response to anti-IL5/IL5R α therapies. In BORA study, an
78 extension of phase III clinical trials, 28% of 527 patients who received benralizumab still
79 experienced at least one exacerbation by week 56 [14]. In MENSA, phase III study on
80 mepolizumab, 38 % of patients experienced no significant improvement with mepolizumab [15].
81 In clinical practice, patient's selection before the beginning of biological therapies has been very
82 challenging because none predictive biomarkers have been identified except blood eosinophil
83 count. Despite this latter, clinicians are still unable to accurately predict the response to these
84 therapies. Therefore, predictive biomarkers of anti-IL5/IL5R α therapies are urgently needed
85 [16].

Immunoglobulins (Igs) are circulating heterodimeric proteins primarily involved in adaptive immunity [17]. In asthma, it has been established that a low level of serum IgG is associated with recurrent exacerbations [18]. Moreover, the serum IgG level is significantly lower when asthma exacerbations are associated with positive viral samples [19]. Asthma patients with hypogammaglobulinemia have low type-2 inflammation markers [20]. According to this, it would be interesting to assess serum IgG concentrations as a biomarker of anti-IL5/IL5R α therapies in severe asthma.

The aim of our study was to determine whether baseline serum IgG concentrations are a predictive biomarker of anti-IL5/IL5R α therapies.

Methods

Study design

A retrospective "real-life" study was carried out on severe asthma patients between March 2018 and October 2019 at Toulouse University Hospital Center. The patients were included if they had a quantification of serum Ig concentration at baseline and after a 6-month treatment of mepolizumab or benralizumab prescribed for severe asthma. Severe asthma was defined according to the ATS/ERS guidelines [21]. Benralizumab or mepolizumab were administered according to drug manufacturers' recommendations. Considering our study as a "real life" one, the prescription of mepolizumab or benralizumab was at the discretion of the clinicians. Regarding the study design, severe asthma patients had serum immunoglobulin quantification at baseline before the beginning of mepolizumab or benralizumab. After a 6-month treatment of mepolizumab or benralizumab, patients received a second serum immunoglobulin quantification. The database was anonymous and compliant with the restrictive requirements of the National Commission for Data Protection (CNIL number: 2206723 v 0), the body that oversees the enforcement of data privacy laws in France. Our study was conducted in accordance with the

French law. Moreover, the study protocol was approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine (Société de Pneumologie de Langue Française) (CEPRO 2020-042). In accordance with French law, information was provided to the patients and oral non-opposition was collected.

Clinical data and response to biological therapies

Age, gender, BMI, smoking history, the annualized rate of asthma exacerbations, asthma control test (ACT) score, the presence of nasal polyposis, positive prick tests to aeroallergens, the daily dose of inhaled corticosteroids and the use of long-term oral corticosteroids (defined by systemic corticosteroids for more than 6 months) were collected.

The response to mepolizumab or benralizumab was evaluated at 6 months using the GETE score (global evaluation of treatment effectiveness) [22]. Patients with Excellent or good response were classified as responders, while those with a GETE score rated as moderate, poor, or worsening response were classified as non-responders.

Serum immunoglobulins

The concentration of serum Igs was collected at the initiation of mepolizumab or benralizumab and at 6 months of treatment. Serum Igs were quantified by turbidimetry and expressed in g/l. IgE were quantified by an immunoenzymofluorimetric technique and expressed in kIU/l.

Lung function tests

Lung function tests were carried out using a spirometer (Jaeger Vyntus, CareFusion, Germany). Values for Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) were expressed in percentages of mean predicted values according to gender, height and age. Measurements were performed in accordance with ATS/ERS guidelines [23, 24]. The mean

predicted values were those of ERS for FEV1 and FVC [25]. Fractional exhaled nitric oxide (FeNO) were obtained using an electrochemical device (Hypair FeNO, Medisoft®, Belgium). Briefly, repeated and reproducible exhalations were performed, until obtaining at least two nitric oxide (NO) plateau values differing by less than 10%. Flow rate exhalation was 50 ml/sec. The retained FeNO value was the mean of two reproducible measurements and was expressed in parts per billions (ppb). FeNO was measured according to ATS/ERS guidelines [24].

Statistical analysis

Quantitative data are expressed as median and [interquartile range] whereas qualitative data are expressed as number of patients (%). The Wilcoxon test is used to compare two quantitative variables. Statistical significance is defined as a p value of <0.05.

Receiver operator characteristics (ROC) curves are used to assess blood eosinophil count or serum IgG concentrations as potential predictive biomarkers of response to mepolizumab or benralizumab. Sensitivity and specificity of IgG cut-off for predicting responders to mepolizumab or benralizumab are also defined. The best IgG cut-off is determined using Youden's index.

Results

A total of 50 severe asthma patients treated with mepolizumab or benralizumab were included. The details of patients' characteristics at baseline are indicated in Table 1. Median age was 56.0 [48.8-65.3] years and 25 (50%) patients were female. Thirty-seven (74%) patients were treated with mepolizumab and thirteen (26%) with benralizumab. Mean predictive values of pre-bronchodilator FEV1 were 71.2 [53.0-88.1].

At 6 months, the ACT score significantly improved with mepolizumab or benralizumab (median ACT score was 13 [9-16] at baseline and 21 [13-23] at 6 months; $p < 0.0001$) (Table 2). A significant reduction of the annualized rate of exacerbations was also observed after a 6-month

162 treatment of mepolizumab or benralizumab (6.0 [4.0-11.5] at baseline vs 0.0 [0.0-2.0] at 6
 163 months; $p < 0.0001$). In patients treated with a long-term use of oral steroids, the daily dose of
 164 OCS was significantly reduced with mepolizumab or benralizumab at 6 months (17.5 [10.0-20.0]
 165 mg at baseline vs 6.3 [0.0-10.0] mg at 6 months; $p < 0.0001$). Regarding lung function tests at 6
 166 months, median prebronchodilator FEV1 increased from 71.2 [53.0-88.1]% of mean predicted
 167 values to 83.0 [67.0-99.0]% of mean predicted values. At 6 months, 37 (74%) patients were
 168 considered as being responders to mepolizumab or benralizumab (Excellent or good response
 169 according to GETE score).

170 Regarding the change over time of serum immunoglobulin concentrations after a 6-month
 171 treatment of mepolizumab or benralizumab, IgA and IgM were not influenced by those
 172 treatments. However, IgG significantly increased from 9.2 [7.8-10.2] g/l at baseline to 10.1
 173 [8.38-11.1] g/l at 6 months ($p = 0.001$) (Figure 1). The long-term use of oral steroids seems to
 174 have no impact on the change in serum Ig concentrations over time. Actually, at 6 months, a
 175 similar increase in serum IgG concentrations was observed between patients treated with oral
 176 steroids and those with no oral steroids at baseline (+10.1 [-4.9-+22.0]% and +8.2 [+0.1-
 177 +17.5]%, respectively; $p = 0.93$) (Table 3). However, among patients with OCS at baseline, we
 178 compare those with a 50% decrease in OCS dose and those with a decrease less than 50% at 6
 179 months. There is a statistical difference between groups (+18.3 [+12.4-+26.6]% and -3.4 [-8.7-
 180 +0.2]%, respectively ($p = 0.0009$)). Regarding the concentrations of other serum Igs, the change
 181 over time was similar in patients with oral steroids and those with no oral steroids at baseline.

182 According to ROC curves, we determined whether serum IgG concentrations at baseline may be
 183 a good predictive biomarker of a response to mepolizumab or benralizumab (Figure 2). The area
 184 under the ROC curves for predicting the treatment response was 0.58 [95%IC 0.40-0.77] for
 185 blood eosinophil count ($p = 0.37$) and 0.75 [95%IC: 0.58-0.92] for serum IgG concentrations
 186 ($p = 0.009$). According to Youden's index, the best sensitivity and specificity were 69.2% and

62.9%, 76.9% and 75.7%, respectively for blood eosinophil count (0.48 G/l cut-off) and serum IgG concentrations (9.2 g/l cut off).

Discussion

A significant increase in serum IgG concentrations was observed 6 months after the beginning of anti-IL5/IL5R α therapies. Moreover, sensitivity and specificity were determined for baseline serum IgG concentrations as a predictor of a good response to mepolizumab or benralizumab (76.9% and 75.7%, respectively for a 9.2 g/l cut-off).

Eosinophils are innate immune cells originated in pluripotent progenitor cells in the bone marrow and their survival, expansion, and terminal differentiation are mainly driven by IL5 [26].

The physiological role of eosinophils has not been fully elucidated yet. However, their involvement in asthma pathophysiology (airway dysfunction and tissue remodelling) has been clearly established [27]. The beneficial effect of anti-IL5/IL5R α therapies on asthma outcomes in severe eosinophilic asthma patients has been demonstrated but the mechanism involved has not been fully understood yet [28]. Eosinophils are more multifunctional than originally shown and these cells interact with several other immune cells such as T cells, B cells, macrophages or dendritic cells. For example, eosinophils release cytokines that influence T cell differentiation and also secrete chemoattractants for the recruitment of T cells, macrophages, and dendritic cells to tissue sites [29, 30]. The effect of eosinophils on immunoglobulin production has not been extensively studied. Interestingly, it has been shown that bone marrow eosinophils are the key providers of plasma cell survival factors in mice [31]. Eosinophils are crucial for the retention of plasma cells in the bone marrow [31, 32]. Regarding the increase in serum IgG concentrations in our study, we hypothesise that mepolizumab or benralizumab may lead to plasma cell release into the bloodstream with eosinophil inhibition. However, it has also been shown that eosinophils promote B cell survival, proliferation, and immunoglobulin secretion in *in vitro*

212 studies [33]. A positive correlation between blood eosinophils and B cells has also been observed
213 in hypereosinophilic patients [33]. The interaction between eosinophils and the immune system
214 is probably more complex and further studies are warranted [34].

215 Systemic steroids may play a role in serum IgG increase within biological therapies. In fact, it is
216 well known that anti-IL5/IL5R α therapies are associated with a reduction of OCS use. In
217 addition, steroids impact immunoglobulin production. Indeed, a significant reduction of serum
218 IgG level has been observed with short-term [35, 36] or long-term [37] use of OCS. There was
219 no influence in IgA or IgM. In our study, a growth in serum IgG was particularly found at 6
220 months after the initiation of biological therapies in patients who had a significant reduction of
221 OCS (long-term users). However, no difference in terms of IgG increase was observed between
222 patients with or without long-term use of OCS at baseline. Therefore, we hypothesize that even
223 in patients with no long-term use of OCS, a reduction of short-term courses of OCS with
224 biological therapies may have an impact on serum IgG. Moreover, no change was observed in
225 other immunoglobulins, given IgG are more sensitive to OCS than IgA or IgM.

226 Another explanation may be an artificial increase in serum IgG since patients were given
227 injections of mepolizumab or benralizumab which are IgG1. The low amount of drugs
228 administered to these patients cannot lead to such an increase in serum IgG. Moreover, no
229 increase in IgG1 was observed. Immune complexes between anti-drug antibodies and
230 mepolizumab or benralizumab have also been described in clinical trials. Given the method of
231 serum IgG quantification, an artificial increase in serum IgG may be explained by immune
232 complexes. However, this phenomenon is uncommon and does not explain such an increase [38].
233 The usefulness of serum IgG in severe asthma management is still controversial. The prevalence
234 of hypogammaglobulinemia seems to be higher in asthma patients compared to the general
235 population [39]. In this study, hypogammaglobulinemia was strongly associated with the use of
236 systemic corticosteroids. Asthma patients with hypogammaglobulinemia can be integrated in a

specific phenotype with low type-2 inflammation [20]. In primary immune deficiency, low serum immunoglobulin concentrations expose asthma patients to a higher risk of asthma exacerbations and severe asthma. In fact, it has been estimated that the relative risk of asthma exacerbation was 1.70 times higher in patients with low serum immunoglobulin concentrations (low IgG, A, M or IgG subclasses) compared to those with normal concentrations [18]. Moreover, severe asthma prevalence also appears to be significantly higher in patients with low serum immunoglobulin concentrations compared to those with normal concentrations (32.5% and 13.0%, respectively) [18]. As observed in patients with common variable deficiency, it has been suggested that the recurrence of viral or bacterial infections is a mechanism of asthma exacerbations in patients with low serum IgG concentrations [20, 40, 41]. In asthma patients, serum IgG levels have been found to be significantly lower when asthma exacerbations were associated with positive viral samples [19].

In literature, it seems that low serum IgG levels tend to be associated with severe asthma and infection-induced asthma exacerbations (mostly viral). We hypothesize that severe eosinophilic asthma patients with the lowest IgG levels may combine both eosinophilic and infection-induced asthma exacerbations. Patients presenting the highest IgG levels might experience mostly eosinophilic exacerbations. This may explain that serum IgG concentrations appear to be a predictive biomarker of response to anti-IL5/IL5R α therapies in our study. The highest levels of serum IgG found in excellent responders may reflect a “purest” eosinophilic phenotype leading to a more beneficial effect of anti-IL5/IL5R α therapies. Moreover, poor responders who exhibit the lowest levels of serum IgG may experience a mix between eosinophilic and infection-induced exacerbations. However, the effect of anti-IL5/IL5R α therapies on viral infections has not extensively been assessed yet. In a study carried out on mild asthma patients challenged with rhinovirus 16, mepolizumab enhanced local B cells and reduced neutrophils as well as their activation [42]. Mepolizumab also enhanced secretory IgA and decreased tryptase in

262 bronchoalveolar lavage [42]. Further studies are needed to determine whether anti-IL5/IL5R α
263 therapies have any effect on virus-induced asthma exacerbations.

264 The role of serum IgG concentrations as a predictive biomarker of response to anti-IL5/IL5R α
265 therapies needs further studies. The quality criteria of a reliable biomarker remains unclear in
266 severe asthma. Although, no definition has been established yet, it is obvious that a good
267 predictive biomarker should appear in easy-to-collect fluid and be simply detected or quantified
268 in assays being both affordable and robust [43, 44]. Regarding the performance of a predictive
269 biomarker, there is no specific definition. It has been established that the area under the ROC
270 curve of blood eosinophil for predicting mepolizumab response ranges from 0.79 to 0.89 [45,
271 46]. In our study, the area under the ROC curve of serum IgG is 0.75. Although the AUC values
272 are close, serum IgG should be confirmed in further prospective clinical studies as a predictive
273 biomarker.

274 Our study has several limitations. Firstly, the assessment of the response to mepolizumab or
275 benralizumab is based on the GETE score, which is a subjective score with its inherent bias.
276 However, no objective markers of response have been developed for anti-IL5/IL5R α therapies.
277 Furthermore, the GETE score has been validated with omalizumab being the first biological
278 therapy used in severe asthma [22]. Secondly, whereas the increase in serum IgG concentrations
279 with mepolizumab or benralizumab was statistically significant, it remains uncertain whether this
280 difference is clinically relevant or not. This should be determined in specific clinical trials.
281 However, in order to provide clinically relevant data, we determined if serum IgG concentrations
282 were a useful predictive biomarker of response to anti-IL5/IL5R α therapies. In fact, we found out
283 that a 9.2 g/l cut-off may be used to determine good and bad responders. Thirdly, Ig
284 quantification is not systematically performed at 6 months in our centre. Thus, the patients'
285 selection based on a quantification at 6 months after the initiation of biological therapies could
286 introduce a bias in the results. Finally, we pooled benralizumab and mepolizumab data but we

287 found no relevant differences between mepolizumab and benralizumab (data not shown).
288 However, given the small number of patients treated with benralizumab, the comparison between
289 mepolizumab and benralizumab has to be interpreted with caution. Although their mechanisms
290 of action are close but not identical, further comparisons are needed.

291 In severe asthma patients, mepolizumab or benralizumab are associated with a significant
292 increase in serum IgG concentrations at 6 months. The mechanisms involved in this change over
293 time are not fully understood but could be due to a reduction of OCS use with biological
294 therapies. Thus, further mechanistic studies are required to better elucidate eosinophil-B cells
295 interaction. Moreover, baseline serum IgG concentrations seem to be helpful to predict a good
296 response to anti-IL5/IL5R α therapies. In order to confirm this hypothesis, this biomarker should
297 be tested in a larger cohort.

298

299 Authors' contributions:

300 Simon Lauret made substantial contributions to conception and design, acquisition of data, and
301 analysis and interpretation of data; drafted the article; gave final approval of the version to be
302 published and agrees to be accountable for all aspects of the work related to its accuracy or
303 integrity.

304 Elise Noel-Savina made substantial contributions to conception and design, recruitment of
305 patients and interpretation of data; reviewed the manuscript critically for important intellectual
306 content; gave final approval of the version to be published; and agrees to be accountable for all
307 aspects of the work related to its accuracy or integrity.

308 Grégoire Prévot made substantial contributions to conception and design, recruitment of patients
309 and interpretation of data; reviewed the manuscript critically for important intellectual content;
310 gave final approval of the version to be published; and agrees to be accountable for all aspects of
311 the work related to its accuracy or integrity.

312 Laurent Reber made substantial contributions to conception and design, recruitment of patients
313 and interpretation of data; reviewed the manuscript critically for important intellectual content;
314 gave final approval of the version to be published; and agrees to be accountable for all aspects of
315 the work related to its accuracy or integrity.

316 Nicolas Guibert made substantial contributions to conception and design, recruitment of patients
317 and interpretation of data; reviewed the manuscript critically for important intellectual content;
318 gave final approval of the version to be published; and agrees to be accountable for all aspects of
319 the work related to its accuracy or integrity.

320 Danièle Brouquières made substantial contributions to conception and design, recruitment of
321 patients and interpretation of data; reviewed the manuscript critically for important intellectual
322 content; gave final approval of the version to be published; and agrees to be accountable for all
323 aspects of the work related to its accuracy or integrity.

324 Alain Didier made substantial contributions to conception and design, recruitment of patients and
325 interpretation of data; reviewed the manuscript critically for important intellectual content; gave
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327 work related to its accuracy or integrity.

328 Laurent Guilleminault made substantial contributions to conception and design, acquisition of
329 data, and analysis and interpretation of data; drafted the article; gave final approval of the
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331 accuracy or integrity.

332

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457

458 Figure 1: Concentrations of serum immunoglobulins at baseline and at 6 months of treatment
459 with anti-IL5 therapies. * $p=0.01$

460 Figure 2: Receiver operating characteristics (ROC) curve analysis of A) baseline blood
461 eosinophil count B) baseline serum IgG concentrations and C) baseline serum IgG4
462 concentration for the prediction of an excellent or good response to mepolizumab or
463 benralizumab. The area under the ROC curve for the prediction of the treatment response was
464 0.58 [95%IC 0.40-0.77] for blood eosinophil count ($p=0.37$) and 0.75 [95%IC: 0.58-0.92] for
465 serum IgG concentration ($p=0.009$).

466

467 Table 1: Baseline characteristics of patients hospitalized for asthma exacerbation. ACT: asthma
 468 control test; FEV1: forced expiratory volume in 1 second; FVC: forced volume capacity; FeNO:
 469 fraction of exhaled nitric oxide; IgE: Immunoglobulin E

	n=50
Age (years)	56.0 [48.8-65.3]
Female	25 (50)
Active or former smokers	19 (38)
BMI (kg/m ²)	24.7 [21.8-28.1]
Allergen sensitization	15 (30)
Nasal polyposis	26 (52)
ACT score	13 [9-16]
Inhaled corticosteroid dose (beclomethasone equivalent doses) (µg/d)	1000 [800-2000]
Annualized rate of exacerbation within 12 months	6.0 [4.0-11.5]
Oral steroids at baseline	29 (58)
Daily dose of oral steroids (mg/d)	17.5 [10.0-20.0]
Patients treated with mepolizumab	37 (74)
Patients treated with benralizumab	13 (26)
Prebronchodilator FEV1 (% mean predicted values)	71.2 [53.0-88.1]
FEV1/FVC (%)	68.0 [64.0-74.0]
FeNO (ppb)	38.5 [22.0-64.3]
Blood eosinophil count (G/l)	0.50 [0.23-0.80]
Total IgE (kIU/l)	244 [85-491]

470

471 Table 2: Clinical and functional parameters at baseline and at 6 months of treatment with anti-
 472 IL5 therapies. ACT: asthma control test; FEV1: forced expiratory volume in 1 second; FVC:
 473 forced volume capacity; FeNO: fraction of exhaled nitric oxide; IgE: Immunoglobulin E

	Baseline	6 months	p
ACT score	13 [9-16]	21 [13-23]	<0.0001
Annualized rate of exacerbations	6.0 [4.0-11.5]	0.0 [0.0-2.0]	<0.0001
Daily dose of oral steroids (µg/d)	17.5 [10.0-20.0]	6.3 [0.0-10.0]	<0.0001
Prebronchodilator FEV1 (% mean predicted values)	71.2 [53.0-88.1]	83.0 [67.0-99.0]	0.0001
FEV1/FVC (%)	68.0 [64.0-74.0]	68.5 [63.0-76.3]	0.14
FeNO (ppb)	38.5 [22.0-64.3]	46.5 [23.5-89.8]	0.69
Blood eosinophils (G/L)	0.50 [0.23-0.80]	0.0 [0.0-0.1]	<0.0001
GETE 1 or 2	-	37 (74)	-

474
 475

476 Table 3: Change in serum immunoglobulins concentrations at 6 months of treatment with anti-
 477 IL5 therapies in patients with oral steroids and those with no oral steroids at baseline. The
 478 change is expressed as a percentage.

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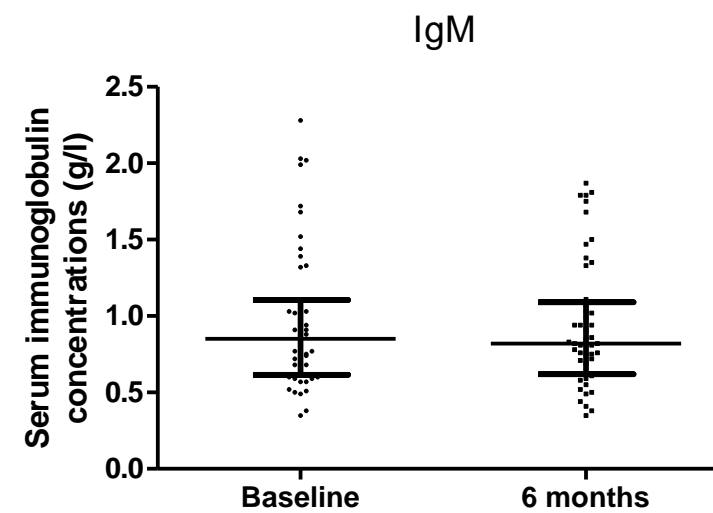
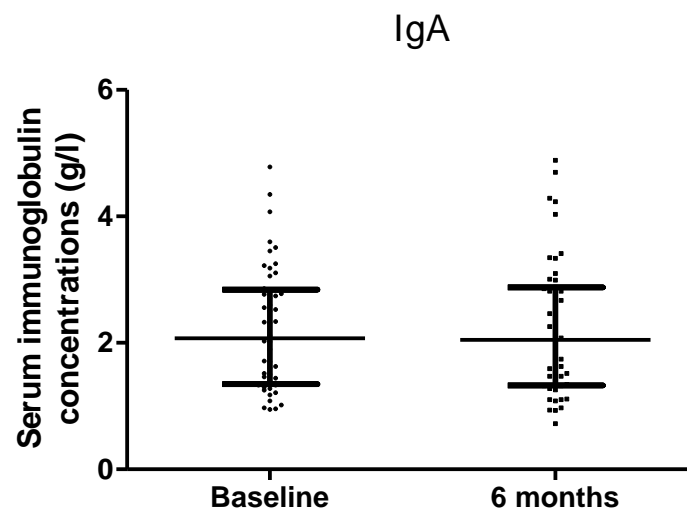
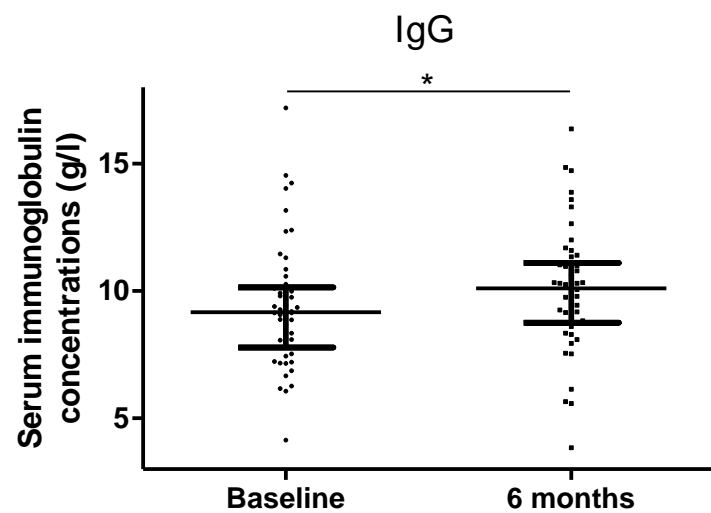
	Oral steroids	No oral steroids	p
IgG (%)	+10.1 [-4.9-+22.0]	+8.2 [+0.1-+17.5]	0.93
IgA (%)	+1.5 [-13.0-+11.7]	+5.8 [-3.5-+12.8]	0.40
IgM (%)	-2.6 [-10.3-+5.2]	0.0 [-9.2-+5.3]	0.72

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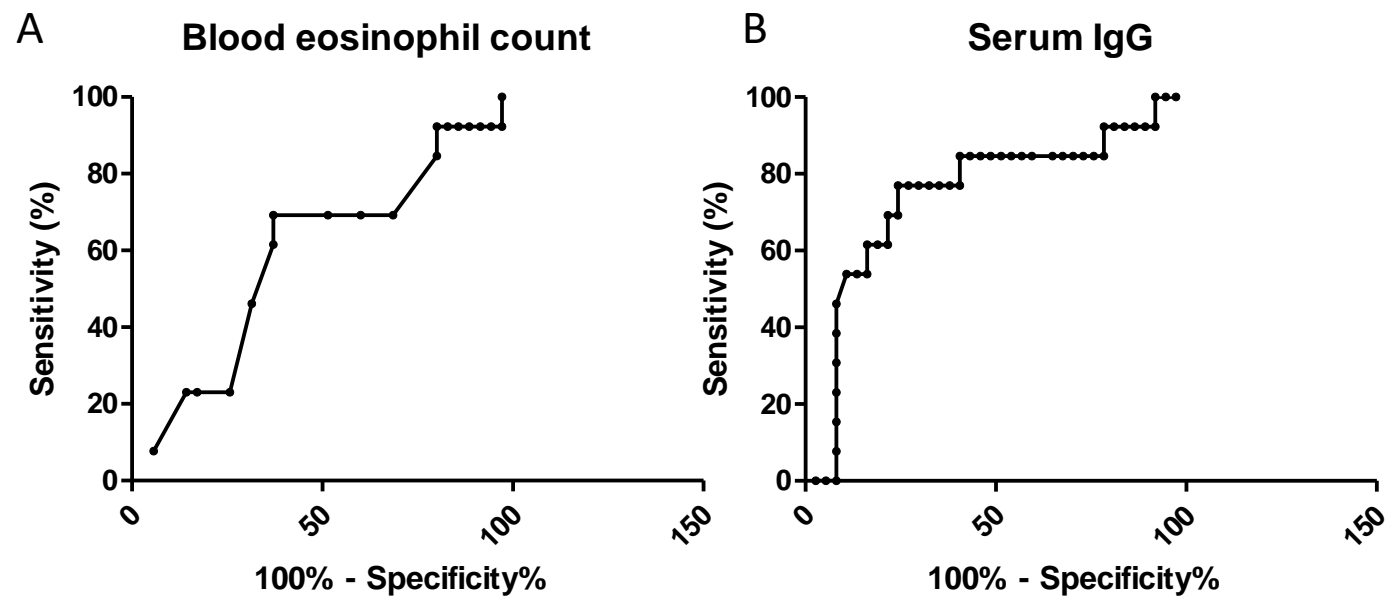


Figure 2