Double-Blind Randomized Controlled Trial on the Efficacy and Safety of Metformin as an Adjunct to Doxycycline and Tretinoin 0.025% Cream in the Treatment of Moderate to Severe Acne Vulgaris*

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ABSTRACT

Objectives: To evaluate the efficacy and safety of metformin as an adjunct to oral doxycycline and tretinoin 0.025% cream in the treatment of moderate to severe acne vulgaris.

Methods: This is a double blind randomized controlled trial with 17 patients per group, and a study period of 12 weeks. Both groups (Dt group and DtM group) received doxycycline for the first 6 weeks and tretinoin for 12 weeks, while only the DtM group received metformin 1500mg/day for the entire treatment period. Follow up visits were done every 2 weeks from baseline. Non-inflammatory, inflammatory and total acne lesion count, and the modified global severity, subjective patient assessment, and Dermatology Life Quality Index scores, scores of cutaneous adverse events, and incidence and frequency of systemic adverse events were the outcome measures.

Results: The DtM group showed significant statistical benefit for the treatment of noninflammatory lesions (comedones) in the 4th, 6th, 8th and 12th week. Outcome measures of global severity, subjective patient assessment, and DLQI scores, mean reduction rate of inflammatory and total lesion counts, and mean pain, erythema, dryness and scaling counts between groups were comparable. The incidence and frequency of reported systemic adverse events such as diarrhea, nausea and headache, were higher in the DtM group.

Conclusion: The addition of metformin to standard treatment is beneficial in reducing non-inflammatory lesion counts. It offers comparable benefit for inflammatory and total lesion counts. Cutaneous and systemic adverse events in both groups were mild and self-limited, and did not warrant discontinuation of treatment.

Keywords: metformin, tretinoin, doxycycline, treatment, acne

**First Place, Residents Category, University of Santo Tomas Annual Scientific Research Forum / Benavides Cancer Institute Auditorium, UST Hospital / December 6, 2012*
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INTRODUCTION

Acne vulgaris is a common inflammatory dematologic condition that afflicts all ages, particularly adolescents and young adults. Its sequela of permanent scarring has its impact on the emotional and psychological well-being of patients. It leads to anxiety, depression, low selfesteem, and withdrawal from society, resulting to a negative impact on the quality of life.1 Acne vulgaris involves the pathology of the pilosebaceous unit, with pleomorphic manifestations of both inflammatory (papules, pustules, nodules, and cysts) and noninflammatory (comedones) lesions. The primary pathogenic processes are follicular hyperkeratinization, excessive sebum production, hypercolonization of the ducts by *Propionibacterium acnes*, and inflammation.[2] Agents in different combinations are used to treat acne, to maximize their synergistic and complementary effects through the different pathogenic processes they target.

Systemic antibiotics such as doxycycline, strongly inhibits proliferation of P. acnes.[3] Topical retinoids, particularly tretinoin, decreases proliferation and differentiation of keratinocytes,[4] consequently suppressing microcomedo formation. In combination, systemic antibiotics and topical retinoids are a suitable choice of treatment in controlling moderate to severe acne, with a treatment rate ranging from 58.7% to 62.4%.[5] This is an increase in efficacy with faster therapeutic response when compared to either agent used as monotherapy. However, due to the rising trend of antibiotic resistance, use of antibiotics should be minimized. These should be discontinued once inflammatory lesions begin to resolve, taking effect approximately 6 weeks into treatment.[3] Relapse or deterioration, however, is common upon antibiotic discontinuation. There is, therefore, a need for alternatives in the treatment of moderate to severe acne that obviates long-term antibiotic use, and shortens the course of treatment.

Metformin is a well-tolerated drug that has been used in the treatment of Type 2 diabetes. It lowers fasting plasma insulin concentrations by inducing greater peripheral uptake of glucose, and decreasing hepatic glucose output without causing hypoglycemia.[6] It has been utilized in several studies involving non-diabetic patients[7,8,9] and for treatment of polycystic ovarian syndrome[10] (PCOS), with no significant untoward decline in blood glucose levels that warranted discontinuation of the study.

The clinical potential of metformin in the treatment of acne in association with PCOS has been well documented. It has been hypothesized that the effects of Metformin are mediated by a decrease in insulin levels as a result of the reduction in hepatic glucose production. Metformin also reduces androgen production by a direct action on the ovaries.[11] Since hyperandrogenemia and increased insulin signaling are involved in the pathogenesis of acne, a reduction in the levels of serum androgens and insulin by metformin, should ameliorate acne and seborrhea.[12]

An uncontrolled study by Kolodziejczyk[13] addressed acne as a specific endpoint in assessing the response of PCOS to metformin. At a dose of 1500 mg/day for a period of 12 weeks, significant decrease in acne score, as well as other parameters related to hyperandrogenism, was demonstrated.

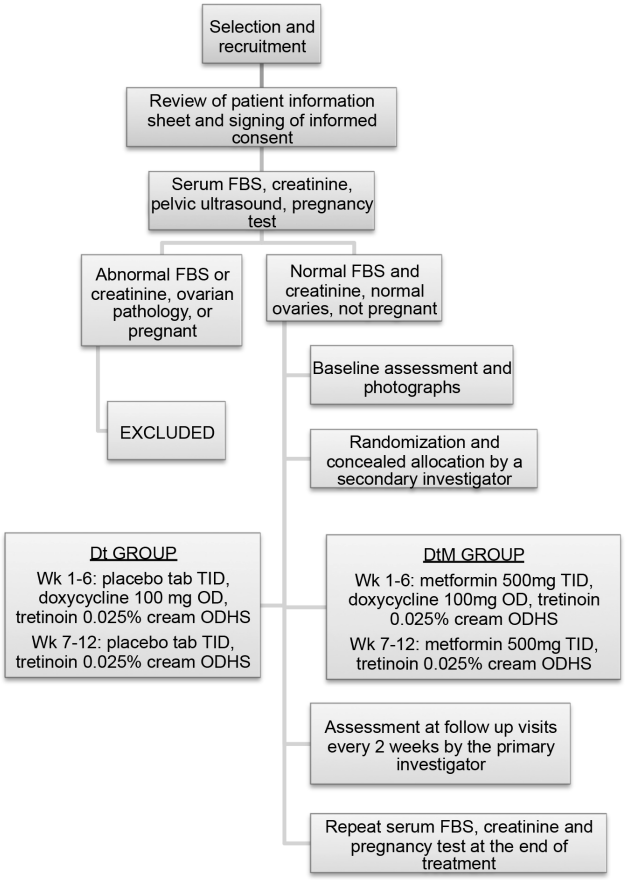
OBJECTIVES

This study compares the efficacy and safety of metformin in combination with doxycycline and tretinoin 0.025% cream vs. doxycycline with tretinoin 0.025% cream in the treatment of moderate to severe acne vulgaris. Specifically, it aims to determine and compare the improvement of acne lesions in both treatment groups through the evaluation of the following:

1. The reduction in number of the non-inflammatory, inflammatory and total lesion count, based on the Leeds Acne Lesion Counting System (Appendix A).
2. The improvement of the modified global severity score (Appendix B)
3. The improvement in severity as reported by the patient during each follow up visit using a subjective self-assessment scale (Appendix C).
4. The improvement in the quality of life as reported by the patient using the Dermatology Life Quality Index or DLQI scores (Appendix D and E), before and after treatment.
5. The grading of cutaneous adverse events on the skin of the face (erythema, pain, scaling and dryness) reported by the patient and/or observed by the investigator.
6. Incidence and frequency of systemic adverse events reported by the patient.

STUDY DESIGN AND METHODOLOGY

Figure 1. Schematic diagram of the study design



This is a phase III clinical trial with a double blind randomized controlled study design (Figure 1). Treatment duration for each patient lasted 12 weeks. Two treatment groups were compared: one group (Dt group) received oral doxycycline and tretinoin 0.025% cream for the first 6 weeks, and tretinoin 0.025% cream alone for the next 6 weeks; the other group (DtM Selection and recruitment Review of patient information sheet and signing of informed consent Serum FBS, creatinine, pelvic ultrasound, pregnancy test Abnormal FBS or creatinine, ovarian pathology, or pregnant EXCLUDED Normal FBS and creatinine, normal ovaries, not pregnant Baseline assessment and photographs Randomization and concealed allocation by a secondary investigator DtM GROUP Wk 1-6: metformin 500mg TID, doxycycline 100mg OD, tretinoin 0.025% cream ODHS Wk 7-12: metformin 500mg TID, tretinoin 0.025% cream ODHS Dt GROUP Wk 1-6: placebo tab TID, doxycycline 100 mg OD, tretinoin 0.025% cream ODHS Wk 7-12: placebo tab TID, tretinoin 0.025% cream ODHS Assessment at follow up visits every 2 weeks by the primary investigator Repeat serum FBS, creatinine and pregnancy test at the end of treatment 4 of 31 group), received oral metformin and doxycycline, and tretinoin 0.025% cream for the first 6 weeks, and oral metformin and tretinoin 0.025% cream for the next 6 weeks. Oral doxycycline was discontinued 6 weeks into the treatment for both groups, in concordance with the guidelines that recommend that the effects of oral antibiotics in acne vulgaris can usually be observed in 6 weeks.[3] Metformin was given at a dose of 1500 mg/day to the DtM group for 12 weeks, the same regimen given in the study by Kolodziejczyk[13] that achieved significant decrease in acne scores.

Subject Selection and Recruitment

Patients selected for this study were both male and female, aged 16 to 40 years old, diagnosed with moderate to severe acne by the primary investigator, with a global severity score of 2 to 4 (moderate to severe). Recruitment and evaluation of subjects was done at the dermatology outpatient department of a tertiary hospital. It commenced in February 2012, and ended in September 2012. Exclusion criteria were those with history of tetracycline hypersensitivity, diabetes mellitus, renal, cardiac and hepatic disease, alcoholism, serious infection, severe diarrhea or vomiting, fever, poor oral intake, conditions predisposing to tissue anoxia, and females with pregnancy or polycystic ovaries.

Once assessed as suitable to participate in the trial, the patient was asked to read the information sheet (Appendix F) and sign the informed consent (Appendix G). Legal representatives of those aged 18 and below were asked to sign the consent form as well. Baseline fasting blood glucose and serum creatinine were acquired prior to the beginning of treatment. Female patients underwent a pregnancy test, and a transvaginal/transrectal ultrasound done by a licensed OB-Gynecology sonologist, to rule out pregnancy and polycystic ovaries. Patients with abnormal fasting blood glucose or serum creatinine, pregnancy, or polycystic ovaries, were excluded from the study and referred to a medical internist or an obstetrician-gynecologist, respectively, for appropriate management.

Females who fulfilled the inclusion criteria were informed of the harms and risks of pregnancy for the duration of the study. They were advised on the recommended contraception methods (i.e. abstinence, natural rhythm method).

Demographic profiles and the following baseline data were recorded in a data collection sheet (Appendix H):

1. Weight in kg
2. Height in cm
3. Body mass index (BMI)
4. Non-inflammatory, inflammatory and total lesion count using the Leeds' Acne Lesion Count System (Appendix A), and the corresponding modified global severity score (Appendix B)
5. Fasting blood glucose (FBS) level
6. Serum creatinine level
7. For female patients, results of the transvaginal/ transrectal ultrasound and pregnancy test.
8. DLQI scores

Study Methods and Data Collection

The sample size was computed based on the mean difference in total number of lesions from a previous study,14 reported as 0.3014, and a mean difference estimated at 0.55 for the current study. Seventeen (17) subjects were included in each group to detect a statistically significant clinical response between lesion counts, with a power of 80% and α=0.05 level of significance. Patients were assigned a study number in the order that they were recruited, and assigned to either of the 2 treatment groups using computerized block randomization (Microsoft Excel Version 12.0: RAND and SORT functions) by a secondary investigator.

Sealed envelopes, prepared and given to the patients by the secondary investigator, were labeled according to the week these were supposed to be opened. Patients were instructed to open a designated envelope for each week, and to take the capsules at bedtime and the tablets 1-2 hours after meals. Metformin 500mg/tablet was titrated in 500 mg increments to the full dose of 1500 mg in the first three days in order to lessen gastrointestinal side effects. The placebo tablets given to the Dt group were titrated the same way.

The envelopes given to the DtM group contained the following:

Weeks 1-6:
Day 1: 1 tablet of metformin 500mg/tab, 1 capsule of doxycycline 100mg/cap
Day 2: 2 tablets of metformin 500mg/tab, 1 capsule of doxycycline 100mg/cap
Days 3-42: 3 tablets of metformin 500mg/tab, 1 capsule of doxycycline 100mg/cap

Weeks 7-12:
Days 43-84: 3 tablets of metformin 500mg/tab

The envelopes given to the Dt group contained the following:

Weeks 1-6:
Day 1: 1 capsule of doxycycline 100mg/tab, 1 placebo tablet
Day 2: 1 capsule of doxycycline 100mg/tab, 2 placebo tablets
Days 3-42: 1 capsule of doxycycline 100mg/tab, 3 placebo tablets

Weeks 7-12:
Days 43-84: 3 placebo tablets

In addition, for both treatment groups, tretinoin 0.025% cream was applied thinly over the entire face nightly, and a mild facial soap was used twice daily. The patients, as well as the primary investigator who assessed them at baseline and during their follow up visits, were blinded to the treatment being given. The following data were recorded at every follow up visit, scheduled at week 2, 4, 6, 8, 10 and 12 from the beginning of treatment:

1. Weight in kg
2. BMI
3. Non-inflammatory, inflammatory and total lesion count using the Leeds' Acne Lesion Count System (Appendix A), and the corresponding modified global severity score (Appendix B).
4. Subjective Self-Assessment Score of Change in Acne Severity (Appendix C) as reported by the patient, to be graded (0) worsened, (1) no change, (2) mild improvement, (3) moderate improvement, or (4) marked improvement
5. Systemic adverse events to treatment as reported by the patient.
6. Cutaneous adverse events of erythema, pain, scaling and dryness of the skin over the face, reported by the patient and observed by the clinical investigator, assessed as none (0), mild (1), moderate (2), and severe (3)
7. DLQI score on the 12th week of treatment.

Photographs were taken at baseline and at every follow up visit, 1 foot away from the subject, using a Panasonic Lumix camera (Model DMC-LX3, macro mode setting, ISO 100). Full anterior, right and left views of the face were photographed. Patients were instructed to contact the primary investigator immediately if any adverse events are experienced during the course of treatment. Serum fasting blood sugar and creatinine, and pregnancy test for females, were repeated upon completion of the treatment. Data collected were securely recorded, filed, and protected from inadvertent or inappropriate access by the primary investigator.

Statistical Analysis

Descriptive analysis for continuous variables (age and body mass index), were performed using central tendency measures of mean and standard deviation. For bivariate analysis of categorical variables such as gender, Fisher's exact test was used.

Shapiro-Wilk test for normality was done to determine if parametric or non-parametric tests are indicated for each variable.

The Student's t-test was used to analyze the difference between groups for age and FBS at baseline and at the end of treatment. The Mann-Whitney U test was used to determine the difference between groups for BMI and DLQI at baseline and at the end of treatment. The mean reduction rates from baseline to each follow up visit of non-inflammatory, inflammatory, and total lesion counts for each group were compared using the Mann-Whitney U test to determine if a statistically significant differ ence would be demonstrated. The mean scores for every follow-up visit of global severity and subjective self assessment, and the mean DLQI scores at baseline and at the end of treatment, were compared using the Mann -Whitney U test as well.

For cutaneous adverse events, the grading of erythema, pain, scaling and dryness, between the two groups were compared using the Mann-Whitney U test. Incidence and frequency of systemic adverse events between the two groups were determined, and the Mann-Whitney U test was again used to compare the frequency of systemic adverse events per follow-up visit between the two groups.

Unless otherwise noted, all results are expressed as the mean $\pm$ standard deviation. For all parameters, a p-value of <0.05 was deemed statistically significant.

An intent-to-treat analysis was performed, with the study population defined as those assigned to their respective treatment arms and received the dispensed medications, regardless of outcome, whether the subjects completed the study or not. For missing data and withdrawals, it was assumed that there was no change or improvement in the variable of interest after the period of non-compliance.

All data were analyzed using Stata Version 10.0.

Efficacy end points

Primary efficacy end points were the mean reduction rates of non-inflammatory, inflammatory and total acne lesion counts at each follow up visit until the end of treatment. Secondary efficacy end points were the modified global severity score, subjective self-assessment score, and the DLQI, on the 12th week of treatment.

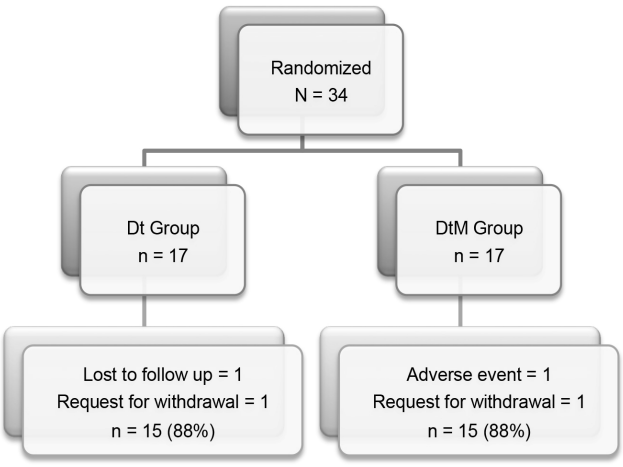
Safety end points

Safety end points were the comparison between the two treatment groups of the following parameters: (1) mean grades of erythema, pain, scaling and dryness at each follow-up visit, as a result of topical application of tretinoin cream; and (2) the incidence and frequency of systemic adverse events as reported by the patient (e.g. diarrhea, nausea, vomiting, abdominal pain)

RESULTS

Subjects

Figure 2. Summary of subject disposition



A total of 35 patients were recruited in this study, but one female patient was excluded due to high fasting blood sugar, and was referred to Endocrine Medicine. None of the female patients had pregnancy or polycystic ovaries. The intent-to-treat population included all the randomized subjects who were dispensed the study medication.

The remaining 34 patients were randomized into two groups (Figure 2): 17 subjects in the DtM group, and 17 subjects in the Dt group.

In the DtM group, only 15 patients (88%) completed the study. One patient acquired furunculosis on the face during the 8th week of treatment. The patient admitted to have been habitually picking on his lesions. Culture of wound discharge showed heavy growth of Staphylococcus epidermidis. The patient was treated with first generation cephalosporins for a week, which resolved the condition. The second patient dropped out after the 4th week of treatment because of time conflict with school.

In the Dt group, only 15 patients (88%) completed the study. One patient had to go home to the province, and requested to be pulled out of the study after the second week of treatment. The second patient was lost to follow-up after baseline assessment, and could not be contacted.

Discontinuation rates between the DtM group and the Dt group had no statistical difference, having the same number of patients completing the study.

Both treatment groups were comparable as to their demographic characteristics of age and gender, with no statistically significant difference (Table 1).

Table 1. Demographic characteristics of the study population treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt)

Parameter	DtM group (N=15)	Dt group (N=15)	p value
Age in yrs (mean ± SD)	19.65 ± 4.09	19.82 ± 3.94	0.8989[a]
Gender			
Female [n (%)]	8 (47.06)	6 (35.29)	0.364[b]
Male [n (%)]	9 (52.94)	11 (64.71)	

[a]Student's t-test; [b]Fisher's exact test

Baseline and final scores of body mass index and fasting blood sugar between the two groups (Table 2) showed no statistical difference as well.

Table 2. Mean baseline and final body mass index, fasting blood sugar, and serum creatinine of study populations treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt)

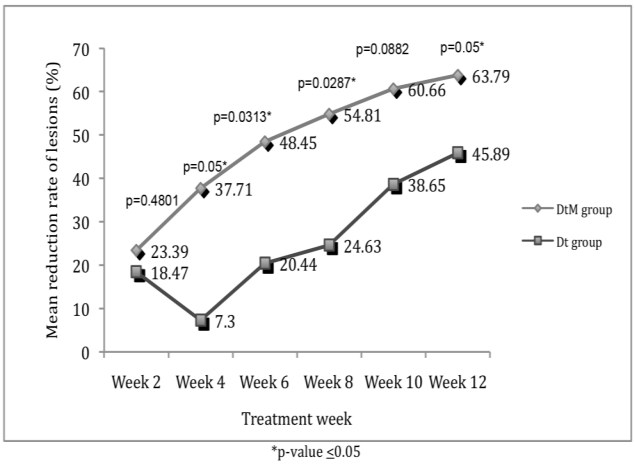
Parameter	DtM group (mean ± SD)	Dt group (mean ± SD)	p value
Baseline body mass index (kg/m^2)	20.27 ± 2.43	19.16 ± 2.30	0.1431[a]
Final body mass index (kg/m^2)	19.15 ± 5.49	19.18 ± 2.58	0.3262[a]
Baseline fasting blood sugar (mmol/L)	4.99 ± 0.35	4.85 ± 0.39	0.2700[b]
Final fasting blood sugar (mmol/L)	4.79 ± 0.49	4.69 ± 0.50	0.6192[b]

[a]Mann-Whitney U test; [b]Student's t-test

Efficacy Outcomes

The mean reduction rate of non-inflammatory (comedonal) lesions at each follow up visit (Figure 3), showed consistent improvement when compared to baseline. For the 4th week of treatment, there was a statistically significant difference in the mean reduction rate between the DtM (37.71%) and the Dt (7.30%) group, with a p-value of 0.05. On the 6th treatment week, the DtM group showed a statistically significant higher mean reduction rate as well (48.45%) compared to the Dt group (20.44%) with a p -value of 0.0313. A statistically significant benefit was still demonstrated in the 8th treatment week in the DtM group (54.81%) over the Dt group (24.63%) with a p-value of 0.0287. On the 12th week of treatment, the DtM group again showed a significant statistical benefit (63.79%) compared to the Dt group (45.89%) with a p-value of 0.05.

Figure 3. Mean reduction rate of non-inflammatory (comedonal) lesions in patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12



*p-value ≤0.05

Both treatment groups showed improvement in the mean reduction rate of inflammatory and total lesion counts on all follow up visits compared to baseline. There was no statistically significant difference in the reduction rates of both treatment groups during all follow up visits with p-values greater than 0.05 (Figure 4 and 5).

Figure 4. Mean reduction rate of inflammatory lesions in patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12

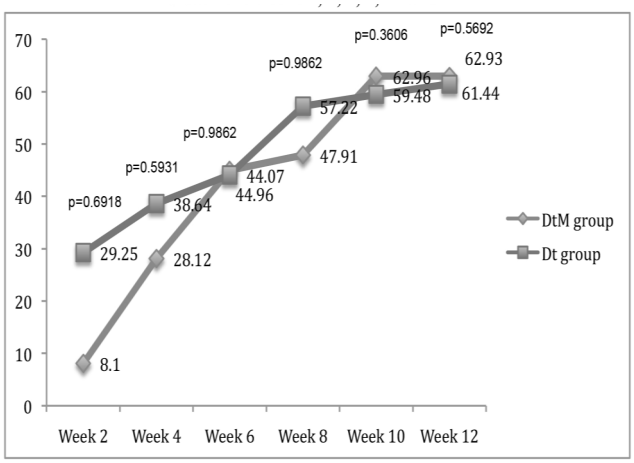
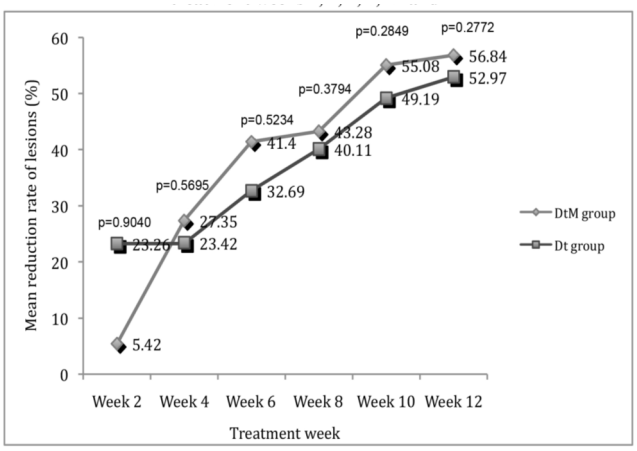


Figure 5. Mean reduction rate of total acne lesions in patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12



Both groups showed improvement in their modified global severity and subjective selfassessment scores (Figure 6 and 7) at each follow up visit and their DLQI (Table 3) at the end of treatment. Comparison of the two treatment groups showed no statistical difference.

Figure 6. Mean global severity score for patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12

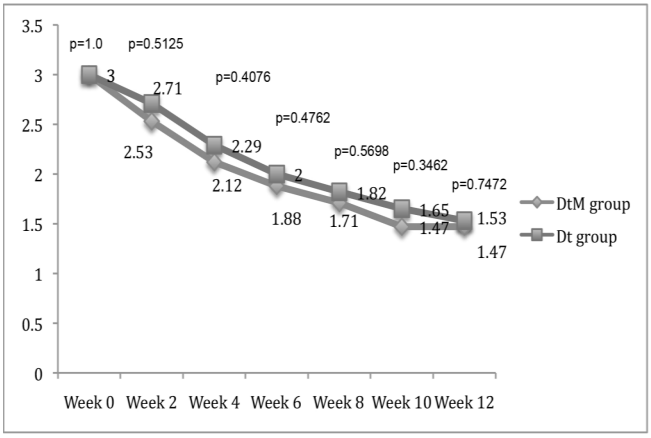


Figure 7. Mean subjective self-assessment score for patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12

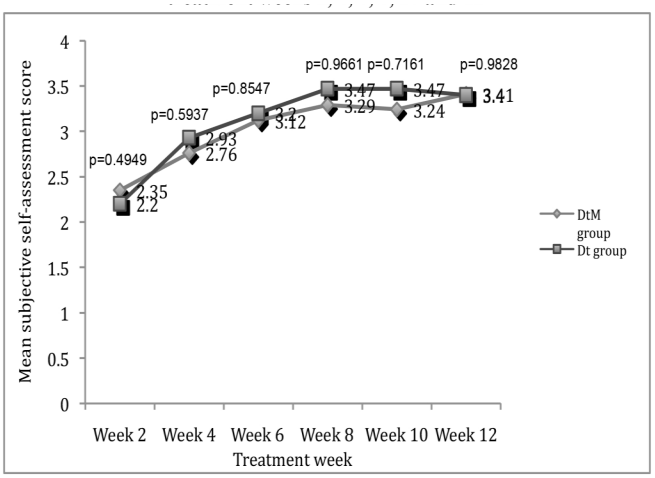


Table 3. Mean DLQI scores of patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and at the end of treatment

Parameter	DtM group (mean ± SD)	Dt group (mean ± SD)	p value[a]
Baseline DLQI score	12.76 ± 5.76	9.88 ± 6.29	0.1662
Final DLQI score	2.33 ± 1.84	3.13 ± 2.42	0.3762

[a]Mann Whitney U test

Safety Outcomes

Erythema scores (Table 4) for the DtM group showed a decreasing trend from the 2nd (1.0) to the 12th week (0.38) of treatment. The Dt group, on the other hand, showed a fluctuating but a general decrease in trend of erythema scores, increasing from the 2nd week (0.75) to the 4th week (0.81) of treatment, going back down on the 6th week (0.75), further decreasing up to the 10th week (0.44), and increasing on the 12th week (0.69). Between the two treatment groups, there was no observed statistical difference in erythema scores for all follow-up visits.

Pain scores (Table 4) also showed a decreasing trend in both groups. The DtM group score decreased from the 2nd week (0.38) to the 8th week (0.06). The Dt group pain scores decreased from the 2nd week (0.19) to 4th week (0.13), and maintained scores until the 8th week of treatment. There was no report of pain in all subjects beginning at the 10th week of treatment. No statistical difference was observed in the pain scores between the DtM and Dt groups for all follow-up visits.

Table 4. Mean erythema and pain count of patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at treatment weeks 2, 4, 6, 8, 10 and 12

	Mean erythema count			Mean pain count		
	DtM Group (mean ± SD)	*Dt Group* (mean ± SD)	*p value*[a]	*DtM Group* (mean ± SD)	*Dt Group* (mean ± SD)	*p value*[a]
Week 2	1.0 ± 0.63	0.75 ± 0.93	0.2961	0.38 ± 0.62	0.19 ± 0.40	0.3816
Week 4	0.81 ± 0.40	0.81 ± 0.91	0.7566	0.19 ± 0.40	0.13 ± 0.34	0.6318
Week 6	0.63 ± 0.62	0.75 ± 0.86	0.8053	0.13 ± 0.34	0.13 ± 0.34	1.0
Week 8	0.50 ± 0.63	0.56 ± 0.73	0.8814	0.06 ± 0.25	0.13 ± 0.34	0.5506
Week 10	0.38 ± 0.50	0.44 ± 0.73	0.9280	0	0	-
Week 12	0.38 ± 0.13	0.69 ± 0.95	0.5117	0	0	-

[a]Mann-Whitney U test

The mean scaling count (Table 5) in the DtM group showed a decreasing trend from the 2nd (0.56) to the 10th week (0.138), maintaining values up to the 12th week (0.138) of treatment. The Dt group showed decreasing scores from the 2nd week (0.25) to the 6th week (0.06), increasing on the 8th week (0.25), decreasing on the 10th week (0.13) and maintaining the same 13 of 31 score on the end of treatment (0.13). Between the two groups, no significant statistical difference was observed.

For the DtM group, the mean dryness count (Table 5) showed a decreasing trend until the end of treatment. For the Dt group, mean scores showed a decreasing trend until the 6th week of treatment. There was an increase in the mean dryness score on the 8th week of treatment, and the mean score went back to baseline on the 12th week of treatment. Comparing the mean dryness count between the DtM and Dt group showed no statistically significant difference.

Table 5. Mean scaling and dryness count of patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at treatment weeks 2, 4, 6, 8, 10 and 12

	Mean scaling count			Mean dryness count		
	DtM Group (mean ± SD)	*Dt Group* (mean ± SD)	*p value*[a]	*DtM Group* (mean ± SD)	*Dt Group* (mean ± SD)	*p value*[a]
Week 2	0.56 ± 0.73	0.25 ± 0.45	0.2058	0.38 ± 0.62	0.25 ± 0.45	0.6304
Week 4	0.38 ± 0.50	0.19 ± 0.54	0.1471	0.38 ± 0.50	0.25 ± 0.58	0.3123
Week 6	0.19 ± 0.40	0.06 ± 0.25	0.2927	0.31 ± 0.48	0.06 ± 0.25	0.0746
Week 8	0.19 ± 0.40	0.25 ± 0.45	0.6738	0.13 ± 0.34	0.31 ± 0.60	0.3449
Week 10	0.138 ± 0.34	0.13 ± 0.34	1.0	0.19 ± 0.54	0.31 ± 0.60	0.4055
Week 12	0.138 ± 0.34	0.13 ± 0.34	1.0	0.06 ± 0.25	0.25 ± 0.45	0.1506

[a]Mann-Whitney U test

The most frequent systemic adverse event noted (Table 6) in the DtM group was diarrhea, reported by 10.64% of patients. Nausea was experienced by 8.51% of patients in the DtM group, and in 1.20% in the Dt group. Diarrhea, headache, vomiting and abdominal pain were adverse events found only in the DtM group.

Loss of appetite (4.40%) was the most frequent systemic adverse event noted in the Dt group. None of the patients in the DtM group complained of this.

Table 6. Incidence of systemic adverse events reported per treatment group

Adverse effect	DtM group [n(%)]	Dt group [n(%)]
Diarrhea	10 (10.64)	0 (0)
Nausea	8 (8.51)	1 (1.20)
Vomiting	3 (3.19)	0 (0)
Headache	4 (4.26)	0 (0)
Dizziness	2 (2.13)	2 (2.20)
Loss of appetite	0 (0)	4 (4.40)
Heartburn	2 (2.13)	1 (1.20)
Abdominal pain	2 (2.13)	0 (0)

The frequency of systemic adverse events (Table 7) on the 2nd week of treatment was statistically higher in the DtM group (68.75%) compared to the Dt group (18.75%), with a pvalue of 0.006. On the 4th week of treatment, the DtM group still showed a statistically higher frequency (50%) of systemic adverse events, while the Dt group demonstrated no systemic adverse events (0%), with a p-value of 0.001. On the other hand, there was no statistical difference demonstrated between the two groups for the 6th (DtM group 33.33% vs. Dt group 6.25%) and 8th (DtM group 13.33% vs. Dt group 0%) weeks of treatment with p-values greater than 0.05. No adverse events were reported during the 10th and 12th week for both groups.

Table 7. Frequency of systemic adverse events per follow up visit

Week	DtM group [n(%)]	Dt group [n(%)]	p value
2	11 (68.75)	3 (18.75)	0.006[a]
4	8 (50)	0 (0)	0.001[a]
6	5 (33.33)	1 (6.25)	0.072
8	2 (13.33)	0 (0)	0.226
10	-[b]	-[b]	-
12	-[b]	-[b]	-

[a]p-value ≤0.05; [b]no reported systemic adverse events

DISCUSSION

Acne occurs in the pilosebaceous unit, composed of the sebaceous glands, rudimentary hair and a wide follicular canal lined by the stratified squamous epithelium.[3] For years, the four key pathogenetic factors that have been recognized include follicular epithelial hyperproliferation and resultant follicular plugging; excess sebum; inflammation; and the presence and activity of *Propionibacterium acnes*.[15] Follicular epithelial hyperproliferation and follicular plugging leads to formation of non-inflammatory lesions known as comedones. Excessive sebum production and chemotaxis triggered by hypercolonization of sebaceous ducts by *Propionibacterium acnes*, stimulate inflammation of the pilosebaceous unit, producing the inflammatory lesions of papules, pustules, nodules, and cysts.[15]

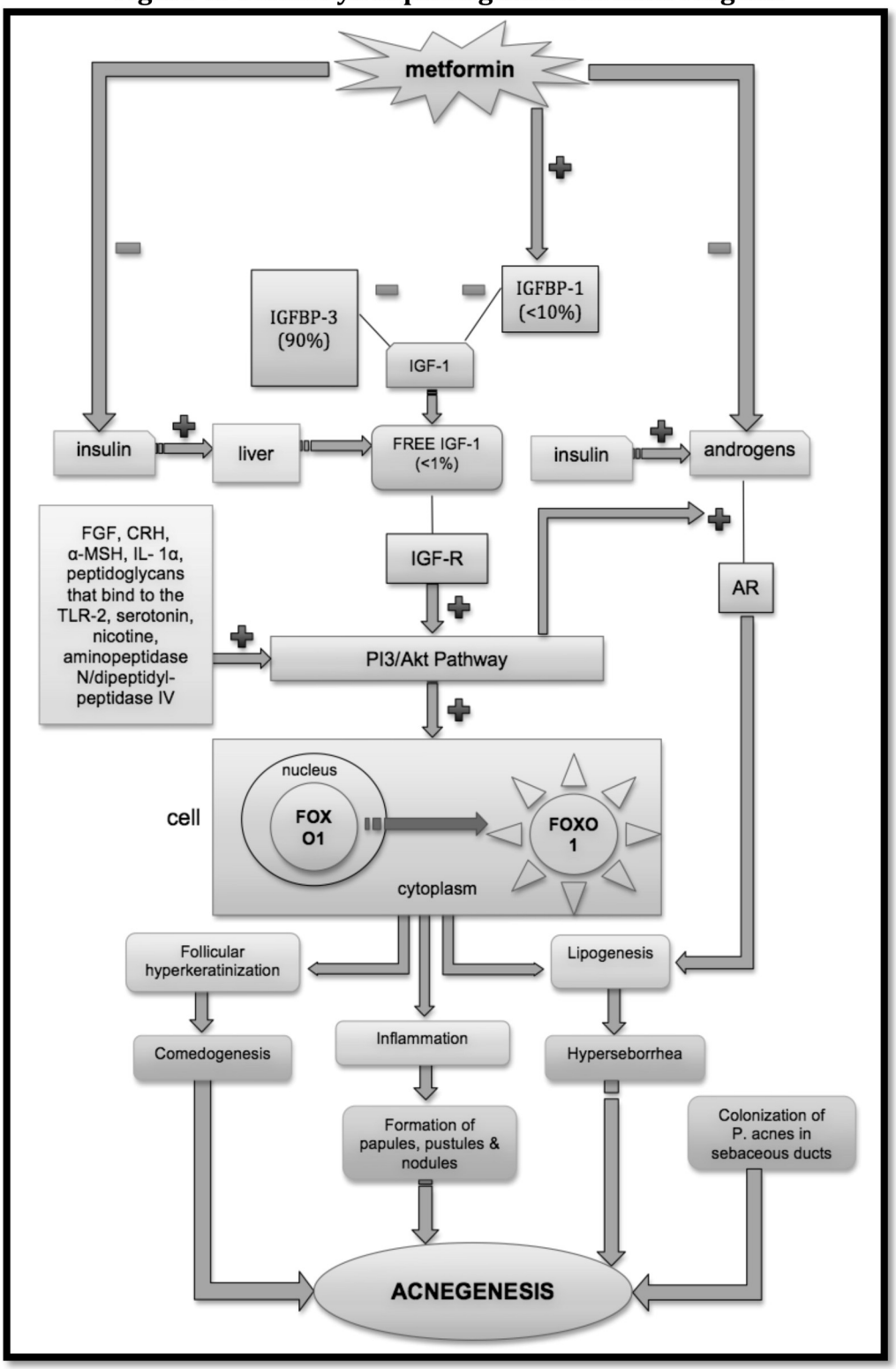
The pathogenesis of acne involves complex and multifactorial processes. Despite many research studies done on acne, its exact pathogenesis is still not completely understood. New developments in its pathogenesis are continuously being discovered to develop better treatment strategies.

Androgen plays a crucial role in the pathogenesis of acne. The interaction of androgen other biological factors, including growth factors, are required for the normal development, growth and differentiation of the pilosebaceous unit.[16] The sebaceous gland has been shown to express the necessary enzymes for the biosynthesis of testosterone from circulating dehydroepiandrosterone sulfate (DHEA-S) and subsequent conversion of testosterone to 5α-dihydrotestosterone (DHT).[17] Testosterone and DHT form complexes with the nuclear androgen receptors, which are expressed in the basal cell layer of the sebaceous glands and in the keratinocytes lining the outer root sheath of hair follicles. The androgen-receptor complex then interacts with DNA in the nuclei of sebaceous gland cells to regulate genes involved in cell growth and lipid production.[18] Increased DHT may act on infundibular keratinocytes, leading to abnormal hyperkeratinization,[19] which is the most crucial initial event in the development of acne lesions. The retention hyperkeratosis in the follicular infundibulum and sebaceous duct leads to occlusion, blocking the outward flow of sebum secretion, resulting in the formation of non-inflammatory microcomedo which is the initial lesion seen in acne. The trapped sebum and shed cells promote bacterial proliferation, immune reactions and inflammation, resulting in the development of inflammatory lesions.[3]

Several studies have shown that metformin treatment decreases androgen levels,[20] or levels of DHEA-S and testosterone.[21] The decrease in the androgen levels, the crucial hormone for the hyperkeratosis and lipogenesis, may, therefore, explain the beneficial effect of metformin in decreasing the manifestation of the non-inflammatory lesions of acne, which are the comedones.[21]

The complex pathogenesis of acne may also be explained at the level of genomic regulation (Figure 8). Recent studies by Melnik[22,23] claim that acneigenic stimuli converge in the phosphoinositol-3 kinase (PI3K)/Akt/Fox01 signal pathway. Various growth factors and acneigenic stimuli activate the P13K/Akt signal transduction. Activated kinase Akt triggers phosphorylation of Fox01, promoting export into the cytoplasm from the nucleus. It is hypothesized that the deficiency of transcription factor Fox01 in the nucleus underlies all pathogenic pathways of acne. This results to derepression of target genes and activation of nuclear receptors that trigger acneigenesis by 3 pathways: First is by activating androgen receptors located on sebaceous glands and ducts, leading to hyperseborrhea. Second is by activating antimicrobial peptides, matrix metalloproteinases, & other inflammatory mediators, resulting to formation of papules, pustules and nodules. Third is by regulating key genes of cell cycle control, triggering follicular hyperkeratinization and comedogenesis.

Figure 8. Pathways of pathogenesis of acne vulgaris



(IGFBP-3, insulin-like growth factor binding protein-3; IGFBP-1, insulin-like growth factor binding protein-1; IGF-1, insulin-like growth factor-1; IGF-R, insulin-like growth factor receptor; AR, androgen receptor; PI3/Akt, phosphoinositol-3/Akt kinase; P. acnes, Propionibacterium acnes; FGF, fibroblast growth factor; CRH, corticotrophin releasing hormone; α-MSH, α-melanocyte-stimulating hormone; IL-1α)

Insulin and insulin-like growth factor-1 (IGF-1) are some of the acneigenic stimuli that upregulate P13K/Akt signaling. The homology of insulin and IGF -1 allows one to bind to the receptor of the other. Insulin, therefore, also binds to the insulin-like growth factor-1 receptor (IGF-1R), explaining the significant overlap in signal transduction. Insulin also directly stimulates hepatic secretion of IGF-1 by the liver, and increases serum androgens16 through biosynthesis. IGF-1 and its receptors are strongly expressed in the epidermis, sebocytes and suprabasal cells of sebaceous ducts.[24,25] IGF-1 thereby directly regulates seborrhea and lipogenesis, and cell differentiation that facilitates follicular hyperkeratinization. Interestingly, a study by Rebecca et al26 found higher glucose levels in acne patients compared to healthy controls. This relative hyperglycemia may also stimulate secretion of insulin.

Metformin treatment has been shown to decrease serum levels of IGF-1 and insulin.[20, 21] This in turn, also decreases the hyperandrogenemia that results from the action of insulin on androgen biosynthesis (Figure 8). These findings elucidate further the regulatory effect of metformin in the process of lipogenesis, seborrhea and hyperkeratinization. This is an additional explanation for the decrease in the non-inflammatory lesions noted in this study.

The free or unbound IGF-1 is the active component involve in the P13K/Akt pathway. Only less than 1% of IGF-1 circulates unbound in the serum. Ninety percent is bound to insulinlike growth factor binding protein-3 (IGFBP-3), and less than 10% is bound to IGFBP-1, -2, -4, -5 and -6.[24] Any factor that would increase serum IGFBPs would then decrease circulating IGF-1, the magnitude of which will be dependent on the type of IGFBP that is increased. Metformin has been shown to increase IGFBP1 levels, decreasing free circulating IGF-1, and downgrading acnegenesis.[27]

The role of *Propionibacterium acnes*, the predominant microorganism in acne, in the transformation of non-inflammatory acne lesions to inflammatory ones, is well recognized. Studies have suggested that sebum represents a growth substrate for *P. acnes* proliferation.[28] The microcomedo with its trapped sebum becomes filled with *P. acnes*, whose cell wall and biological byproducts are chemoattractant and proinflammatory. Cell-mediated immune responses and activation of the complement system and humoral responses have been shown to be involved in the process.[3] As a result, inflammatory cells surround the follicle, diffuse through the follicular wall, and produce enzymes that disrupt the follicular wall.[14] The movement of sebum into the dermis is also highly inflammatory.[3]

Systemic antibiotics such as the tetracyclines (tetracycline, minocycline, doxycycline and lymecycline) suppress the growth of *P. acnes* and have been widely used for the treatment of moderate to severe inflammatory acne.[3] In this study, doxycycline was used for both treatment groups, Dt and DtM. It is expected, therefore, that both treatment groups will show decrease in the inflammatory lesions due to the suppression of *P. acnes* colonization. Metformin does not have antibacterial effects and its beneficial effects in the management of acne, as explained previously, involve a different pathway. This may explain why there was no statistically significant difference in the reduction of inflammatory lesions, as shown in this study.

At the level of genomic regulation as explained by Melnik[22], there are other growth factors and acneigenic stimuli that activate the P13k/Alt/FOXO1 signaling pathway which can lead to inflammation. Among these factors are fibroblast growth factor, corticotrophin releasing hormone, α-melanocyte-stimulating hormone, interleukin 1α, peptidoglycans that bind to the toll-like receptors 2, serotonin, nicotine, and aminopeptidase N/dipeptidylpeptidase IV. The binding of these factors is not inhibited by metformin, thus explaining the absence of its additional benefit in decreasing the inflammatory lesions.

Another explanation is that several external and uncontrolled environmental factors may influence the inflammatory pathway. Recently, it has been shown that hyperglycemic food and milk consumption, smoking, and stress,26 may also trigger insulin/IGF-1 signaling or the phosphorylation of FoxO1 itself.

In this study the group that received metformin also had the standard treatment of doxycycline and tretinoin. It was not compared to a placebo but to a group that received the standard treatment as well. This may explain why both groups had improvement in patient's subjective self-assessment score of change in acne severity and DLQI scores with no statistical difference.

The pathophysiology of acne indicates that inflammatory lesions originate from comedones or non-inflammatory lesions. Therefore, the positive

effect of metformin in decreasing the non-inflammatory lesions should ultimately have an appreciable benefit on inflammatory lesions as well. It is possible that a longer treatment duration may have provided better results.

Adverse Events of Treatment

In this study, mild to moderate erythema, scaling, and dryness were noted during the entire treatment duration for both groups, but with a general trend of decreasing severity upon continued use. These manifestations, together with pain, are known common cutaneous adverse effects of tretinoin, which was part of the treatment regimen of both groups. Interestingly, pain was not reported by any of the subjects in both treatment groups at the 10th and 12th weeks of treatment. These findings support general observations that these predictable side effects of topical retinoids are temporary, peaking within the first month of use and diminishing thereafter.[29]

The group that received metformin significantly had a higher incidence and frequency of systemic adverse events, with diarrhea, nausea and headache being the most common. Although diarrhea has been reported as a common side effect upon intake of doxycycline[30], the lack of subjects reporting diarrhea in the Dt group suggests that there is no additive side effect from doxycycline in this study. On the other hand, nausea, headache and heartburn have also been reported as common side effects of doxcycline[30]. Therefore, an additive effect by doxycycline cannot be ruled out.

Gastrointestinal side effects of metformin may be addressed by intake of the drug after meals and by slower titration of dose. The patients who reported these symptoms claimed that they were not consistent or persistent, resolving spontaneously within the first month without need for treatment. The levels of fasting blood sugar of all subjects who received metformin remained normal by the end of treatment. Metformin is thus a well-tolerated and safe oral medication that can be used in the treatment of moderate to severe acne.

Limitations and Recommendations

The primary limitation of this study is its short treatment duration. For future studies, a longer treatment time might be able to detect a statistically significant difference in the reduction of inflammatory and total lesion counts, and improvement of subjective and objective scores.

Other variables, proven or anecdotal, that have been reported to affect the course and severity of acne, such as smoking, psychosocial stress, hours of sleep, and diet in relation to glycemic index, may also be considered in the assessment of baseline characteristics.

CONCLUSION

In the treatment of moderate to severe acne vulgaris, the addition of metformin to oral doxycycline and tretinoin 0.025% cream, offers significant additional benefit in the reduction of non-inflammatory acne lesions.

The inflammatory and total acne lesion counts, and scores of global severity, subjective self-assessment, and DLQI improved in both treatment groups, with no significant difference at the end of the 12-week period.

The cutaneous side effects of erythema, pain, scaling, and dryness of the skin, attributed to be due to tretinoin cream, were noted in both treatment groups, but were self-limited. The metformin-treated group had more non-cutaneous side effects of diarrhea, nausea, and headache, but these were mild, and likewise self-limited. These adverse effects did not warrant the discontinuation of treatment.

DISCLOSURE

This is an investigator-initiated, self-funded research trial. There is no potential conflict of interest.

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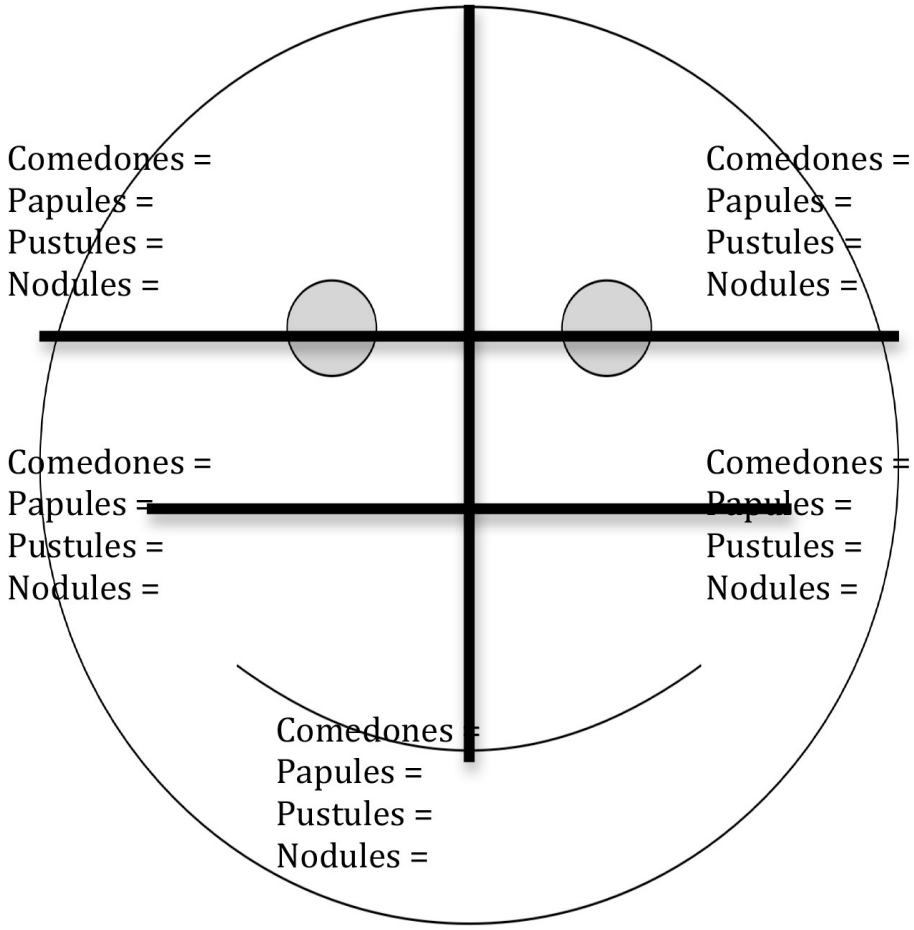
Appendix A

Leeds Acne Lesion Counting System



	Lesion Type			
Area	**Comedones**	**Papules**	**Pustules**	**Nodules**
Right forehead				
Left forehead				
Right cheek				
Left cheek				
Chin				
Total lesions				

Appendix B

Modified Global Severity Score

Global Severity Score	Description	Simplified Classification
1	Comedones are the main lesions. < 10 papules and pustules ± < 6 nodules	Mild
2	<10 papules & pustules ± ≥ 6 nodules or 10-40 papules & pustules ± < 6 nodules	Moderate
3	10-40 papules & pustules ± ≥ 6 nodules or 40-100 papules & pustules ± < 6 nodules	Moderately Severe
4	40-100 papules & pustules ± ≥ 6 nodules or >100 papules & pustules or Nodulocystic	Severe

Appendix C

Subjective Self-Assessment Score of Change in Acne Severity

0	Worsened *Lumala*
1	No change *Walang pagbabago*
2	Mild improvement *May konting pagbabago*
3	Moderate improvement *May katamtamang pagbabago*
4	Marked improvement *Malaki ang pagbabago*

APPENDIX D
Dermatology Life Quality Index (DLQI)

Indeks sa kalidad ng Pamumuhay sa may Sakit sa Balat (IKPAS)
DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Layunin ng pagtatanong ito na masukat ang epekto ng sakit sa balat sa iyong pamumuhay sa **NAKARAANG LINGGO.** Paki-tsek (✔) ang isang sagot sa bawat tanong. Anumang impormasyong nakalathala rito ay mananatiling lihim at ang iyong duktor lamang ang nakaaalam.

The Aim of this questionnaire is to measure how much your skin problems has affected your life **OVER THE LAST WEEK**. Please tick ☐ box for each question.

1. *Sa nakaraang linggo, gaano **kakati, kahapdi o kasakit** ang iyong balat?*
   Over the last week, how **itchy, sore, painful or stinging** has your skin been?
   ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala
   ☐Very much ☐ A lot ☐ A little ☐ Not at all

2. *Sa nakaraang linggo, **nahihiya** ka ba dahil sa iyong balat?*
   Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?
   ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala
   ☐Very much ☐ A lot ☐ A little ☐ Not at all

3. *Sa nakaraang linggo, gaanong abala ito sa iyong pag-**shopping** o **pamamalengke** o **gawaing bahay**?*
   Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?
   ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala
   ☐Very much ☐ A lot ☐ A little ☐ Not at all

4. *Sa nakaraang linggo, naaaperktuhan ba ang iyong **pananamit** nito?*
   Over the last week, how much has your skin influenced the **clothes** you wear?
   ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
   ☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

5. *Sa nakaraang linggo, paano naapektuhan ang iyong gawaing **pansosyal** o pan**libangan** (halimbawa, panunood ng sine) ng dahil sa iyong sakit sa balat?*
   Over the last week, how much has your skin affected any **social** or **leisure** activities?
   ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
   ☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

6. *Sa nakaraang linggo, paano ka nahirapan sa paglaro ng anumang **isport** o pag-gawa ng anumang **ehersisyo** ng dahil sa iyong sakit sa balat?*
   Over the last week, how much has your skin made it difficult for you to do any **sport**?
   ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
   ☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

7. *Sa nakaraang linggo, napigilan ka bang makapag**trabaho** o makapag **aral** ng dahil sa iyong sakit sa balat?*
   Over the last week, has your skin prevented you from **working** or **studying**?
   ☐ Oo ☐ Hindi ☐ Walang kinalaman
   ☐ Yes ☐ No ☐ Not relevant

*Kung "Hindi" ang sagot, sa nakaraang linggo, paano nakaapekto sa iyong **trabaho** o pag-a**aral** ang iyong sakit sa balat?*
If no, over the last week how much has your skin been a problem at **work** or **studying**?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

8. *Sa nakaraang linggo, paano naging problema sa iyong **partner** o matalik na **kaibigan** o **kamag-anak** ang iyong sakit sa balat?*
Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

9. *Sa nakaraang linggo, paano nagpahirap sa pakikipagtalik (**sex**) ang iyong sakit sa balat?*
Over the last week, how much has your skin caused any **sexual difficulties**?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

10. *Sa nakaraang linggo, paano naging problema ang **paggamot** ng iyong sakit sa balat, halimbawa, dahil sa idinulot nitong kalat sa bahay o sa pagkaubos ng iyong oras na iyong inuukol dito?*
Over the last week, how much of a problem has the **treatment** for your skin been, for example, by making your home **messy**, or by taking up your time?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

Paki-tsek kung nasagot mo ang lahat ng tanong. Maraming salamat!
Please check your have answered EVERY question. Thank you.

Appendix E
Dermatology Life Quality Index
Scoring System

The scoring of each question is as follows:

Very much / *Sobra-sobra*	Scored 3
A lot / *Sobra*	Scored 2
A little / *Medyo*	Scored 1
Not at all / *Wala*	Scored 0
Question unanswered / *Walang kinalaman*	Scored 0
Question 7: "prevented work or studying" / "*nakaapekto sa iyong trabaho o pag-aaral*"	Scored 3

The sum of the score of each question results to a DLQI maximum score of 30 and a minimum of 0. A higher score means there is more impairment of the quality of life.

Interpretation of DLQI Scores
0-1 = no effect at all on patient's life
2-5 = small effect on patient's life
6-10 = moderate effect on patient's life
11-20 = very large effect on patient's life
21-31 = extremely large effect on patient's life