

Clinical and laboratory features of antihistamine-resistant chronic idiopathic urticaria

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ABSTRACT

Chronic idiopathic (spontaneous) urticaria (CIU) is sometimes resistant to the conventional and high doses of antihistamines (AHs). This study compares the clinical and laboratory characteristics of AH responsive and AH-resistant CIU subjects. Clinical and laboratory data were retrospectively collected from 385 CIU patients. Urticaria activity score (UAS), concomitant angioedema, dermatographism, positive autologous serum skin (ASST), and laboratory data were collected. The control group consisted of 44 sex- and age-matched healthy individuals. Two hundred forty-five CIU patients controlled with AH medications were included in the CIU group. Forty-six patients failed to show clinical improvement during 8 weeks of treatment with fourfold AH doses and were included in the resistant CIU (R-CIU) group. The R-CIU group was characterized with a higher incidence (58.7%) of angioedema than the CIU group (28.5%; $p < 0.001$), more cases concomitant physical urticaria (23.9% in R-CIU versus 12.2% in CIU; $p = 0.014$), more positive ASST (73.9% in R-CIU versus 45.4% in CIU; $p < 0.001$), and higher baseline UAS (5.28 ± 0.81 in R-CIU versus 3.32 ± 1.25 in CIU; <0.001). R-CIU was characterized with more severe basopenia (0.04 ± 0.07 cell/mm³ versus 0.16 ± 0.13 cell/mm³; $p < 0.001$), higher mean platelet volume (10.87 ± 2.21 femtoliter (fl) versus 8.65 ± 1.74 fl; $p < 0.001$), higher levels of C-reactive protein (8.62 ± 3.91 mg/L versus 2.49 ± 1.34 mg/L; <0.001), and higher levels of serum C3 (1.66 ± 0.36 g/L versus 1.19 ± 0.35 g/L; $p < 0.001$). R-CIU is a clinically more severe disease with laboratory features of low-grade inflammation and platelet activation.

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Urticaria is widely regarded as a heterogeneous group of diseases that share a distinct skin reaction pattern, *i.e.*, the development of urticarial skin lesions.^{1,2} Chronic idiopathic urticaria (CIU) is defined as wheals arising spontaneously without any external physical stimuli, and the disease lasts >6 weeks.¹

Patients with CIU, which is also referred to chronic spontaneous urticaria (CSU), are often unsatisfied with the standard treatment and their quality of life is differentially impaired.³ The recent guidelines recommend as a first-line therapy, non-sedating H₁-antihistamines (AHs), increasing their dosage as second-line treatment, adding a leukotriene antagonist or switching to another AH as the third-line treatment.⁴ Although guideline-recommended AH up-dosing improves symptom control in the majority of affected subjects, both our clinical experience and published clinical studies show that a considerable number of patients have only little benefit from higher doses of AHs.^{5–9} Currently, all other treatments of AH-resistant CIU are off-label.

There are four aspects that seem to be associated with a prognosis of CIU: (i) disease severity, (ii) angioedema, (iii) combination of CIU with physical urticaria, and (iv) autoreactivity (positivity in the autologous serum skin test [ASST]).^{10,11} Recent findings indicate that activation of the coagulation cascade resulting in thrombin production¹² is a prominent feature of exacerbations in CIU and that intradermal injection of autologous plasma causes wheal-and-flare reactions with a higher frequency than autologous serum injections.¹² Moreover, severe exacerbations of CIU are associated with a strong activation of the coagulation cascade and fibrinolysis.¹³ Within the coagulation cascade, thrombin is a serine protease that induces activation of platelets and may play a key role in chronic urticaria.¹⁴ Several studies indicate that platelet volume is in direct correlation with platelet function, because large platelets are more reactive and a presence of large platelets in blood is an *in vivo* indicator of platelet activity.¹⁵ Large platelets are denser, they produce more thromboxane B₂ per unit volume of platelet cytoplasm,¹⁶ they contain more α - and dense granules, and preferential aggregation of large platelets is observed after addition of adenosine diphosphate,¹⁴ collagen, and thrombin.¹⁷ They also release more serotonin and other granule contents and express more glycoprotein Ib per unit area.¹⁸

In the previous study, we observed a positive correlation between clinical severity of CIU with ASST autoreactivity, increased mean platelet volume (MPV),

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and C-reactive protein.¹⁹ The objectives of this study were to estimate the proportion of patients with CIU at an outpatient allergy clinic who do not respond to AHs and to examine if AH-resistant CIU patients have any clinical and laboratory characteristics distinguishing them from the AH responders.

PATIENTS AND METHODS

Patients

We retrospectively studied cases of adult (age, >18 years) patients who were referred to the outpatient allergy clinic from the Ashdod region (Ashdod, Israel) between January 2007 and January 2011 because of a diagnosis of CIU and/or angioedema of at least 6-week duration. The study was approved by the Regional Committee for Medical Research Ethics.

Patients with urticarial vasculitis (UV) were excluded. All those included in the study had negative skin-prick tests to a large panel of commercial food allergens. All CIU patients were treated according to the current guidelines on the management of urticaria.⁴

Clinical Evaluation of CSU

Clinical and laboratory evaluation and classification of chronic urticaria were performed according to a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology, the EU-funded network of excellence, the Global Allergy and Asthma European Network, the European Dermatology Forum and the World Allergy Organization guidelines.^{1,4} ASST was performed with 50 μ L of the patient's undiluted serum after allowing blood to clot at room temperature for 30 minutes and after sample blood centrifugation at $500 \times g$ for 10 minutes, which was then injected intradermally into the volar aspect of the forearm together with simultaneously injected controls, including saline and 10 μ g/mL of histamine. The mean diameters of the wheals were measured at 30 minutes. The test was considered positive if the serum-injected site manifested a wheal with a diameter of at least 1.5 mm greater than that of the saline. Dermographism was assessed using firm stroking of the skin by a dermatographometer with a pressure of 4900 g/cm² and induction of linear itchy wheals within several minutes.

Assessment of Urticaria Severity

For CIU, several scoring systems have been proposed using scales from 0 to 3 or up to 10 points.⁴ A unified and simple scoring system, the urticaria activity score (UAS), was proposed in the last version of a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology, the EU-funded network of excellence, the Global Allergy and Asthma European Network, the European

Dermatology Forum and the World Allergy Organization guidelines.¹ This scoring system is suitable for the evaluation of disease activity by urticaria patients and their treating physicians.

UAS represents a simple semiquantitative assessment of disease activity and it calculates key urticaria symptoms, wheals, and itching. The patients were asked to document a number of wheals and intensity of pruritus during 24 hours. The following scoring system was used: for wheals, no wheals = 0, <20 wheals/24 hours = 1, 20–50 wheals/24 hours = 2, >50 wheals/24 hours or large confluent areas of wheals = 3; for pruritus, no pruritus = 0, mild pruritus without troublesome = 1, moderate pruritus that is troublesome but not interfering with normal daily activity or sleep = 2, and intense pruritus = 3. The UAS is the sum score of 7 consecutive days, used routinely in our clinical practice to determine disease activity and response to treatment of CIU patients. The UAS was applied during each consultation and was recorded in the medical records.

AH Treatment and Response Assessment

The modern nonsedating H₁-AHs were used by all patients as first-line treatment. We usually use fexofenadine hydrochloride (Telfast, 180 mg q.d.; sanofi-aventis, Netanya, Israel), desloratadine at 5 mg q.d. (Aerius; Schering-Plough, Hod Hasharon, Israel), or cetirizine at 10 mg q.d. (Zylergy; Dexcel Pharma, Jerusalem, Israel) as drugs of choice in the treatment of patients with CIU. Patients with significant improvement of CIU (at least a 50% reduction of their UAS) under conventional doses of AH medications were included in the CIU group.

In CIU patients who did not respond sufficiently to the approved dose, an up dosing of the H₁-AHs up to fourfold was performed. AH treatment was considered effective if the patient reported the total or near-total disappearance of wheals and the absence of angioedema and pruritus. The patients with persisting pruritus and recurrent wheals (with or without angioedema), despite a full 8-week AH treatment, were considered as having AH treatment failure and were included in the resistant CIU (R-CIU) group. No H₂-blockers, corticosteroids, or immunomodulatory medications were prescribed before the up dosing of AH medications. The control group consisted of 44 sex- and age-matched healthy individuals recruited from the hospital and the primary care center staff. Written informed consent was given by control group participants.

Laboratory Evaluation of CIU

All of the patients did their laboratory investigations before beginning the treatment with AH medications,

which began the next day after the first allergology consultation. Blood samples were drawn from each subject by antecubital venipuncture between 8 and 10 A.M.. All analyses were performed within a period of 2–3 hours after blood collection. Citrated blood was used with an automated blood counter (Sysmex; Roche) for determination of blood count and MPV. C3 and C4 component levels were measured by the ABICAP assay (Biognosis, Jülich, Germany). The normal standardized values for each component were 80–180 mg/dL for C3 and 10–40 mg/dL for C4. Blood levels of high-sensitivity C-reactive protein (hs-CRP) were measured by immunonephelometry using BN Systems (Dade Behring, Marburg, Germany) and the reference interval for hs-CRP was 1–3 mg/L.

Statistical Analysis

Comparison of categorical variables between groups was performed by chi-square test and Fisher's exact test (two-tailed) as appropriate. Continuous variables are expressed as mean $\pm$ SD and were compared between groups by Student's *t*-test (two-tailed). For all tests the value of $p < 0.05$ was considered significant. All statistical analyses were performed using the software Statistica 6 (StatSoft, Inc., Chicago, IL).

RESULTS

During the study period, 385 patients with urticarial diseases lasting >6 weeks were referred to our allergy clinic. Two hundred eighty-nine patients were diagnosed as having CIU. Among them, 46 (15.9%) patients failed to show at least a 50% UAS reduction during 8-week treatment with fourfold AH doses. These subjects were included in the R-CIU group. The remaining 245 patients whose urticaria was controlled with AH medications were included in the CIU group.

Demographic characteristics of the study groups are presented in Table 1. The R-CIU group was characterized with a longer duration of urticaria; women were more frequently involved in both group CIU and group R-CIU (Table 1).

Clinical Characteristics of Study Groups

Angioedema. The R-CIU group was characterized with a higher incidence (58.7%) of angioedema than the CIU group (28.5%; $p < 0.001$).

Concomitant Dermatographism/Pressure Urticaria. The prevalence of concomitant physical urticaria (dermatographism and/or pressure urticaria) was significantly higher in the R-CIU group (23.9%) than in the CIU group (12.2%; $p = 0.014$).

Autoreactivity/Positive ASST. Among the CIU patients, ASST was performed in 174 subjects, and the test was positive in 79 (45.4%) of them. ASST was performed in all R-CIU patients and the test was positive in 34 (73.9%; $p < 0.001$) subjects.

Urticaria Activity Score. No differences between the study groups were observed in urticarial wheal distribution on the skin surfaces. Nevertheless, baseline UAS was higher in the R-CIU group (5.28 ± 0.81) than in the CIU group (3.32 ± 1.25 ; $p < 0.001$); significant differences in UAS between the study groups were observed also after 8 weeks (R-CIU group, 4.35 ± 0.94 , versus CIU group, 1.14 ± 0.62 ; $p < 0.001$) and 16 weeks (R-CIU group, 1.42 ± 0.76 , versus CIU group, 0; $p < 0.001$) of treatment. Clinical response rate assessment to the treatment with standard and fourfold doses of AHs is presented in Table 2.

Laboratory Characteristics of Study Groups

Blood Count. There were no significant differences in white blood cell, lymphocytes, or eosinophils, but a lower number of circulating basophils was detected in the blood of R-CIU group subjects (0.04 ± 0.07 cell/mm³) than in the CIU group subjects (0.16 ± 0.13 cell/mm³; $p < 0.001$) and healthy controls (0.18 ± 0.15 cell/mm³; $p < 0.001$).

Mean Platelet Volume. There were no significant differences in platelet counts between the groups; nevertheless, the platelets in the R-CIU group were characterized by a higher MPV (10.87 ± 2.21 femtoliter [fl]) than the platelets in the CIU group (8.65 ± 1.74 fl; $p < 0.001$) and healthy controls (7.59 ± 1.08 fl; $p < 0.001$).

Antinuclear Antibodies. In the R-CSU group, the incidence of antinuclear antibodies was significantly higher (9 [19.6%]) than in the CSU group (11 [6.3%]; $p = 0.003$) and in healthy controls (2 [4.5%]; $p = 0.048$).

Liver Enzymes. In subjects with R-CIU, there was a slight but statistically significant elevation of liver transaminases [alanine aminotransferase (47.6 ± 14.2) versus (21.8 ± 13.7 ; $p = 0.024$) in the CIU group and versus healthy controls (23.5 ± 12.9 ; $p < 0.001$)] and [AST (28.3 ± 11.4) versus (18.5 ± 10.2 ; $p < 0.001$) in CIU group and versus healthy controls (17.3 ± 11.1 ; $p < 0.001$)].

C-Reactive Protein. Higher levels of hs-CRP were measured in the R-CIU group (8.62 ± 3.91 mg/L) than in the CIU group (2.49 ± 1.34 ; $p < 0.001$) and the control group (2.76 ± 1.63 ; $p < 0.001$).

Table 1 Demographic and laboratory data of study groups

Characteristics	Resistant CSU <i>n</i> = 46	CSU <i>n</i> = 245	Controls <i>n</i> = 44	<i>p</i> ¹	<i>p</i> ²	<i>p</i> ³
Sex; female (<i>n</i> ; %)	39 (84.8%)	162 (66.1%)	35 (79.5%)	0.33	0.99	0.91
Age (yr)*	42.4 ± 7.9	43.5 ± 9.1	42.7 ± 9.2	0.44	0.81	0.92
BMI (kg/m ²)	26.9 ± 4.8	27.2 ± 4.5	26.9 ± 4.1	0.68	0.89	0.71
Positive ASST	34 (73.9%)	79 (45.4%)#	15 (34.1%)	<0.001	<0.001	0.60
Angioedema	27 (58.7%)	49 (20%)	0	<0.001		
Physical urticaria	11 (23.9%)	21 (12.2%)	0	0.014		
Baseline UAS*	5.28 ± 0.81	3.32 ± 1.25	0	<0.001		
Total IgE (U/mL)	114.7 ± 42.1	109.5 ± 52.4	101.6 ± 56.8	0.52	0.91	0.78
ESR (mm/hr)	13.9 ± 11.3	15.3 ± 12.1	14.2 ± 11.7	0.47	0.87	0.93
WBC (cell/mm ³)	7.1 ± 3.8	7.9 ± 4.3	7.3 ± 3.2	0.24	0.58	0.84
Lymphocytes (cell/mm ³)	2.4 ± 0.9	2.7 ± 1.1	2.6 ± 1.7	0.08	0.62	0.35
Eosinophils (cell/mm ³)	0.39 ± 0.15	0.41 ± 0.21	0.44 ± 0.19	0.54	0.31	0.91
Basophils (cell/mm ³)	0.04 ± 0.07	0.16 ± 0.13	0.18 ± 0.15	<0.001	<0.001	0.26
Platelets (cell × 10 ⁸ /mm ³)	273 ± 138	291 ± 129	262 ± 141	0.39	0.79	0.57
MPV (fl)	10.87 ± 2.21	8.65 ± 1.74	8.59 ± 1.08	<0.001	<0.001	0.82
C3 (g/L)	1.66 ± 0.36	1.19 ± 0.35	1.13 ± 0.29	<0.001	<0.001	0.28
C4 (g/L)	0.34 ± 0.12	0.35 ± 0.17	0.32 ± 0.21	0.71	0.58	0.30
TSH (μg/dL)	2.81 ± 0.94	2.64 ± 0.86	2.58 ± 1.0	0.23	0.15	0.23
ANA (positive >1/80; <i>n</i> ; %)	9 (19.6%)	11 (6.3%)	2 (4.5%)	0.003	0.048	0.69
C-reactive protein (mg/L)	8.62 ± 3.91	2.49 ± 1.34	2.76 ± 1.63	<0.001	<0.001	0.24
ALT (IU/L)	47.6 ± 14.2	21.8 ± 13.7	23.5 ± 12.9	<0.001	<0.001	0.62
AST (IU/L)	28.3 ± 11.4	18.5 ± 10.2	17.3 ± 11.1	<0.001	<0.001	0.48
ALP (IU/L)	76.1 ± 29.8	73.7 ± 32.5	69.8 ± 30.7	0.64	0.33	0.46

Physical urticaria—symptomatic dermographism/dermographic urticaria and delayed pressure urticaria.

*Baseline UAS and UAS at 8 wk.

#In CSU group ASST was performed in 174 patients.

MPV = mean platelet volume; fl = femtoliter; TSH = thyroid stimulating hormone; BMI = body mass index; CSU = chronic spontaneous urticaria; ANA = antinuclear antibodies; ESR = erythrocyte sedimentation rate; ASST = autologous serum skin test; ALT = serum alanine aminotransferase (normal range, 8–41 IU/L); AST = serum aspartate aminotransferase (normal range, 10–38 IU/L); ALP = serum alkaline phosphatase (normal range, 39–117 IU/L); WBC = white blood cell count; *p*¹ = *p* value between resistant CSU and CSU groups; *p*² = *p* value between resistant CSU and control groups; *p*³ = *p* value between CSU and control groups.

Complement C3 and C4 Components. In the R-CIU group, serum C3 (1.66 ± 0.36 g/L) was higher than in the CIU group (1.19 ± 0.35; *p* < 0.001) and healthy controls (1.13 ± 0.29; *p* < 0.001). No significant difference in C4 between the groups was observed (Table 1). In the CIU group, there was a weak but statistically significant positive correlation (*r* = 0.23138; *p* = 0.002) between baseline UAS and serum C3 levels. More powerful statistically significant positive correlation (*r* = 0.36920; *p* = 0.012) between baseline UAS and serum C3 levels were observed in the R-CSU group.

DISCUSSION

In the study, we investigated clinical and laboratory characteristics of CIU patients with different response patterns to H₁-AHs. In our CIU cohort only 46 (15.9%) patients were defined to be resistant to fourfold AH

doses. The previous studies show that one-half or less of CIU patients responded with a complete control of symptoms to licensed AH doses; in those who did not succeed with standard AH doses, increasing the AH dose improved treatment responses but still every third to fourth patient remained symptomatic.²⁰ Although we identified less AH-resistant subjects in our CIU population, it is difficult to compare the AH response rates with the previous studies because different authors examined different urticarial populations with different disease severities.

Our study clearly shows that women suffer from CIU more frequently than men do and this finding is consistent with the previous epidemiological studies.^{21,22} For AHs neither resistance nor other clinical factors (angioedema, ASST positivity, and concomitant dermatographism) seem to alter this proportion.

Table 2 Urticaria activity score and response rate assessment for the treatment with standard and fourfold dose of antihistamines

	Resistant CSU <i>n</i> = 46	CSU <i>n</i> = 245	<i>p</i>
Baseline UAS*	5.28 ± 0.81	3.32 ± 1.25	<0.001
Completely symptom free under treatment with standard dose of AHs (at wk 8; <i>n</i> ; %)	0	132 (58.9%)	
UAS at 8 wk* (no. of subjects)	4.35 ± 0.94 (<i>n</i> = 46)	1.14 ± 0.62 (<i>n</i> = 113)	<0.001
Completely symptom free under treatment with fourfold dose of AHs (at wk 16; <i>n</i> ; %)	0	83 (33.9%)	
UAS at 16 wk# (no. of subjects)	1.42 ± 0.76 (<i>n</i> = 46)	0	<0.001

*Under treatment with standard dose AHs.

#Under treatment with fourfold dose AHs.

AHs = antihistamines; CSU = chronic spontaneous urticaria; UAS = urticaria activity score; *p* = *p* value between resistant CSU and CSU groups.

The prevalence of symptomatic dermatographism/pressure urticaria occurring in combination with CIU was also higher in the R-CIU group. These observations are similar to previous observations^{23–26} and probably reflect a predominance of moderate-to-severe cases in the R-CIU group. CIU severity could furthermore explain the fact that AH-resistant patients were characterized by higher auto-reactivity (more cases of ASST⁺ patients). As it was previously observed, ASST⁺ CIU patients require more AH medications than ASST[−] patients.²⁷

We also found basopenia in both study groups, and R-CIU patients were characterized by lowest number of blood basophils. Basophils are the least frequent of the granulocytes, in humans ordinarily accounting for <0.5% of circulating leukocytes and under physiological conditions, they have a short life-span of several days.²⁸ Distinguishing the contributions between basophils and mast cells in IgE-mediated hypersensitivity reactions has centered on their disparate anatomic locations. In contrast to mast cells, basophils enter the circulation fully mature, but their recruitment to tissues is generally believed to be restricted to delayed late-phase allergic inflammation that occurs hours after antigen exposure²⁹ and in several model systems, optimal basophil accumulation in tissues was highly CD4⁺ T-cell dependent.³⁰

Basopenia in CIU is a well-known phenomenon, and it may reflect enhanced basophil consumption. Besides the basopenia, intrinsic defects of the anti-IgE cross-linking signaling pathway of basophiles have been described in CIU.³¹ Basophil activation marker (CD63, CD69, and CD203c) expression is increased in CIU subjects and is not associated with serum factors.³² CIU basophils have several specific features that distin-

guish them from basophils of a healthy population. They are fewer respondents to anti-IgE and C5a with no difference when stimulated with bradykinin and monocyte chemotactic protein-1 and have a much higher release when incubated with serum.³³ Additional studies need to be performed to determine if there are more profound defects in signaling and/or activation pathways of basophils in R-CIU that could play some role in mechanisms of AH resistance. An increase in CRP in R-CIU may reflect a possible role of a systemic inflammatory process in pathophysiology of the disease. IL-6 is involved in megakaryocyte maturation *in vitro* and is increased in CIU patients.³⁴ In patients with acute allergic reactions, elevations of serum interleukin IL-6 were also felt to be key in promoting CRP elevations.³⁵ These IL-6 elevations occur later than elevations in blood histamine or tryptase levels. Because many studies of IL-6 have shown that CRP and IL-6 are correlated in disease and in normal humans, it suggests the possibility that acute-phase responses may also occur in CIU and it would be speculated that the CRP elevations in ASST⁺ CIU relates, to some degree, to systemic mast cell and basophil activation.³⁶

We believe the most interesting finding of our study is the significant difference in complement C3 component between the study groups. To the best of our knowledge, it is the first description of a relation between C3, clinical severity, and AH resistance in CIU using a relatively large CIU population. In the recent study, a reduction in C3 and C4 was found in a small group of CIU ASST⁺ patients.³⁷ Our study of a larger group of CIU subjects provided opposite results. It is accepted that some patients admitted to the hospital for investigation of severe chronic urticaria are found

to have UV. In one retrospective single-center study, 18% of patients with biopsy-confirmed UV exhibited a hypocomplementemic form of chronic urticaria.³⁸ However, our CIU patients did not have diagnostic criteria for UV and, actually, UV was an exclusion criterion of the study.

Complement C3 protein synthesis is increased in response to inflammation and infection but at a slower rate than for traditional acute phase proteins.^{38,40} The liver (mainly hepatocytes) is responsible for the biosynthesis of 90% of plasma complement components and their soluble regulators, including C3.⁴¹ C3a has been reported to induce histamine release from human skin mast cells.⁴² Moreover, C3a is an active mediator in stimulating chemotaxis and mobilization of cord blood-derived and cutaneous mast cells.⁴³ C3, C4, and anaphylatoxins are known to be elevated in the serum of patients with inflammatory diseases.⁴⁴ We can speculate that elevated circulating amounts of C3 and liver transaminases levels may be related to hepatic fat accumulation and of a general low-grade inflammatory response in CR-CIU patients.⁴⁵

We understand that the study has several limitations, mainly related to its retrospective nature, *viz.*, a lack of randomization and blinding. Second, recording bias is an important possible limitation. Third, we did not investigate a possible role of the observed "low-grade inflammation" in the pathophysiology of AH resistance in CIU.⁴⁶ These issues remain to be studied in future experiments.

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Erratum

Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen

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The analysis of symptom/medication score data employed ANCOVA which requires normally distributed data. Logarithmic transformation of the data was performed and then ANCOVA conducted. The original subtraction of placebo minus active became a ratio of placebo to active with the difference calculated as *placebo- relative- to- active* and not as is customary assessing *active- relative- to- placebo*. All results have now been recalculated as *active- relative- to- placebo*. No changes in statistical significances of any data including p-values were subsequently noted consequent to this change in reference from *placebo- relative- to- active* to *active- relative- to- placebo*.

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